



## Clinical trial results:

### Phase 2, Open-Label, Single Arm Study of the Efficacy and Safety of PF-02341066 in Patients With Advanced Non-Small-Cell Lung Cancer (NSCLC) Harboring a Translocation or Inversion Involving the Anaplastic Lymphoma Kinase (ALK) Gene Locus

#### Summary

|                          |                                     |
|--------------------------|-------------------------------------|
| EudraCT number           | 2009-012504-13                      |
| Trial protocol           | GB NL DE ES HU PL GR IT FR IE BG SE |
| Global end of trial date | 29 December 2015                    |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1            |
| This version publication date  | 01 April 2016 |
| First version publication date | 01 April 2016 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | A8081005 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |                                |
|------------------------------------|--------------------------------|
| ISRCTN number                      | -                              |
| ClinicalTrials.gov id (NCT number) | NCT00932451                    |
| WHO universal trial number (UTN)   | -                              |
| Other trial identifiers            | EudraCT Number: 2009-012504-13 |

Notes:

#### Sponsors

|                              |                                                                                                                 |
|------------------------------|-----------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Pfizer, Inc.                                                                                                    |
| Sponsor organisation address | 235 East 42nd Street, New York, United States, 10017                                                            |
| Public contact               | Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 18007181021 x, ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact           | Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 18007181021 x, ClinicalTrials.gov_Inquiries@pfizer.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 December 2015 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 16 March 2015    |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 29 December 2015 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

1.) To assess the anti-tumor efficacy of oral single agent PF - 02341066 administered to patients with advanced NSCLC after failure of at least one line of chemotherapy and harbor a translocation or inversion event involving the ALK gene locus as measured by ORR; 2.) To assess the safety and tolerability of oral PF-02341066

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed; in particular, those affording greater protection to the safety of study participants.

Background therapy: -

Evidence for comparator: -

|                                                           |                 |
|-----------------------------------------------------------|-----------------|
| Actual start date of recruitment                          | 07 January 2010 |
| Long term follow-up planned                               | Yes             |
| Long term follow-up rationale                             | Safety          |
| Long term follow-up duration                              | 5 Years         |
| Independent data monitoring committee (IDMC) involvement? | Yes             |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                         |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Australia: 17           |
| Country: Number of subjects enrolled | Brazil: 11              |
| Country: Number of subjects enrolled | Bulgaria: 3             |
| Country: Number of subjects enrolled | Canada: 11              |
| Country: Number of subjects enrolled | China: 190              |
| Country: Number of subjects enrolled | France: 45              |
| Country: Number of subjects enrolled | Germany: 45             |
| Country: Number of subjects enrolled | Greece: 4               |
| Country: Number of subjects enrolled | Hong Kong: 10           |
| Country: Number of subjects enrolled | Hungary: 2              |
| Country: Number of subjects enrolled | Ireland: 3              |
| Country: Number of subjects enrolled | Italy: 82               |
| Country: Number of subjects enrolled | Japan: 77               |
| Country: Number of subjects enrolled | Korea, Republic of: 143 |
| Country: Number of subjects enrolled | Netherlands: 5          |
| Country: Number of subjects enrolled | Poland: 3               |

|                                      |                       |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Russian Federation: 6 |
| Country: Number of subjects enrolled | Spain: 52             |
| Country: Number of subjects enrolled | Sweden: 3             |
| Country: Number of subjects enrolled | Taiwan: 34            |
| Country: Number of subjects enrolled | United Kingdom: 18    |
| Country: Number of subjects enrolled | United States: 302    |
| Worldwide total number of subjects   | 1066                  |
| EEA total number of subjects         | 265                   |

Notes:

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### 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)                      | 894 |
| From 65 to 84 years                       | 172 |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

A total of 1069 participants were enrolled and 1066 participants received greater than or equal to 1 dose of crizotinib. The 3 participants who were enrolled and not treated were withdrawn from the study before receiving treatment because they were not eligible and were mistakenly entered into the interactive voice response system.

### Pre-assignment

Screening details:

A total of 144 participants in study NCT00932893 were also enrolled in this study to receive treatment with crizotinib, including 143 participants randomized to the chemotherapy arm then crossed over in this study and 1 participant initially erroneously randomized in the crizotinib arm but not treated.

### Period 1

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

### Arms

|           |                       |
|-----------|-----------------------|
| Arm title | Crizotinib 250 mg BID |
|-----------|-----------------------|

Arm description:

Participants were administered crizotinib at a starting dose of 250 mg orally, BID on a continuous dosing period as two 100-mg tablets and one 50-mg tablet at approximately 12 hours apart the same time each day.

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Crizotinib   |
| Investigational medicinal product code |              |
| Other name                             | PF-02341066  |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

starting dose 250 mg orally, BID, continuous dosing schedule

| Number of subjects in period 1   | Crizotinib 250 mg BID |
|----------------------------------|-----------------------|
| Started                          | 1066                  |
| Completed                        | 0                     |
| Not completed                    | 1066                  |
| Consent withdrawn by subject     | 64                    |
| Adverse event, non-fatal         | 76                    |
| Death                            | 134                   |
| Ongoing                          | 122                   |
| Other reasons                    | 52                    |
| Lost to follow-up                | 3                     |
| Objective progression or relapse | 329                   |

|                                |     |
|--------------------------------|-----|
| Global deterioration of health | 286 |
|--------------------------------|-----|

## Baseline characteristics

### Reporting groups

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | Crizotinib 250 mg BID |
|-----------------------|-----------------------|

Reporting group description:

Participants were administered crizotinib at a starting dose of 250 mg orally, BID on a continuous dosing period as two 100-mg tablets and one 50-mg tablet at approximately 12 hours apart the same time each day.

| Reporting group values                             | Crizotinib 250 mg BID | Total |  |
|----------------------------------------------------|-----------------------|-------|--|
| Number of subjects                                 | 1066                  | 1066  |  |
| Age categorical<br>Units: Subjects                 |                       |       |  |
| In utero                                           | 0                     | 0     |  |
| Preterm newborn infants (gestational age < 37 wks) | 0                     | 0     |  |
| Newborns (0-27 days)                               | 0                     | 0     |  |
| Infants and toddlers (28 days-23 months)           | 0                     | 0     |  |
| Children (2-11 years)                              | 0                     | 0     |  |
| Adolescents (12-17 years)                          | 0                     | 0     |  |
| Adults (18-64 years)                               | 894                   | 894   |  |
| > 65 years                                         | 172                   | 172   |  |
| Age Continuous  <br>Units: years                   |                       |       |  |
| arithmetic mean                                    | 52.2                  |       |  |
| standard deviation                                 | ± 12.3                | -     |  |
| Gender, Male/Female<br>Units: Participants         |                       |       |  |
| Female                                             | 601                   | 601   |  |
| Male                                               | 465                   | 465   |  |
| Race/Ethnicity, Customized<br>Units: Subjects      |                       |       |  |
| Chinese                                            | 252                   | 252   |  |
| Japanese                                           | 81                    | 81    |  |
| Korean                                             | 144                   | 144   |  |
| White                                              | 532                   | 532   |  |
| Black                                              | 20                    | 20    |  |
| Other                                              | 19                    | 19    |  |
| Other-Asian                                        | 18                    | 18    |  |

### Subject analysis sets

|                            |             |
|----------------------------|-------------|
| Subject analysis set title | PF-06260182 |
|----------------------------|-------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

PF-06260182 was a PF-02341066 metabolite measured in this study.

|                            |                                 |
|----------------------------|---------------------------------|
| Subject analysis set title | Crizotinib 250 mg BID-ALT cases |
|----------------------------|---------------------------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Participants were administered crizotinib at a starting dose of 250 milligram [mg] orally, twice daily (BID) on a continuous dosing period as two 100-mg tablets and one 50-mg tablet at approximately 12 hours apart the same time each day.

|                            |                                    |
|----------------------------|------------------------------------|
| Subject analysis set title | Crizotinib 250 mg BID-ALT controls |
| Subject analysis set type  | Full analysis                      |

Subject analysis set description:

Participants were administered crizotinib at a starting dose of 250 milligram [mg] orally, twice daily (BID) on a continuous dosing period as two 100-mg tablets and one 50-mg tablet at approximately 12 hours apart the same time each day.

| Reporting group values                                                    | PF-06260182   | Crizotinib 250 mg BID-ALT cases | Crizotinib 250 mg BID-ALT controls |
|---------------------------------------------------------------------------|---------------|---------------------------------|------------------------------------|
| Number of subjects                                                        | 904           | 74                              | 115                                |
| Age categorical<br>Units: Subjects                                        |               |                                 |                                    |
| In utero                                                                  | 0             | 0                               | 0                                  |
| Preterm newborn infants (gestational age < 37 wks)                        | 0             | 0                               | 0                                  |
| Newborns (0-27 days)                                                      | 0             | 0                               | 0                                  |
| Infants and toddlers (28 days-23 months)                                  | 0             | 0                               | 0                                  |
| Children (2-11 years)                                                     | 0             | 0                               | 0                                  |
| Adolescents (12-17 years)                                                 | 0             | 0                               | 0                                  |
| Adults (18-64 years)                                                      | 0             | 0                               | 0                                  |
| > 65 years                                                                | 0             | 0                               | 0                                  |
| Age Continuous  <br>Units: years<br>arithmetic mean<br>standard deviation | <br><br><br>± | <br><br><br>±                   | <br><br><br>±                      |
| Gender, Male/Female<br>Units: Participants                                |               |                                 |                                    |
| Female                                                                    |               |                                 |                                    |
| Male                                                                      |               |                                 |                                    |
| Race/Ethnicity, Customized<br>Units: Subjects                             |               |                                 |                                    |
| Chinese                                                                   |               |                                 |                                    |
| Japanese                                                                  |               |                                 |                                    |
| Korean                                                                    |               |                                 |                                    |
| White                                                                     |               |                                 |                                    |
| Black                                                                     |               |                                 |                                    |
| Other                                                                     |               |                                 |                                    |
| Other-Asian                                                               |               |                                 |                                    |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                    |                                    |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                              | Crizotinib 250 mg BID              |
| Reporting group description:<br>Participants were administered crizotinib at a starting dose of 250 mg orally, BID on a continuous dosing period as two 100-mg tablets and one 50-mg tablet at approximately 12 hours apart the same time each day.                                |                                    |
| Subject analysis set title                                                                                                                                                                                                                                                         | PF-06260182                        |
| Subject analysis set type                                                                                                                                                                                                                                                          | Sub-group analysis                 |
| Subject analysis set description:<br>PF-06260182 was a PF-02341066 metabolite measured in this study.                                                                                                                                                                              |                                    |
| Subject analysis set title                                                                                                                                                                                                                                                         | Crizotinib 250 mg BID-ALT cases    |
| Subject analysis set type                                                                                                                                                                                                                                                          | Full analysis                      |
| Subject analysis set description:<br>Participants were administered crizotinib at a starting dose of 250 milligram [mg] orally, twice daily (BID) on a continuous dosing period as two 100-mg tablets and one 50-mg tablet at approximately 12 hours apart the same time each day. |                                    |
| Subject analysis set title                                                                                                                                                                                                                                                         | Crizotinib 250 mg BID-ALT controls |
| Subject analysis set type                                                                                                                                                                                                                                                          | Full analysis                      |
| Subject analysis set description:<br>Participants were administered crizotinib at a starting dose of 250 milligram [mg] orally, twice daily (BID) on a continuous dosing period as two 100-mg tablets and one 50-mg tablet at approximately 12 hours apart the same time each day. |                                    |

### Primary: Objective response rate

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Objective response rate <sup>[1]</sup> |
| End point description:<br>The objective response rate (ORR) as a measure of anti-tumor efficacy of oral PF-02341066 in participants with advanced NSCLC with an ALK gene translocation or inversion after failure of at least one line of chemotherapy. Response-evaluable populations: defined as participants in either the SA-ALK positive by IUO population or SA-ALK positive by non-IUO population, respectively, who had adequate baseline tumor assessment. |                                        |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Primary                                |
| End point timeframe:<br>5 years                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                        |
| Notes:<br>[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.<br>Justification: No statistical analyses were done for this endpoint.                                                                                                                                                                                                                |                                        |

| End point values                     | Crizotinib 250 mg BID |  |  |  |
|--------------------------------------|-----------------------|--|--|--|
| Subject group type                   | Reporting group       |  |  |  |
| Number of subjects analysed          | 1066                  |  |  |  |
| Units: Percentage                    |                       |  |  |  |
| number (confidence interval 95%)     |                       |  |  |  |
| ALK Positive by IUO; N=908           | 54.1 (50.8 to 57.4)   |  |  |  |
| ALK Positive by non-IUO only, N= 158 | 40.5 (32.8 to 48.6)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of participants with adverse events

|                 |                                                           |
|-----------------|-----------------------------------------------------------|
| End point title | Number of participants with adverse events <sup>[2]</sup> |
|-----------------|-----------------------------------------------------------|

End point description:

Incidence of adverse events and laboratory abnormalities (severity graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], version 4.0). The safety analysis population included all participants who were enrolled and received at least 1 dose of study medication (excluding day-7 pharmacokinetic [PK] dosing).

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

End point timeframe:

5 years

Notes:

[2] - 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: No statistical analyses were done for this endpoint.

| End point values                  | Crizotinib 250 mg BID |  |  |  |
|-----------------------------------|-----------------------|--|--|--|
| Subject group type                | Reporting group       |  |  |  |
| Number of subjects analysed       | 1066                  |  |  |  |
| Units: Percentage of Participants |                       |  |  |  |
| number (not applicable)           |                       |  |  |  |
| Serious AEs (all causalities)     | 50                    |  |  |  |
| Grade 3/4 AEs (all causalities)   | 65.2                  |  |  |  |
| Grade 5 AEs (all causalities)     | 22.6                  |  |  |  |
| Serious AEs (treatment related)   | 11.2                  |  |  |  |
| Grade 3/4 AEs (treatment related) | 39.9                  |  |  |  |
| Grade 5 AEs (treatment related)   | 1.4                   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of response (DR)

|                 |                           |
|-----------------|---------------------------|
| End point title | Duration of response (DR) |
|-----------------|---------------------------|

End point description:

DR was defined as the time from the first documentation of objective tumor response (CR or PR) that was subsequently confirmed, to the first documentation of objective tumor progression or to death on study due to any cause, whichever occurred first. DR (in months) was calculated as (first date of PD or death – first date of CR or PR that was subsequently confirmed + 1)/30.4. Response-evaluable populations: defined as participants in either the SA-ALK positive by IUO population or SA-ALK positive by non-IUO population, respectively, who had adequate baseline tumor assessment.

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

End point timeframe:

5 years

|                                    |                       |  |  |  |
|------------------------------------|-----------------------|--|--|--|
| <b>End point values</b>            | Crizotinib 250 mg BID |  |  |  |
| Subject group type                 | Reporting group       |  |  |  |
| Number of subjects analysed        | 1066                  |  |  |  |
| Units: Months                      |                       |  |  |  |
| median (confidence interval 95%)   |                       |  |  |  |
| ALK Positive by IUO, N=491         | 11.8 (10.4 to 12.8)   |  |  |  |
| ALK Positive by non-IUO only, N=64 | 9.5 (6.9 to 15.2)     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Tumor Response (TTR)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                              |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Time to Tumor Response (TTR) |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                              |
| TTR was defined as the time (in weeks) from the date of Cycle 1 Day 1 dose to first documentation of objective tumor response (CR or PR) that was subsequently confirmed. For participants proceeding from PR to CR, the onset of PR was taken as the onset of response. Response-evaluable populations: defined as participants in either the SA-ALK positive by IUO population or SA-ALK positive by non-IUO population, respectively, who had adequate baseline tumor assessment. |                              |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Secondary                    |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                              |
| 5 years                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                              |

|                                     |                       |  |  |  |
|-------------------------------------|-----------------------|--|--|--|
| <b>End point values</b>             | Crizotinib 250 mg BID |  |  |  |
| Subject group type                  | Reporting group       |  |  |  |
| Number of subjects analysed         | 1066                  |  |  |  |
| Units: Weeks                        |                       |  |  |  |
| median (full range (min-max))       |                       |  |  |  |
| ALK Positive by IUO (n=491)         | 6.1 (2.7 to 164)      |  |  |  |
| ALK Positive by non-IUO only (n=64) | 6.3 (4.7 to 65.9)     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Disease Control Rate (DCR)

|                                                                                                                                                                                                    |                            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| End point title                                                                                                                                                                                    | Disease Control Rate (DCR) |
| End point description:                                                                                                                                                                             |                            |
| DCR at 6 and 12 weeks was defined as the percentage of participants with a confirmed CR, confirmed PR, or SD (according to RECIST v 1.1) at 6 weeks and 12 weeks, respectively. Response-evaluable |                            |

populations: defined as participants in either the SA-ALK positive by IUO population or SA-ALK positive by non-IUO population, respectively, who had adequate baseline tumor assessment.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| 5 years              |           |

| End point values                          | Crizotinib 250 mg BID |  |  |  |
|-------------------------------------------|-----------------------|--|--|--|
| Subject group type                        | Reporting group       |  |  |  |
| Number of subjects analysed               | 1066                  |  |  |  |
| Units: Percentage                         |                       |  |  |  |
| number (confidence interval 95%)          |                       |  |  |  |
| ALK Positive by IUO at Week 6, N=908      | 81.7 (79 to 84.2)     |  |  |  |
| ALK Positive by IUO at Week 12, N=908     | 70.8 (67.7 to 73.8)   |  |  |  |
| ALK Positive by non-IUO at Week 6, N=158  | 69.6 (61.8 to 76.7)   |  |  |  |
| ALK Positive by non-IUO at Week 12, N=158 | 61.4 (53.3 to 69)     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Progression Free Survival (PFS)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                 |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Progression Free Survival (PFS) |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                 |
| PFS was defined as the time from the date of the Cycle 1 Day 1 dose to the date of the first documentation of objective tumor progression or death on study due to any cause, whichever occurred first. The safety analysis populations included all participants who received at least 1 dose of study medication (excluding day-7 pharmacokinetic [PK] dosing), and were ALK positive either by IUO (SA-ALK positive by IUO population) or by non-IUO (SA-ALK positive by non-IUO population), respectively. |                                 |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Secondary                       |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                 |
| 5 years                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                 |

| End point values                     | Crizotinib 250 mg BID |  |  |  |
|--------------------------------------|-----------------------|--|--|--|
| Subject group type                   | Reporting group       |  |  |  |
| Number of subjects analysed          | 1066                  |  |  |  |
| Units: Months                        |                       |  |  |  |
| median (confidence interval 95%)     |                       |  |  |  |
| ALK Positive by IUO , N= 908         | 8.4 (7.1 to 9.7)      |  |  |  |
| ALK Positive by non-IUO only , N=158 | 6.9 (5.6 to 9.4)      |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Mean change from Baseline in QLQ-C30 Global Quality of Life scores.

|                 |                                                                     |
|-----------------|---------------------------------------------------------------------|
| End point title | Mean change from Baseline in QLQ-C30 Global Quality of Life scores. |
|-----------------|---------------------------------------------------------------------|

End point description:

The EORTC QLQ-C30 consists of 30 questions which assess five functional domains (physical, role, cognitive, emotional, and social), global health status/quality of life, disease/treatment related symptoms (fatigue, pain, nausea/vomiting, dyspnea, appetite loss, sleep disturbance, constipation, and diarrhoea), and the perceived financial impact of disease. "n" is the number of participants who completed the scale at baseline and at the respective Cycles. The patient reported outcomes (PRO) evaluable population was defined as the participants from the safety analysis (SA) population who completed a baseline assessment and at least one post-baseline assessment.

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

End point timeframe:

5 years

| End point values                     | Crizotinib 250 mg BID |  |  |  |
|--------------------------------------|-----------------------|--|--|--|
| Subject group type                   | Reporting group       |  |  |  |
| Number of subjects analysed          | 976                   |  |  |  |
| Units: Units on a scale              |                       |  |  |  |
| arithmetic mean (standard deviation) |                       |  |  |  |
| CYCLE2/DAY1                          | 7.9 (± 22.2)          |  |  |  |
| CYCLE3/DAY1                          | 10.6 (± 23.7)         |  |  |  |
| CYCLE4/DAY1                          | 12.2 (± 24.9)         |  |  |  |
| CYCLE5/DAY1                          | 11.5 (± 23.9)         |  |  |  |
| CYCLE6/DAY1                          | 11.9 (± 24.8)         |  |  |  |
| CYCLE7/DAY1                          | 12.3 (± 24.7)         |  |  |  |
| CYCLE8/DAY1                          | 12.3 (± 24.1)         |  |  |  |
| CYCLE9/DAY1                          | 11.8 (± 23.5)         |  |  |  |
| CYCLE10/DAY1                         | 11.5 (± 23.6)         |  |  |  |
| CYCLE11/DAY1                         | 10.4 (± 23.9)         |  |  |  |
| CYCLE12/DAY1                         | 10.1 (± 21.6)         |  |  |  |
| CYCLE13/DAY1                         | 11 (± 24)             |  |  |  |
| CYCLE14/DAY1                         | 10.4 (± 21.5)         |  |  |  |
| CYCLE15/DAY1                         | 9.5 (± 23.9)          |  |  |  |
| CYCLE16/DAY1                         | 7.4 (± 23.2)          |  |  |  |
| CYCLE17/DAY1                         | 8 (± 24.3)            |  |  |  |
| CYCLE18/DAY1                         | 7.8 (± 22)            |  |  |  |
| CYCLE19/DAY1                         | 7.8 (± 23.1)          |  |  |  |
| CYCLE20/DAY1                         | 9.1 (± 22.4)          |  |  |  |
| CYCLE21/DAY1                         | 7.8 (± 22.5)          |  |  |  |

|                  |              |  |  |  |
|------------------|--------------|--|--|--|
| CYCLE22/DAY1     | 5.9 (± 23.7) |  |  |  |
| CYCLE23/DAY1     | 6.7 (± 24)   |  |  |  |
| CYCLE24/DAY1     | 6.4 (± 25)   |  |  |  |
| CYCLE25/DAY1     | 4.7 (± 23.3) |  |  |  |
| CYCLE26/DAY1     | 8.3 (± 24.7) |  |  |  |
| CYCLE27/DAY1     | 5.9 (± 23.2) |  |  |  |
| CYCLE28/DAY1     | 6.7 (± 24.2) |  |  |  |
| CYCLE29/DAY1     | 5.7 (± 23.3) |  |  |  |
| CYCLE30/DAY1     | 6.4 (± 24.9) |  |  |  |
| End of treatment | -1 (± 27.2)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean Change from Baseline of EORTC QLQ-C30 Functional and Symptom Scale Scores

|                 |                                                                                |
|-----------------|--------------------------------------------------------------------------------|
| End point title | Mean Change from Baseline of EORTC QLQ-C30 Functional and Symptom Scale Scores |
|-----------------|--------------------------------------------------------------------------------|

End point description:

The EORTC QLQ-C30 consists of 30 questions which assess five functional domains (physical, role, cognitive, emotional, and social), global health status/quality of life, disease/treatment related symptoms (fatigue, pain, nausea/vomiting, dyspnoea, appetite loss, sleep disturbance, constipation, and diarrhoea), and the perceived financial impact of disease. "n" is the number of participants who completed the scale at baseline and at the respective Cycles. The PRO evaluable population was defined as the participants from the SA population who completed a baseline assessment and at least one post-baseline assessment.

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

End point timeframe:

5 years

| End point values                              | Crizotinib 250 mg BID |  |  |  |
|-----------------------------------------------|-----------------------|--|--|--|
| Subject group type                            | Reporting group       |  |  |  |
| Number of subjects analysed                   | 976                   |  |  |  |
| Units: Units on a scale                       |                       |  |  |  |
| arithmetic mean (standard deviation)          |                       |  |  |  |
| Physical Functioning (Cycle 2/Day 1) (N=936)  | 4.3 (± 17.1)          |  |  |  |
| Physical Functioning (Cycle 3/Day 1) (N=879)  | 6.6 (± 18.6)          |  |  |  |
| Physical Functioning (Cycle 4/Day 1) (N=836)  | 8.2 (± 19.1)          |  |  |  |
| Physical Functioning (Cycle 5/Day 1) (N=810)  | 8.8 (± 18.8)          |  |  |  |
| Physical Functioning (Cycle 6/Day 1) (N=778)  | 9.5 (± 18.6)          |  |  |  |
| Physical Functioning (Cycle 7/Day 1) (N=739)  | 10 (± 19.3)           |  |  |  |
| Physical Functioning (Cycle 8/Day 1) (N= 704) | 10.1 (± 18.8)         |  |  |  |

|                                                    |               |  |  |  |
|----------------------------------------------------|---------------|--|--|--|
| Physical Functioning (Cycle 9/Day 1)<br>(N= 673)   | 10.5 (± 18.2) |  |  |  |
| Physical Functioning (Cycle 10/Day 1)<br>(N= 637)  | 9.5 (± 17.9)  |  |  |  |
| Physical Functioning (Cycle 11/Day 1)<br>(N=577)   | 9.1 (± 17.9)  |  |  |  |
| Physical Functioning (Cycle 12/Day 1)<br>(N=412)   | 8.2 (± 17.3)  |  |  |  |
| Physical Functioning (Cycle 13/Day 1)<br>(N=517)   | 8.7 (± 18.1)  |  |  |  |
| Physical Functioning (Cycle 14/Day 1)<br>(N=358)   | 8.2 (± 16.5)  |  |  |  |
| Physical Functioning (Cycle 15/Day 1)<br>(N=466)   | 7.3 (± 19.2)  |  |  |  |
| Physical Functioning (Cycle 16/Day 1)<br>(N=295)   | 6.3 (± 19.1)  |  |  |  |
| Physical Functioning (Cycle 17/Day 1)<br>(N=424)   | 6 (± 18.9)    |  |  |  |
| Physical Functioning (Cycle 18/Day 1)<br>(N=250)   | 6.1 (± 18.4)  |  |  |  |
| Physical Functioning (Cycle 19/Day 1)<br>(N=380)   | 6.6 (± 16.8)  |  |  |  |
| Physical Functioning (Cycle 20/Day 1)<br>(N=224)   | 5.1 (± 16.8)  |  |  |  |
| Physical Functioning (Cycle 21/Day 1)<br>(N=346)   | 5.7 (± 17.6)  |  |  |  |
| Physical Functioning (Cycle 22/Day 1)<br>(N=182)   | 3.8 (± 17)    |  |  |  |
| Physical Functioning (Cycle 23/Day 1)<br>(N=311)   | 3.7 (± 17.1)  |  |  |  |
| Physical Functioning (Cycle 24/Day 1)<br>(N=156)   | 2.4 (± 18.9)  |  |  |  |
| Physical Functioning (Cycle 25/Day 1)<br>(N=296)   | 4 (± 18)      |  |  |  |
| Physical Functioning (Cycle 26/Day 1)<br>(N=129)   | 5.3 (± 18.1)  |  |  |  |
| Physical Functioning (Cycle 27/Day 1)<br>(N=275)   | 3.8 (± 16.1)  |  |  |  |
| Physical Functioning (Cycle 28/Day 1)<br>(N=121)   | 3.6 (± 20.4)  |  |  |  |
| Physical Functioning (Cycle 29/Day 1)<br>(N=251)   | 3.7 (± 15.8)  |  |  |  |
| Physical Functioning (Cycle 30/Day 1)<br>(N=109)   | 2.8 (± 21.9)  |  |  |  |
| Physical Functioning (End of treatment)<br>(N=451) | 0.1 (± 25)    |  |  |  |
| Cognitive functioning (Cycle 2/Day 1)<br>(N=930)   | 1 (± 18.4)    |  |  |  |
| Cognitive Functioning (Cycle 3/Day 1)<br>(N=874)   | 2.1 (± 19.4)  |  |  |  |
| Cognitive Functioning (Cycle 4/Day 1)<br>(N=829)   | 2.1 (± 18.6)  |  |  |  |
| Cognitive Functioning (Cycle 5/Day 1)<br>(N=806)   | 2.3 (± 18.4)  |  |  |  |
| Cognitive Functioning (Cycle 6/Day 1)<br>(N=773)   | 2.5 (± 18.2)  |  |  |  |
| Cognitive Functioning (Cycle 7/Day 1)<br>(N=734)   | 3.2 (± 18.6)  |  |  |  |
| Cognitive Functioning (Cycle 8/Day 1)<br>(N=699)   | 3.3 (± 18.5)  |  |  |  |
| Cognitive Functioning (Cycle 9/Day 1)<br>(N=667)   | 3 (± 18.4)    |  |  |  |

|                                                     |               |  |  |  |
|-----------------------------------------------------|---------------|--|--|--|
| Cognitive Functioning (Cycle 10/Day 1)<br>(N=632)   | 2.7 (± 19)    |  |  |  |
| Cognitive Functioning (Cycle 11/Day 1)<br>(N=571)   | 3 (± 18.5)    |  |  |  |
| Cognitive Functioning (Cycle 12/Day 1)<br>(N=411)   | 1.5 (± 17.1)  |  |  |  |
| Cognitive Functioning (Cycle 13/Day 1)<br>(N=512)   | 2 (± 19.3)    |  |  |  |
| Cognitive Functioning (Cycle 14/Day 1)<br>(N=352)   | 1.2 (± 17.8)  |  |  |  |
| Cognitive Functioning (Cycle 15/Day 1)<br>(N=462)   | 1.3 (± 19.7)  |  |  |  |
| Cognitive Functioning (Cycle 16/Day 1)<br>(N=294)   | -0.1 (± 18.1) |  |  |  |
| Cognitive Functioning (Cycle 17/Day 1)<br>(N=419)   | 0 (± 19.4)    |  |  |  |
| Cognitive Functioning (Cycle 18/Day 1)<br>(N=247)   | 0.1 (± 19.2)  |  |  |  |
| Cognitive Functioning (Cycle 19/Day 1)<br>(N=376)   | 0.1 (± 19.2)  |  |  |  |
| Cognitive Functioning (Cycle 20/Day 1)<br>(N=222)   | 0.9 (± 18.1)  |  |  |  |
| Cognitive Functioning (Cycle 21/Day 1)<br>(N=340)   | -0.1 (± 17.8) |  |  |  |
| Cognitive Functioning (Cycle 22/Day 1)<br>(N=179)   | -1.1 (± 17.5) |  |  |  |
| Cognitive Functioning (Cycle 23/Day 1)<br>(N=305)   | -0.3 (± 17.6) |  |  |  |
| Cognitive Functioning (Cycle 24/Day 1)<br>(N=154)   | -3.6 (± 21.2) |  |  |  |
| Cognitive Functioning (Cycle 25/Day 1)<br>(N=293)   | -1.3 (± 18.1) |  |  |  |
| Cognitive Functioning (Cycle 26/Day 1)<br>(N=127)   | -0.3 (± 20.2) |  |  |  |
| Cognitive Functioning (Cycle 27/Day 1)<br>(N=269)   | -0.9 (± 17.7) |  |  |  |
| Cognitive Functioning (Cycle 28/Day 1)<br>(N=120)   | -0.6 (± 20.7) |  |  |  |
| Cognitive Functioning (Cycle 29/Day 1)<br>(N=247)   | -0.2 (± 16)   |  |  |  |
| Cognitive Functioning (Cycle 30/Day 1)<br>(N=106)   | -2.5 (± 23.7) |  |  |  |
| Cognitive Functioning (End of<br>treatment) (N=449) | -2.3 (± 21.7) |  |  |  |
| Emotional Functioning (Cycle 2/Day 1)<br>(N=928)    | 5.5 (± 18.4)  |  |  |  |
| Emotional Functioning (Cycle 3/Day 1)<br>(N=873)    | 6.8 (± 18.8)  |  |  |  |
| Emotional Functioning (Cycle 4/Day 1)<br>(N=827)    | 8.2 (± 18.3)  |  |  |  |
| Emotional Functioning (Cycle 5/Day 1)<br>(N=804)    | 7.8 (± 18.3)  |  |  |  |
| Emotional Functioning (Cycle 6/Day 1)<br>(N=772)    | 8.6 (± 18)    |  |  |  |
| Emotional Functioning (Cycle 7/Day 1)<br>(N=731)    | 8.3 (± 18.3)  |  |  |  |
| Emotional Functioning (Cycle 8/Day 1)<br>(N=697)    | 9.2 (± 18.9)  |  |  |  |
| Emotional Functioning (Cycle 9/Day 1)<br>(N=665)    | 8.7 (± 18.6)  |  |  |  |
| Emotional Functioning (Cycle 10/Day 1)<br>(N=630)   | 8.5 (± 18.9)  |  |  |  |

|                                                     |               |  |  |  |
|-----------------------------------------------------|---------------|--|--|--|
| Emotional Functioning (Cycle 11/Day 1)<br>(N=571)   | 8.5 (± 17.6)  |  |  |  |
| Emotional Functioning (Cycle 12/Day 1)<br>(N=410)   | 8.4 (± 17.6)  |  |  |  |
| Emotional Functioning (Cycle 13/Day 1)<br>(N=511)   | 8.5 (± 19.1)  |  |  |  |
| Emotional Functioning (Cycle 14/Day 1)<br>(N=352)   | 7.9 (± 16.6)  |  |  |  |
| Emotional Functioning (Cycle 15/Day 1)<br>(N=461)   | 8.3 (± 18.7)  |  |  |  |
| Emotional Functioning (Cycle 16/Day 1)<br>(N=293)   | 7.5 (± 16.8)  |  |  |  |
| Emotional Functioning (Cycle 17/Day 1)<br>(N=418)   | 6.9 (± 19.2)  |  |  |  |
| Emotional Functioning (Cycle 18/Day 1)<br>(N=246)   | 7.5 (± 17.2)  |  |  |  |
| Emotional Functioning (Cycle 19/Day 1)<br>(N=376)   | 7.4 (± 18.3)  |  |  |  |
| Emotional Functioning (Cycle 20/Day 1)<br>(N=221)   | 7.4 (± 17.6)  |  |  |  |
| Emotional Functioning (Cycle 21/Day 1)<br>(N=340)   | 6.7 (± 17.5)  |  |  |  |
| Emotional Functioning (Cycle 22/Day 1)<br>(N=178)   | 5.2 (± 17.9)  |  |  |  |
| Emotional Functioning (Cycle 23/Day 1)<br>(N=305)   | 6.6 (± 17.6)  |  |  |  |
| Emotional Functioning (Cycle 24/Day 1)<br>(N=153)   | 4.4 (± 19.5)  |  |  |  |
| Emotional Functioning (Cycle 25/Day 1)<br>(N=293)   | 6.2 (± 17.4)  |  |  |  |
| Emotional Functioning (Cycle 26/Day 1)<br>(N=126)   | 7.5 (± 18.9)  |  |  |  |
| Emotional Functioning (Cycle 27/Day 1)<br>(N=269)   | 6.3 (± 17.6)  |  |  |  |
| Emotional Functioning (Cycle 28/Day 1)<br>(N=119)   | 4.1 (± 19.2)  |  |  |  |
| Emotional Functioning (Cycle 29/Day 1)<br>(N=247)   | 5.9 (± 17.7)  |  |  |  |
| Emotional Functioning (Cycle 30/Day 1)<br>(N=105)   | 3.2 (± 21.5)  |  |  |  |
| Emotional Functioning (End of<br>treatment) (N=448) | 1.9 (± 22.3)  |  |  |  |
| Role Functioning (Cycle 2/Day 1)<br>(N=935)         | 4.2 (± 25)    |  |  |  |
| Role Functioning (Cycle 3/Day 1)<br>(N=879)         | 7.3 (± 27.8)  |  |  |  |
| Role Functioning (Cycle 4/Day 1)<br>(N=835)         | 9.3 (± 28.7)  |  |  |  |
| Role Functioning (Cycle 5/Day 1)<br>(N=809)         | 9.5 (± 28.4)  |  |  |  |
| Role Functioning (Cycle 6/Day 1)<br>(N=778)         | 10.5 (± 28.7) |  |  |  |
| Role Functioning (Cycle 7/Day 1)<br>(N=738)         | 10.4 (± 30.2) |  |  |  |
| Role Functioning (Cycle 8/Day 1)<br>(N=702)         | 10.8 (± 28.5) |  |  |  |
| Role Functioning (Cycle 9/Day 1)<br>(N=671)         | 10.9 (± 28.1) |  |  |  |
| Role Functioning (Cycle 10/Day 1)<br>(N=635)        | 10.8 (± 28.8) |  |  |  |
| Role Functioning (Cycle 11/Day 1)<br>(N=576)        | 10 (± 29)     |  |  |  |

|                                                |               |  |  |  |
|------------------------------------------------|---------------|--|--|--|
| Role Functioning (Cycle 12/Day 1)<br>(N=413)   | 8.4 (± 28)    |  |  |  |
| Role Functioning (Cycle 13/Day 1)<br>(N=516)   | 9 (± 28.8)    |  |  |  |
| Role Functioning (Cycle 14/Day 1)<br>(N=358)   | 8.4 (± 26.5)  |  |  |  |
| Role Functioning (Cycle 15/Day 1)<br>(N=465)   | 8.8 (± 28.7)  |  |  |  |
| Role Functioning (Cycle 16/Day 1)<br>(N=296)   | 6 (± 28.3)    |  |  |  |
| Role Functioning (Cycle 17/Day 1)<br>(N=424)   | 6.1 (± 30.4)  |  |  |  |
| Role Functioning (Cycle 18/Day 1)<br>(N=250)   | 5.2 (± 27.8)  |  |  |  |
| Role Functioning (Cycle 19/Day 1)<br>(N=380)   | 8 (± 27.5)    |  |  |  |
| Role Functioning (Cycle 20/Day 1)<br>(N=224)   | 5.8 (± 25.1)  |  |  |  |
| Role Functioning (Cycle 21/Day 1)<br>(N=346)   | 5.3 (± 27.1)  |  |  |  |
| Role Functioning (Cycle 22/Day 1)<br>(N=182)   | 4.1 (± 26.7)  |  |  |  |
| Role Functioning (Cycle 23/Day 1)<br>(N=311)   | 3.2 (± 27.9)  |  |  |  |
| Role Functioning (Cycle 24/Day 1)<br>(N=157)   | 2.7 (± 29.5)  |  |  |  |
| Role Functioning (Cycle 25/Day 1)<br>(N=297)   | 2.2 (± 27.2)  |  |  |  |
| Role Functioning (Cycle 26/Day 1)<br>(N=129)   | 6.1 (± 28)    |  |  |  |
| Role Functioning (Cycle 27/Day 1)<br>(N=275)   | 2.4 (± 27.6)  |  |  |  |
| Role Functioning (Cycle 28/Day 1)<br>(N=121)   | 1.5 (± 30)    |  |  |  |
| Role Functioning (Cycle 29/Day<br>1)(N=251)    | 1.6 (± 24.6)  |  |  |  |
| Role Functioning (Cycle 30/Day 1)<br>(N=109)   | 1.1 (± 34)    |  |  |  |
| Role Functioning (End of treatment)<br>(N=451) | -1.6 (± 31.9) |  |  |  |
| Social Functioning (Cycle 2/Day 1)<br>(N=928)  | 6.8 (± 25.9)  |  |  |  |
| Social Functioning (Cycle 3/Day 1)<br>(N=872)  | 9.1 (± 26.2)  |  |  |  |
| Social Functioning (Cycle 4/Day 1)<br>(N=828)  | 10.4 (± 27.2) |  |  |  |
| Social Functioning (Cycle 5/Day 1)<br>(N=805)  | 10.6 (± 26.7) |  |  |  |
| Social Functioning (Cycle 6/Day 1)<br>(N=773)  | 11.1 (± 27)   |  |  |  |
| Social Functioning (Cycle 7/Day 1)<br>(N=733)  | 12.1 (± 26.5) |  |  |  |
| Social Functioning (Cycle 8/Day 1)<br>(N=698)  | 12.3 (± 26.4) |  |  |  |
| Social Functioning (Cycle 9/Day 1)<br>(N=666)  | 12 (± 26.4)   |  |  |  |
| Social Functioning (Cycle 10/Day 1)<br>(N=631) | 11.8 (± 26.1) |  |  |  |
| Social Functioning (Cycle 11/Day 1)<br>(N=570) | 12.1 (± 27.3) |  |  |  |
| Social Functioning (Cycle 12/Day 1)<br>(N=410) | 10.3 (± 26.3) |  |  |  |

|                                               |                |  |  |  |
|-----------------------------------------------|----------------|--|--|--|
| Social Functioning (Cycle 13/Day 1) (N=512)   | 10.6 (± 27.3)  |  |  |  |
| Social Functioning (Cycle 14/Day 1) (N=352)   | 10.4 (± 25.1)  |  |  |  |
| Social Functioning (Cycle 15/Day 1) (N=462)   | 10.1 (± 28.1)  |  |  |  |
| Social Functioning (Cycle 16/Day 1) (N=293)   | 9 (± 26.4)     |  |  |  |
| Social Functioning (Cycle 17/Day 1) (N=418)   | 8.8 (± 26.9)   |  |  |  |
| Social Functioning (Cycle 18/Day 1) (N=246)   | 6.6 (± 25.4)   |  |  |  |
| Social Functioning (Cycle 19/Day 1) (N=376)   | 8 (± 25.6)     |  |  |  |
| Social Functioning (Cycle 20/Day 1) (N=221)   | 5.7 (± 23.9)   |  |  |  |
| Social Functioning (Cycle 21/Day 1) (N=340)   | 6.7 (± 26.6)   |  |  |  |
| Social Functioning (Cycle 22/Day 1) (N=178)   | 5.3 (± 22.7)   |  |  |  |
| Social Functioning (Cycle 23/Day 1) (N=305)   | 7 (± 24.9)     |  |  |  |
| Social Functioning (Cycle 24/Day 1) (N=153)   | 3.6 (± 26.5)   |  |  |  |
| Social Functioning (Cycle 25/Day 1) (N=293)   | 4.4 (± 25.8)   |  |  |  |
| Social Functioning (Cycle 26/Day 1) (N=126)   | 5.2 (± 26.6)   |  |  |  |
| Social Functioning (Cycle 27/Day 1) (N=269)   | 5.3 (± 26.4)   |  |  |  |
| Social Functioning (Cycle 28/Day 1) (N=119)   | 2.1 (± 31.4)   |  |  |  |
| Social Functioning (Cycle 29/Day 1) (N=247)   | 6.6 (± 24.1)   |  |  |  |
| Social Functioning (Cycle 30/Day 1) (N=105)   | 1.6 (± 29)     |  |  |  |
| Social Functioning (End of treatment) (N=449) | 2.7 (± 31.2)   |  |  |  |
| Appetite loss (Cycle 2/Day 1) (N=936)         | -2.1 (± 30.3)  |  |  |  |
| Appetite loss (Cycle 3/Day 1) (N=877)         | -6.3 (± 31.7)  |  |  |  |
| Appetite loss (Cycle 4/Day 1) (N=833)         | -9.1 (± 31.9)  |  |  |  |
| Appetite loss (Cycle 5/Day 1) (N=810)         | -10.4 (± 31.9) |  |  |  |
| Appetite loss (Cycle 6/Day 1) (N=778)         | -11.4 (± 32.1) |  |  |  |
| Appetite loss (Cycle 7/Day 1) (N=738)         | -11.4 (± 32.4) |  |  |  |
| Appetite loss (Cycle 8/Day 1) (N=704)         | -11.5 (± 32.6) |  |  |  |
| Appetite loss (Cycle 9/Day 1) (N=673)         | -11.7 (± 32.5) |  |  |  |
| Appetite loss (Cycle 10/Day 1) (N=637)        | -11.9 (± 30.9) |  |  |  |
| Appetite loss (Cycle 11/Day 1) (N=577)        | -11.2 (± 30.4) |  |  |  |
| Appetite loss (Cycle 12/Day 1) (N=413)        | -9.1 (± 30.9)  |  |  |  |
| Appetite loss (Cycle 13/Day 1) (N=517)        | -11.3 (± 29.8) |  |  |  |
| Appetite loss (Cycle 14/Day 1) (N=358)        | -9.9 (± 31.8)  |  |  |  |
| Appetite loss (Cycle 15/Day 1) (N=466)        | -10.5 (± 30.6) |  |  |  |
| Appetite loss (Cycle 16/Day 1) (N=296)        | -10.4 (± 32.4) |  |  |  |
| Appetite loss (Cycle 17/Day 1) (N=424)        | -8.6 (± 29.5)  |  |  |  |
| Appetite loss (Cycle 18/Day 1) (N=250)        | -10.1 (± 31.5) |  |  |  |
| Appetite loss (Cycle 19/Day 1) (N=380)        | -8.9 (± 30.9)  |  |  |  |
| Appetite loss (Cycle 20/Day 1) (N=224)        | -12.8 (± 29)   |  |  |  |
| Appetite loss (Cycle 21/Day 1) (N=346)        | -7.5 (± 30.6)  |  |  |  |

|                                             |                |  |  |  |
|---------------------------------------------|----------------|--|--|--|
| Appetite loss (Cycle 22/Day 1) (N=181)      | -9.2 (± 27.7)  |  |  |  |
| Appetite loss (Cycle 23/Day 1) (N=310)      | -4.9 (± 28.5)  |  |  |  |
| Appetite loss (Cycle 24/Day 1) (N=157)      | -10.9 (± 30.1) |  |  |  |
| Appetite loss (Cycle 25/Day 1) (N=297)      | -4.6 (± 29)    |  |  |  |
| Appetite loss (Cycle 26/Day 1) (N=129)      | -12.1 (± 32.3) |  |  |  |
| Appetite loss (Cycle 27/Day 1) (N=275)      | -4.2 (± 29.4)  |  |  |  |
| Appetite loss (Cycle 28/Day 1) (N=121)      | -6.6 (± 34.6)  |  |  |  |
| Appetite loss (Cycle 29/Day 1) (N=251)      | -3.2 (± 27)    |  |  |  |
| Appetite loss (Cycle 30/Day 1) (N=109)      | -7.6 (± 29.3)  |  |  |  |
| Appetite loss (End of treatment)<br>(N=451) | 0 (± 36.9)     |  |  |  |
| Constipation (Cycle 2/Day 1) (N=929)        | 15.4 (± 32.9)  |  |  |  |
| Constipation (Cycle 3/Day 1) (N=870)        | 10.9 (± 33.8)  |  |  |  |
| Constipation (Cycle 4/Day 1) (N=827)        | 7 (± 31)       |  |  |  |
| Constipation (Cycle 5/Day 1) (N=804)        | 5.5 (± 30.4)   |  |  |  |
| Constipation (Cycle 6/Day 1) (N=771)        | 5.4 (± 30.3)   |  |  |  |
| Constipation (Cycle 7/Day 1) (N=732)        | 4.7 (± 30.3)   |  |  |  |
| Constipation (Cycle 8/Day 1) (N=698)        | 4.5 (± 29.8)   |  |  |  |
| Constipation (Cycle 9/Day 1) (N=665)        | 5 (± 29.9)     |  |  |  |
| Constipation (Cycle 10/Day 1) (N=631)       | 3.8 (± 30)     |  |  |  |
| Constipation (Cycle 11/Day 1) (N=571)       | 5.2 (± 29.7)   |  |  |  |
| Constipation (Cycle 12/Day 1) (N=410)       | 6.4 (± 29.6)   |  |  |  |
| Constipation (Cycle 13/Day 1) (N=513)       | 5.2 (± 29)     |  |  |  |
| Constipation (Cycle 14/Day 1) (N=349)       | 5 (± 28.7)     |  |  |  |
| Constipation (Cycle 15/Day 1) (N=464)       | 6 (± 30.1)     |  |  |  |
| Constipation (Cycle 16/Day 1) (N=291)       | 4.4 (± 29.9)   |  |  |  |
| Constipation (Cycle 17/Day 1) (N=420)       | 8.3 (± 30.5)   |  |  |  |
| Constipation (Cycle 18/Day 1) (N=246)       | 6 (± 30.7)     |  |  |  |
| Constipation (Cycle 19/Day 1) (N=376)       | 7.4 (± 30.5)   |  |  |  |
| Constipation (Cycle 20/Day 1) (N=221)       | 5.9 (± 33.2)   |  |  |  |
| Constipation (Cycle 21/Day 1) (N=340)       | 7.7 (± 31.3)   |  |  |  |
| Constipation (Cycle 22/Day 1) (N=178)       | 6.2 (± 31.2)   |  |  |  |
| Constipation (Cycle 23/Day 1) (N=306)       | 9.7 (± 31.9)   |  |  |  |
| Constipation (Cycle 24/Day 1) (N=154)       | 9 (± 34.2)     |  |  |  |
| Constipation (Cycle 25/Day 1) (N=293)       | 10.9 (± 29.4)  |  |  |  |
| Constipation (Cycle 26/Day 1) (N=126)       | 5.6 (± 32)     |  |  |  |
| Constipation (Cycle 27/Day 1) (N=269)       | 8.3 (± 30.7)   |  |  |  |
| Constipation (Cycle 28/Day 1) (N=119)       | 9.8 (± 31.1)   |  |  |  |
| Constipation (Cycle 29/Day 1) (N=247)       | 7.8 (± 29.3)   |  |  |  |
| Constipation (Cycle 30/Day 1) (N=105)       | 11.7 (± 31.3)  |  |  |  |
| Constipation (End of treatment)<br>(N=444)  | 8.9 (± 33)     |  |  |  |
| Diarrhea (Cycle 2/Day 1) (N=927)            | 11.4 (± 25.9)  |  |  |  |
| Diarrhea (Cycle 3/Day 1) (N=872)            | 12.8 (± 26.9)  |  |  |  |
| Diarrhea (Cycle 4/Day 1) (N=826)            | 11.7 (± 25.6)  |  |  |  |
| Diarrhea (Cycle 5/Day 1) (N=805)            | 12.6 (± 26.1)  |  |  |  |
| Diarrhea (Cycle 6/Day 1) (N=772)            | 11.6 (± 26.4)  |  |  |  |
| Diarrhea (Cycle 7/Day 1) (N=732)            | 10.9 (± 26.3)  |  |  |  |
| Diarrhea (Cycle 8/Day 1) (N=698)            | 9.8 (± 25.6)   |  |  |  |
| Diarrhea (Cycle 9/Day 1) (N=665)            | 10.5 (± 25.6)  |  |  |  |
| Diarrhea (Cycle 10/Day 1) (N=632)           | 11.1 (± 26.6)  |  |  |  |
| Diarrhea (Cycle 11/Day 1) (N=570)           | 10.1 (± 25.9)  |  |  |  |

|                                     |                |  |  |  |
|-------------------------------------|----------------|--|--|--|
| Diarrhea (Cycle 12/Day 1) (N=411)   | 8.1 (± 25.2)   |  |  |  |
| Diarrhea (Cycle 13/Day 1) (N=512)   | 8.8 (± 24)     |  |  |  |
| Diarrhea (Cycle 14/Day 1) (N=352)   | 10.1 (± 22.4)  |  |  |  |
| Diarrhea (Cycle 15/Day 1) (N=461)   | 8.5 (± 23.1)   |  |  |  |
| Diarrhea (Cycle 16/Day 1) (N=293)   | 10 (± 22.5)    |  |  |  |
| Diarrhea (Cycle 17/Day 1) (N=419)   | 8.6 (± 23.9)   |  |  |  |
| Diarrhea (Cycle 18/Day 1) (N=247)   | 7.4 (± 22.4)   |  |  |  |
| Diarrhea (Cycle 19/Day 1) (N=376)   | 7.8 (± 22.5)   |  |  |  |
| Diarrhea (Cycle 20/Day 1) (N=222)   | 6.8 (± 22.6)   |  |  |  |
| Diarrhea (Cycle 21/Day 1) (N=340)   | 6.6 (± 20.3)   |  |  |  |
| Diarrhea (Cycle 22/Day 1) (N=179)   | 6.8 (± 24.2)   |  |  |  |
| Diarrhea (Cycle 23/Day 1) (N=305)   | 8.7 (± 22.7)   |  |  |  |
| Diarrhea (Cycle 24/Day 1) (N=154)   | 6.4 (± 23.1)   |  |  |  |
| Diarrhea (Cycle 25/Day 1) (N=293)   | 10.1 (± 23.4)  |  |  |  |
| Diarrhea (Cycle 26/Day 1) (N=127)   | 5 (± 23.8)     |  |  |  |
| Diarrhea (Cycle 27/Day 1) (N=269)   | 8.3 (± 24.5)   |  |  |  |
| Diarrhea (Cycle 28/Day 1) (N=119)   | 5.6 (± 20.5)   |  |  |  |
| Diarrhea (Cycle 29/Day 1) (N=247)   | 9.7 (± 22.6)   |  |  |  |
| Diarrhea (Cycle 30/Day 1) (N=106)   | 10.1 (± 25.3)  |  |  |  |
| Diarrhea (End of treatment) (N=449) | 5.9 (± 24.5)   |  |  |  |
| Dyspnoea (Cycle 2/Day 1) (N=933)    | -9.8 (± 26.2)  |  |  |  |
| Dyspnoea (Cycle 3/Day 1) (N=876)    | -11.4 (± 28.2) |  |  |  |
| Dyspnoea (Cycle 4/Day 1) (N=834)    | -12.3 (± 28.6) |  |  |  |
| Dyspnoea (Cycle 5/Day 1) (N=808)    | -12.2 (± 27.7) |  |  |  |
| Dyspnoea (Cycle 6/Day 1) (N=776)    | -13.7 (± 27.6) |  |  |  |
| Dyspnoea (Cycle 7/Day 1) (N=737)    | -13.8 (± 27.8) |  |  |  |
| Dyspnoea (Cycle 8/Day 1) (N=702)    | -13.8 (± 28.2) |  |  |  |
| Dyspnoea (Cycle 9/Day 1) (N=671)    | -13.3 (± 27.9) |  |  |  |
| Dyspnoea (Cycle 10/Day 1) (N=635)   | -13.4 (± 27.6) |  |  |  |
| Dyspnoea (Cycle 11/Day 1) (N=575)   | -15 (± 27.8)   |  |  |  |
| Dyspnoea (Cycle 12/Day 1) (N=411)   | -13.1 (± 26.8) |  |  |  |
| Dyspnoea (Cycle 13/Day 1) (N=515)   | -13.1 (± 28.1) |  |  |  |
| Dyspnoea (Cycle 14/Day 1) (N=356)   | -12.7 (± 27.5) |  |  |  |
| Dyspnoea (Cycle 15/Day 1) (N=463)   | -12.6 (± 28.5) |  |  |  |
| Dyspnoea (Cycle 16/Day 1) (N=295)   | -12.2 (± 27.6) |  |  |  |
| Dyspnoea (Cycle 17/Day 1) (N=421)   | -11.8 (± 27.9) |  |  |  |
| Dyspnoea (Cycle 18/Day 1) (N=248)   | -11.5 (± 27.4) |  |  |  |
| Dyspnoea (Cycle 19/Day 1) (N=377)   | -14.2 (± 28)   |  |  |  |
| Dyspnoea (Cycle 20/Day 1) (N=222)   | -9.2 (± 26.4)  |  |  |  |
| Dyspnoea (Cycle 21/Day 1) (N=344)   | -13.4 (± 27.1) |  |  |  |
| Dyspnoea (Cycle 22/Day 1) (N=181)   | -8.8 (± 26.4)  |  |  |  |
| Dyspnoea (Cycle 23/Day 1) (N=309)   | -10.9 (± 26.6) |  |  |  |
| Dyspnoea (Cycle 24/Day 1) (N=156)   | -8.5 (± 27.3)  |  |  |  |
| Dyspnoea (Cycle 25/Day 1) (N=295)   | -10.5 (± 26.3) |  |  |  |
| Dyspnoea (Cycle 26/Day 1) (N=129)   | -10.1 (± 27.2) |  |  |  |
| Dyspnoea (Cycle 27/Day 1) (N=273)   | -9.3 (± 24.8)  |  |  |  |
| Dyspnoea (Cycle 28/Day 1) (N=121)   | -12.1 (± 28.9) |  |  |  |
| Dyspnoea (Cycle 29/Day 1) (N=249)   | -8.8 (± 25.4)  |  |  |  |
| Dyspnoea (Cycle 30/Day 1) (N=109)   | -11.6 (± 27.7) |  |  |  |
| Dyspnoea (End of treatment) (N=450) | -4.2 (± 32.8)  |  |  |  |
| Fatigue (Cycle 2/Day 1) (N=936)     | -4.8 (± 21.8)  |  |  |  |
| Fatigue (Cycle 3/Day 1) (N=879)     | -8.9 (± 23.7)  |  |  |  |

|                                                   |                |  |  |  |
|---------------------------------------------------|----------------|--|--|--|
| Fatigue (Cycle 4/Day 1) (N=836)                   | -11.4 (± 24.1) |  |  |  |
| Fatigue (Cycle 5/Day 1) (N=810)                   | -12 (± 24.2)   |  |  |  |
| Fatigue (Cycle 6/Day 1) (N=778)                   | -13.7 (± 24.3) |  |  |  |
| Fatigue (Cycle 7/Day 1) (N=739)                   | -14 (± 24.6)   |  |  |  |
| Fatigue (Cycle 8/Day 1) (N=704)                   | -15.3 (± 23.7) |  |  |  |
| Fatigue (Cycle 9/Day 1) (N=671)                   | -14.9 (± 24)   |  |  |  |
| Fatigue (Cycle 10/Day 1) (N=637)                  | -14.4 (± 24.2) |  |  |  |
| Fatigue (Cycle 11/Day 1) (N=577)                  | -13.7 (± 24.3) |  |  |  |
| Fatigue (Cycle 12/Day 1) (N=413)                  | -12.2 (± 23.4) |  |  |  |
| Fatigue (Cycle 13/Day 1) (N=517)                  | -13.4 (± 23.6) |  |  |  |
| Fatigue (Cycle 14/Day 1) (N=358)                  | -13.2 (± 22.3) |  |  |  |
| Fatigue (Cycle 15/Day 1) (N=466)                  | -13.1 (± 23.9) |  |  |  |
| Fatigue (Cycle 16/Day 1) (N=296)                  | -11.3 (± 24.1) |  |  |  |
| Fatigue (Cycle 17/Day 1) (N=424)                  | -11.3 (± 24.6) |  |  |  |
| Fatigue (Cycle 18/Day 1) (N=250)                  | -10.4 (± 25.2) |  |  |  |
| Fatigue (Cycle 19/Day 1) (N=380)                  | -11.9 (± 23.7) |  |  |  |
| Fatigue (Cycle 20/Day 1) (N=224)                  | -10.6 (± 23.2) |  |  |  |
| Fatigue (Cycle 21/Day 1) (N=346)                  | -11 (± 25)     |  |  |  |
| Fatigue (Cycle 22/Day 1) (N=182)                  | -8.4 (± 23)    |  |  |  |
| Fatigue (Cycle 23/Day 1) (N=311)                  | -8.7 (± 23.3)  |  |  |  |
| Fatigue (Cycle 24/Day 1) (N=157)                  | -6.7 (± 24.1)  |  |  |  |
| Fatigue (Cycle 25/Day 1) (N=297)                  | -7.9 (± 23.2)  |  |  |  |
| Fatigue (Cycle 26/Day 1) (N=129)                  | -12.1 (± 24.8) |  |  |  |
| Fatigue (Cycle 27/Day 1) (N=275)                  | -7 (± 22.3)    |  |  |  |
| Fatigue (Cycle 28/Day 1) (N=121)                  | -6.7 (± 25.2)  |  |  |  |
| Fatigue (Cycle 29/Day 1) (N=251)                  | -7.1 (± 22.1)  |  |  |  |
| Fatigue (Cycle 30/Day 1) (N=109)                  | -7.2 (± 27)    |  |  |  |
| Fatigue (End of treatment) (N=451)                | -5.3 (± 27.5)  |  |  |  |
| Financial Difficulties (Cycle 2/Day 1) (N=928)    | -4.6 (± 24.1)  |  |  |  |
| Financial Difficulties (Cycle 3/Day 1) (N=871)    | -4.2 (± 25.2)  |  |  |  |
| Financial Difficulties (Cycle 4/Day 1) (N=827)    | -5.9 (± 25.7)  |  |  |  |
| Financial Difficulties (Cycle 5/Day 1) (N=803)    | -5.1 (± 25.6)  |  |  |  |
| Financial Difficulties (Cycle 6/Day 1) (N=772)    | -5.5 (± 25.4)  |  |  |  |
| Financial Difficulties (Cycle 7/Day 1) (N=732)    | -6.2 (± 25.8)  |  |  |  |
| Financial Difficulties (Cycle 8/Day 1) (N=697)    | -6.4 (± 26)    |  |  |  |
| Financial Difficulties (Cycle 9/Day 1) (N=663)    | -5.8 (± 25.8)  |  |  |  |
| Financial Difficulties (Cycle 10/Day 1) (N=631)   | -7.4 (± 25)    |  |  |  |
| Financial Difficulties (End of treatment) (N=447) | -2.2 (± 27.5)  |  |  |  |
| Financial Difficulties (Cycle 11/Day 1) (N=569)   | -6.6 (± 25.4)  |  |  |  |
| Financial Difficulties (Cycle 12/Day 1) (N=410)   | -4.8 (± 25.4)  |  |  |  |
| Financial Difficulties (Cycle 13/Day 1) (N=512)   | -6.3 (± 25.8)  |  |  |  |
| Financial Difficulties (Cycle 14/Day 1) (N=352)   | -5.8 (± 25.4)  |  |  |  |

|                                                 |                |  |  |  |
|-------------------------------------------------|----------------|--|--|--|
| Financial Difficulties (Cycle 15/Day 1) (N=461) | -6.1 (± 26.7)  |  |  |  |
| Financial Difficulties (Cycle 16/Day 1) (N=294) | -4 (± 23.8)    |  |  |  |
| Financial Difficulties (Cycle 17/Day 1) (N=418) | -5.5 (± 26.8)  |  |  |  |
| Financial Difficulties (Cycle 18/Day 1) (N=247) | -3.8 (± 25.2)  |  |  |  |
| Financial Difficulties (Cycle 19/Day 1) (N=376) | -5.9 (± 26.8)  |  |  |  |
| Financial Difficulties (Cycle 20/Day 1) (N=220) | -5.2 (± 25.4)  |  |  |  |
| Financial Difficulties (Cycle 21/Day 1) (N=339) | -4.2 (± 25.9)  |  |  |  |
| Financial Difficulties (Cycle 22/Day 1) (N=177) | -2.1 (± 23.1)  |  |  |  |
| Financial Difficulties (Cycle 23/Day 1) (N=304) | -4.4 (± 24.9)  |  |  |  |
| Financial Difficulties (Cycle 24/Day 1) (N=153) | -2.8 (± 27.3)  |  |  |  |
| Financial Difficulties (Cycle 25/Day 1) (N=292) | -4.6 (± 24.8)  |  |  |  |
| Financial Difficulties (Cycle 26/Day 1) (N=126) | -2.9 (± 26)    |  |  |  |
| Financial Difficulties (Cycle 27/Day 1) (N=268) | -4.8 (± 25.5)  |  |  |  |
| Financial Difficulties (Cycle 28/Day 1) (N=119) | -4.2 (± 29.9)  |  |  |  |
| Financial Difficulties (Cycle 29/Day 1) (N=247) | -5.5 (± 25.2)  |  |  |  |
| Financial Difficulties (Cycle 30/Day 1) (N=105) | -3.5 (± 26.5)  |  |  |  |
| Insomnia (Cycle 2/Day 1) (N=934)                | -7.6 (± 29.3)  |  |  |  |
| Insomnia (Cycle 3/Day 1) (N=878)                | -11.3 (± 30.1) |  |  |  |
| Insomnia (Cycle 4/Day 1) (N=833)                | -13 (± 29.7)   |  |  |  |
| Insomnia (Cycle 5/Day 1) (N=808)                | -12.8 (± 29.8) |  |  |  |
| Insomnia (Cycle 6/Day 1) (N=778)                | -13.3 (± 31.1) |  |  |  |
| Insomnia (Cycle 7/Day 1) (N=739)                | -13.9 (± 29.7) |  |  |  |
| Insomnia (Cycle 8/Day 1) (N=703)                | -12.6 (± 29.9) |  |  |  |
| Insomnia (Cycle 9/Day 1) (N=673)                | -13.2 (± 28.8) |  |  |  |
| Insomnia (Cycle 10/Day 1) (N=637)               | -13.2 (± 29.4) |  |  |  |
| Insomnia (Cycle 11/Day 1) (N=576)               | -12.2 (± 30)   |  |  |  |
| Insomnia (Cycle 12/Day 1) (N=413)               | -11.3 (± 29.7) |  |  |  |
| Insomnia (Cycle 13/Day 1) (N=516)               | -13 (± 29.5)   |  |  |  |
| Insomnia (Cycle 14/Day 1) (N=358)               | -11.7 (± 30.3) |  |  |  |
| Insomnia (Cycle 15/Day 1) (N=464)               | -12.4 (± 30)   |  |  |  |
| Insomnia (Cycle 16/Day 1) (N=296)               | -10.9 (± 31.6) |  |  |  |
| Insomnia (Cycle 17/Day 1) (N=424)               | -10.8 (± 29.2) |  |  |  |
| Insomnia (Cycle 18/Day 1) (N=250)               | -10.4 (± 30.3) |  |  |  |
| Insomnia (Cycle 19/Day 1) (N=379)               | -12.6 (± 28.9) |  |  |  |
| Insomnia (Cycle 20/Day 1) (N=224)               | -11.5 (± 27.1) |  |  |  |
| Insomnia (Cycle 21/Day 1) (N=346)               | -10.2 (± 27.6) |  |  |  |
| Insomnia (Cycle 22/Day 1) (N=182)               | -7.9 (± 25.8)  |  |  |  |
| Insomnia (Cycle 23/Day 1) (N=311)               | -10.5 (± 27.2) |  |  |  |
| Insomnia (Cycle 24/Day 1) (N=157)               | -5.7 (± 28)    |  |  |  |
| Insomnia (Cycle 25/Day 1) (N=296)               | -7.7 (± 28.8)  |  |  |  |
| Insomnia (Cycle 26/Day 1) (N=129)               | -10.9 (± 29.2) |  |  |  |

|                                              |                |  |  |  |
|----------------------------------------------|----------------|--|--|--|
| Insomnia (Cycle 27/Day 1) (N=274)            | -10.1 (± 27.4) |  |  |  |
| Insomnia (Cycle 28/Day 1) (N=121)            | -6.9 (± 32.7)  |  |  |  |
| Insomnia (Cycle 29/Day 1) (N=251)            | -8.4 (± 28.5)  |  |  |  |
| Insomnia (Cycle 30/Day 1) (N=109)            | -11.3 (± 32.1) |  |  |  |
| Insomnia (End of treatment) (N=451)          | -5.7 (± 33.6)  |  |  |  |
| Nausea and Vomiting (Cycle 2/Day 1) (N=936)  | 6.2 (± 23.1)   |  |  |  |
| Nausea and Vomiting (Cycle 3/Day 1) (N=879)  | 2.4 (± 23.3)   |  |  |  |
| Nausea and Vomiting (Cycle 4/Day 1) (N=836)  | 0.3 (± 22.6)   |  |  |  |
| Nausea and Vomiting (Cycle 5/Day 1) (N=810)  | -0.4 (± 21.1)  |  |  |  |
| Nausea and Vomiting (Cycle 6/Day 1) (N=779)  | -1.6 (± 19.9)  |  |  |  |
| Nausea and Vomiting (Cycle 7/Day 1) (N=739)  | -2.3 (± 21)    |  |  |  |
| Nausea and Vomiting (Cycle 8/Day 1) (N=704)  | -1.9 (± 19.8)  |  |  |  |
| Nausea and Vomiting (Cycle 9/Day 1) (N=673)  | -1.8 (± 21.2)  |  |  |  |
| Nausea and Vomiting (Cycle 10/Day 1) (N=637) | -1.4 (± 21.6)  |  |  |  |
| Nausea and Vomiting (Cycle 11/Day 1) (N=577) | -1.7 (± 20.9)  |  |  |  |
| Nausea and Vomiting (Cycle 12/Day 1) (N=413) | -1.5 (± 21.8)  |  |  |  |
| Nausea and Vomiting (Cycle 13/Day 1) (N=517) | -0.7 (± 21.2)  |  |  |  |
| Nausea and Vomiting (Cycle 14/Day 1) (N=358) | -0.4 (± 23.3)  |  |  |  |
| Nausea and Vomiting (Cycle 15/Day 1) (N=466) | -0.7 (± 21.2)  |  |  |  |
| Nausea and Vomiting (Cycle 16/Day 1) (N=296) | -0.8 (± 19.5)  |  |  |  |
| Nausea and Vomiting (Cycle 17/Day 1) (N=424) | -0.3 (± 20.2)  |  |  |  |
| Nausea and Vomiting (Cycle 18/Day 1) (N=250) | -0.9 (± 21.7)  |  |  |  |
| Nausea and Vomiting (Cycle 19/Day 1) (N=380) | -0.3 (± 20.1)  |  |  |  |
| Nausea and Vomiting (Cycle 20/Day 1) (N=224) | -2.3 (± 18.7)  |  |  |  |
| Nausea and Vomiting (Cycle 21/Day 1) (N=346) | -1.1 (± 18.6)  |  |  |  |
| Nausea and Vomiting (Cycle 22/Day 1) (N=182) | 0.2 (± 19)     |  |  |  |
| Nausea and Vomiting (Cycle 23/Day 1) (N=311) | 0.8 (± 17.4)   |  |  |  |
| Nausea and Vomiting (Cycle 24/Day 1) (N=157) | -1.3 (± 17.4)  |  |  |  |
| Nausea and Vomiting (Cycle 25/Day 1) (N=297) | 0.6 (± 18)     |  |  |  |
| Nausea and Vomiting (Cycle 26/Day 1) (N=129) | -2.3 (± 20.2)  |  |  |  |
| Nausea and Vomiting (Cycle 27/Day 1) (N=275) | 1.9 (± 17.5)   |  |  |  |
| Nausea and Vomiting (Cycle 28/Day 1) (N=121) | 1.8 (± 19.7)   |  |  |  |
| Nausea and Vomiting (Cycle 29/Day 1) (N=251) | 2.5 (± 18.9)   |  |  |  |

|                                                |                |  |  |  |
|------------------------------------------------|----------------|--|--|--|
| Nausea and Vomiting (Cycle 30/Day 1) (N=109)   | -0.5 (± 17.5)  |  |  |  |
| Nausea and Vomiting (End of treatment) (N=451) | 4 (± 25.3)     |  |  |  |
| Pain (Cycle 2/Day 1) (N=935)                   | -13.1 (± 26.6) |  |  |  |
| Pain (Cycle 3/Day 1) (N=880)                   | -16 (± 28)     |  |  |  |
| Pain (Cycle 4/Day 1) (N=836)                   | -15.7 (± 27.8) |  |  |  |
| Pain (Cycle 5/Day 1) (N=810)                   | -15.5 (± 27.4) |  |  |  |
| Pain (Cycle 6/Day 1) (N=779)                   | -15.5 (± 27.8) |  |  |  |
| Pain (Cycle 7/Day 1) (N=739)                   | -16 (± 29)     |  |  |  |
| Pain (Cycle 8/Day 1) (N=705)                   | -15.9 (± 28.5) |  |  |  |
| Pain (Cycle 9/Day 1) (N=673)                   | -15.5 (± 28.7) |  |  |  |
| Pain (Cycle 10/Day 1) (N=637)                  | -15.1 (± 27.6) |  |  |  |
| Pain (Cycle 11/Day 1) (N=577)                  | -14.6 (± 27.6) |  |  |  |
| Pain (Cycle 12/Day 1) (N=414)                  | -13.6 (± 29.2) |  |  |  |
| Pain (Cycle 13/Day 1) (N=517)                  | -13.8 (± 28)   |  |  |  |
| Pain (Cycle 14/Day 1) (N=357)                  | -13.9 (± 29.5) |  |  |  |
| Pain (Cycle 15/Day 1) (N=466)                  | -12.1 (± 27)   |  |  |  |
| Pain (Cycle 16/Day 1) (N=296)                  | -12.5 (± 27.9) |  |  |  |
| Pain (Cycle 17/Day 1) (N=424)                  | -10.6 (± 25.6) |  |  |  |
| Pain (Cycle 18/Day 1) (N=250)                  | -11.1 (± 27.5) |  |  |  |
| Pain (Cycle 19/Day 1) (N=380)                  | -10.8 (± 24.1) |  |  |  |
| Pain (Cycle 20/Day 1) (N=224)                  | -11 (± 27.2)   |  |  |  |
| Pain (Cycle 21/Day 1) (N=346)                  | -10.1 (± 25.2) |  |  |  |
| Pain (Cycle 22/Day 1) (N=182)                  | -7.7 (± 26.2)  |  |  |  |
| Pain (Cycle 23/Day 1) (N=311)                  | -7.4 (± 26)    |  |  |  |
| Pain (Cycle 24/Day 1) (N=157)                  | -8.8 (± 27.7)  |  |  |  |
| Pain (Cycle 25/Day 1) (N=297)                  | -8.8 (± 24.6)  |  |  |  |
| Pain (Cycle 26/Day 1) (N=129)                  | -12.5 (± 29.5) |  |  |  |
| Pain (Cycle 27/Day 1) (N=275)                  | -7.6 (± 25.3)  |  |  |  |
| Pain (Cycle 28/Day 1) (N=121)                  | -7.9 (± 32.4)  |  |  |  |
| Pain (Cycle 29/Day 1) (N=251)                  | -8.1 (± 24.6)  |  |  |  |
| Pain (Cycle 30/Day 1) (N=109)                  | -7.5 (± 29.8)  |  |  |  |
| Pain (End of treatment) (N=451)                | -5.3 (± 31.2)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean Change from Baseline of QLQ-LC13 Scale Scores

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                    |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Mean Change from Baseline of QLQ-LC13 Scale Scores |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                    |
| The QLQ-LC13 consists of 1 multi-item scale and 9 single items that assess specific symptoms (dyspnoea, cough, haemoptysis, and site-specific pain), side effects (sore mouth, dysphagia, neuropathy, and alopecia), and pain medication use of lung cancer patients. "n" is the number of participants who completed the scale at baseline and at the respective Cycles. The PRO evaluable population was defined as the participants from the SA population who completed a baseline assessment and at least one post-baseline assessment. |                                                    |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Secondary                                          |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                    |
| 5 years                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                    |

| End point values                     | Crizotinib 250 mg BID |  |  |  |
|--------------------------------------|-----------------------|--|--|--|
| Subject group type                   | Reporting group       |  |  |  |
| Number of subjects analysed          | 976                   |  |  |  |
| Units: Units on a scale              |                       |  |  |  |
| arithmetic mean (standard deviation) |                       |  |  |  |
| Alopecia (Cycle 2/Day 1) (N=920)     | -9.1 (± 29.6)         |  |  |  |
| Alopecia (Cycle 3/Day 1) (N=870)     | -10.2 (± 31.6)        |  |  |  |
| Alopecia (Cycle 4/Day 1) (N=829)     | -11.6 (± 30.7)        |  |  |  |
| Alopecia (Cycle 5/Day 1) (N=805)     | -12.2 (± 32.3)        |  |  |  |
| Alopecia (Cycle 6/Day 1) (N=770)     | -10.5 (± 30.9)        |  |  |  |
| Alopecia (Cycle 7/Day 1) (N=734)     | -11.9 (± 32.3)        |  |  |  |
| Alopecia (Cycle 8/Day 1) (N=700)     | -11.9 (± 33.2)        |  |  |  |
| Alopecia (Cycle 9/Day 1) (N=667)     | -11.3 (± 34.7)        |  |  |  |
| Alopecia (Cycle 10/Day 1) (N=633)    | -10.8 (± 33.9)        |  |  |  |
| Alopecia (Cycle 11/Day 1) (N=574)    | -11.3 (± 34.8)        |  |  |  |
| Alopecia (Cycle 12/Day 1) (N=409)    | -7.8 (± 34.8)         |  |  |  |
| Alopecia (Cycle 13/Day 1) (N=512)    | -10.8 (± 35)          |  |  |  |
| Alopecia (Cycle 14/Day 1) (N=353)    | -8.2 (± 36.4)         |  |  |  |
| Alopecia (Cycle 15/Day 1) (N=462)    | -11.8 (± 34.3)        |  |  |  |
| Alopecia (Cycle 16/Day 1) (N=293)    | -7.7 (± 34.1)         |  |  |  |
| Alopecia (Cycle 17/Day 1) (N=419)    | -9.5 (± 32.9)         |  |  |  |
| Alopecia (Cycle 18/Day 1) (N=247)    | -6.4 (± 31.3)         |  |  |  |
| Alopecia (Cycle 19/Day 1) (N=377)    | -8.9 (± 34.1)         |  |  |  |
| Alopecia (Cycle 20/Day 1) (N=222)    | -9 (± 30.7)           |  |  |  |
| Alopecia (Cycle 21/Day 1) (N=342)    | -7.8 (± 32.9)         |  |  |  |
| Alopecia (Cycle 22/Day 1) (N=180)    | -7.6 (± 35.6)         |  |  |  |
| Alopecia (Cycle 23/Day 1) (N=310)    | -7 (± 33.2)           |  |  |  |
| Alopecia (Cycle 24/Day 1) (N=156)    | -4.1 (± 34.1)         |  |  |  |
| Alopecia (Cycle 25/Day 1) (N=293)    | -8.2 (± 31.8)         |  |  |  |
| Alopecia (Cycle 26/Day 1) (N=126)    | -4.5 (± 31.1)         |  |  |  |
| Alopecia (Cycle 27/Day 1) (N=271)    | -8.5 (± 31.5)         |  |  |  |
| Alopecia (Cycle 28/Day 1) (N=119)    | -3.9 (± 33.1)         |  |  |  |
| Alopecia (Cycle 29/Day 1) (N=247)    | -9.2 (± 28.3)         |  |  |  |
| Alopecia (Cycle 30/Day 1) (N=107)    | -5 (± 31.7)           |  |  |  |
| Alopecia (End of treatment) (N=447)  | -9.9 (± 35.3)         |  |  |  |
| Coughing (Cycle 2/Day 1) (N=926)     | -12.9 (± 28.8)        |  |  |  |
| Coughing (Cycle 3/Day 1) (N=879)     | -15.5 (± 31.8)        |  |  |  |
| Coughing (Cycle 4/Day 1) (N=832)     | -17.7 (± 31.1)        |  |  |  |
| Coughing (Cycle 5/Day 1) (N=807)     | -17.3 (± 31.8)        |  |  |  |
| Coughing (Cycle 6/Day 1) (N=775)     | -18.3 (± 32.1)        |  |  |  |
| Coughing (Cycle 7/Day 1) (N=735)     | -20.1 (± 32.2)        |  |  |  |
| Coughing (Cycle 8/Day 1) (N=703)     | -20.8 (± 31.8)        |  |  |  |
| Coughing (Cycle 9/Day 1) (N=669)     | -20.2 (± 30.9)        |  |  |  |
| Coughing (Cycle 10/Day 1) (N=636)    | -19.9 (± 32)          |  |  |  |
| Coughing (Cycle 11/Day 1) (N=575)    | -19.9 (± 31.6)        |  |  |  |
| Coughing (Cycle 12/Day 1) (N=414)    | -19.2 (± 29.5)        |  |  |  |
| Coughing (Cycle 13/Day 1) (N=513)    | -18.6 (± 32.6)        |  |  |  |

|                                      |                |  |  |  |
|--------------------------------------|----------------|--|--|--|
| Coughing (Cycle 14/Day 1) (N=355)    | -17.9 (± 32.1) |  |  |  |
| Coughing (Cycle 15/Day 1) (N=461)    | -17.8 (± 31.7) |  |  |  |
| Coughing (Cycle 16/Day 1) (N=294)    | -17.3 (± 29.5) |  |  |  |
| Coughing (Cycle 17/Day 1) (N=421)    | -18.4 (± 32.5) |  |  |  |
| Coughing (Cycle 18/Day 1) (N=249)    | -16.9 (± 33.1) |  |  |  |
| Coughing (Cycle 19/Day 1) (N=379)    | -18.8 (± 30.3) |  |  |  |
| Coughing (Cycle 20/Day 1) (N=222)    | -18.3 (± 32.7) |  |  |  |
| Coughing (Cycle 21/Day 1) (N=343)    | -18 (± 31)     |  |  |  |
| Coughing (Cycle 22/Day 1) (N=181)    | -16.7 (± 33.1) |  |  |  |
| Coughing (Cycle 23/Day 1) (N=311)    | -18.4 (± 32.1) |  |  |  |
| Coughing (Cycle 24/Day 1) (N=155)    | -18.9 (± 31.3) |  |  |  |
| Coughing (Cycle 25/Day 1) (N=294)    | -18.1 (± 31.3) |  |  |  |
| Coughing (Cycle 26/Day 1) (N=125)    | -21.9 (± 30.8) |  |  |  |
| Coughing (Cycle 27/Day 1) (N=272)    | -17.8 (± 32.2) |  |  |  |
| Coughing (Cycle 28/Day 1) (N=119)    | -19.6 (± 30.8) |  |  |  |
| Coughing (Cycle 29/Day 1) (N=249)    | -17.1 (± 31.3) |  |  |  |
| Coughing (Cycle 30/Day 1) (N=106)    | -16.7 (± 29.5) |  |  |  |
| Coughing (End of treatment) (N=452)  | -11.1 (± 33.5) |  |  |  |
| Dysphagia (Cycle 2/Day 1) (N=926)    | 0 (± 19.6)     |  |  |  |
| Dysphagia (Cycle 3/Day 1) (N=879)    | -1.1 (± 20.1)  |  |  |  |
| Dysphagia (Cycle 4/Day 1) (N=831)    | -2.2 (± 20.8)  |  |  |  |
| Dysphagia (Cycle 5/Day 1) (N=807)    | -2.3 (± 20)    |  |  |  |
| Dysphagia (Cycle 6/Day 1) (N=776)    | -3 (± 19.9)    |  |  |  |
| Dysphagia (Cycle 7/Day 1) (N=737)    | -3.1 (± 20.7)  |  |  |  |
| Dysphagia (Cycle 8/Day 1) (N=702)    | -3.1 (± 18.6)  |  |  |  |
| Dysphagia (Cycle 9/Day 1) (N=670)    | -2.7 (± 20.2)  |  |  |  |
| Dysphagia (Cycle 10/Day 1) (N=637)   | -2.9 (± 19.4)  |  |  |  |
| Dysphagia (End of treatment) (N=449) | 1.9 (± 23.5)   |  |  |  |
| Dysphagia (Cycle 11/Day 1) (N=577)   | -3 (± 19.2)    |  |  |  |
| Dysphagia (Cycle 12/Day 1) (N=414)   | -2.7 (± 18.1)  |  |  |  |
| Dysphagia (Cycle 13/Day 1) (N=513)   | -3.1 (± 17.8)  |  |  |  |
| Dysphagia (Cycle 14/Day 1) (N=355)   | -1.7 (± 18.2)  |  |  |  |
| Dysphagia (Cycle 15/Day 1) (N=463)   | -2.8 (± 17.5)  |  |  |  |
| Dysphagia (Cycle 16/Day 1) (N=294)   | -1.3 (± 20.1)  |  |  |  |
| Dysphagia (Cycle 17/Day 1) (N=422)   | -2.2 (± 19)    |  |  |  |
| Dysphagia (Cycle 18/Day 1) (N=249)   | -2.5 (± 18.4)  |  |  |  |
| Dysphagia (Cycle 19/Day 1) (N=378)   | -2 (± 17.3)    |  |  |  |
| Dysphagia (Cycle 20/Day 1) (N=223)   | -3.4 (± 18.5)  |  |  |  |
| Dysphagia (Cycle 21/Day 1) (N=344)   | -2.5 (± 18.2)  |  |  |  |
| Dysphagia (Cycle 22/Day 1) (N=182)   | -1.8 (± 19.7)  |  |  |  |
| Dysphagia (Cycle 23/Day 1) (N=311)   | -3.4 (± 17)    |  |  |  |
| Dysphagia (Cycle 24/Day 1) (N=156)   | -1.4 (± 16.5)  |  |  |  |
| Dysphagia (Cycle 25/Day 1) (N=295)   | -2.8 (± 17.3)  |  |  |  |
| Dysphagia (Cycle 26/Day 1) (N=126)   | -1.1 (± 15.7)  |  |  |  |
| Dysphagia (Cycle 27/Day 1) (N=274)   | -1.6 (± 17.5)  |  |  |  |
| Dysphagia (Cycle 28/Day 1) (N=120)   | -1.4 (± 16.4)  |  |  |  |
| Dysphagia (Cycle 29/Day 1) (N=248)   | -1.5 (± 16.5)  |  |  |  |
| Dysphagia (Cycle 30/Day 1) (N=107)   | -0.9 (± 18)    |  |  |  |
| Dyspnoea (Cycle 2/Day 1) (N=928)     | -8 (± 19)      |  |  |  |
| Dyspnoea (Cycle 3/Day 1) (N=878)     | -9.7 (± 21.5)  |  |  |  |
| Dyspnoea (Cycle 4/Day 1) (N=833)     | -10.7 (± 21.7) |  |  |  |
| Dyspnoea (Cycle 5/Day 1) (N=809)     | -10.6 (± 21.4) |  |  |  |

|                                      |                |  |  |  |
|--------------------------------------|----------------|--|--|--|
| Dyspnoea (Cycle 6/Day 1) (N=775)     | -10.6 (± 21.7) |  |  |  |
| Dyspnoea (Cycle 7/Day 1) (N=737)     | -11.1 (± 21.1) |  |  |  |
| Dyspnoea (Cycle 8/Day 1) (N=704)     | -12 (± 20.7)   |  |  |  |
| Dyspnoea (Cycle 9/Day 1) (N=669)     | -11 (± 20.7)   |  |  |  |
| Dyspnoea (Cycle 10/Day 1) (N=637)    | -10.7 (± 21.1) |  |  |  |
| Dyspnoea (Cycle 11/Day 1) (N=577)    | -10.6 (± 20.8) |  |  |  |
| Dyspnoea (Cycle 12/Day 1) (N=414)    | -9 (± 20.2)    |  |  |  |
| Dyspnoea (Cycle 13/Day 1) (N=514)    | -9.8 (± 21.1)  |  |  |  |
| Dyspnoea (Cycle 14/Day 1) (N=354)    | -9.2 (± 20)    |  |  |  |
| Dyspnoea (Cycle 15/Day 1) (N=463)    | -8.9 (± 21.6)  |  |  |  |
| Dyspnoea (Cycle 16/Day 1) (N=293)    | -7.7 (± 21.3)  |  |  |  |
| Dyspnoea (Cycle 17/Day 1) (N=421)    | -7.3 (± 20.5)  |  |  |  |
| Dyspnoea (Cycle 18/Day 1) (N=249)    | -6.9 (± 21.3)  |  |  |  |
| Dyspnoea (Cycle 19/Day 1) (N=379)    | -8.6 (± 19.7)  |  |  |  |
| Dyspnoea (Cycle 20/Day 1) (N=223)    | -5.8 (± 19.8)  |  |  |  |
| Dyspnoea (Cycle 21/Day 1) (N=344)    | -7.8 (± 19.5)  |  |  |  |
| Dyspnoea (Cycle 22/Day 1) (N=182)    | -5.6 (± 18.3)  |  |  |  |
| Dyspnoea (Cycle 23/Day 1) (N=311)    | -6.1 (± 19.3)  |  |  |  |
| Dyspnoea (Cycle 24/Day 1) (N=156)    | -6.2 (± 18.3)  |  |  |  |
| Dyspnoea (Cycle 25/Day 1) (N=295)    | -6.1 (± 19.7)  |  |  |  |
| Dyspnoea (Cycle 26/Day 1) (N=126)    | -6.6 (± 19.3)  |  |  |  |
| Dyspnoea (Cycle 27/Day 1) (N=273)    | -5.7 (± 19)    |  |  |  |
| Dyspnoea (Cycle 28/Day 1) (N=120)    | -5.8 (± 19.5)  |  |  |  |
| Dyspnoea (Cycle 29/Day 1) (N=249)    | -3.9 (± 19.2)  |  |  |  |
| Dyspnoea (Cycle 30/Day 1) (N=107)    | -4.6 (± 17.5)  |  |  |  |
| Dyspnoea (End of treatment) (N=448)  | -3 (± 25.7)    |  |  |  |
| Haemoptysis (Cycle 2/Day 1) (N=925)  | -2.6 (± 12.6)  |  |  |  |
| Haemoptysis (Cycle 3/Day 1) (N=879)  | -3 (± 12.6)    |  |  |  |
| Haemoptysis (Cycle 4/Day 1) (N=833)  | -2.9 (± 12.7)  |  |  |  |
| Haemoptysis (Cycle 5/Day 1) (N=808)  | -2.6 (± 12.9)  |  |  |  |
| Haemoptysis (Cycle 6/Day 1) (N=774)  | -2.8 (± 12)    |  |  |  |
| Haemoptysis (Cycle 7/Day 1) (N=735)  | -2.9 (± 12.7)  |  |  |  |
| Haemoptysis (Cycle 8/Day 1) (N=703)  | -3.1 (± 11.9)  |  |  |  |
| Haemoptysis (Cycle 9/Day 1) (N=669)  | -3 (± 11.7)    |  |  |  |
| Haemoptysis (Cycle 10/Day 1) (N=635) | -2.6 (± 11.7)  |  |  |  |
| Haemoptysis (Cycle 11/Day 1) (N=576) | -2.7 (± 11.6)  |  |  |  |
| Haemoptysis (Cycle 12/Day 1) (N=413) | -2.6 (± 10.3)  |  |  |  |
| Haemoptysis (Cycle 13/Day 1) (N=514) | -2.1 (± 12)    |  |  |  |
| Haemoptysis (Cycle 14/Day 1) (N=354) | -2.7 (± 11.3)  |  |  |  |
| Haemoptysis (Cycle 15/Day 1) (N=462) | -2.2 (± 10.8)  |  |  |  |
| Haemoptysis (Cycle 16/Day 1) (N=294) | -2.5 (± 11.4)  |  |  |  |
| Haemoptysis (Cycle 17/Day 1) (N=420) | -1.9 (± 11.4)  |  |  |  |
| Haemoptysis (Cycle 18/Day 1) (N=249) | -2.4 (± 12.1)  |  |  |  |
| Haemoptysis (Cycle 19/Day 1) (N=378) | -2.1 (± 11.5)  |  |  |  |
| Haemoptysis (Cycle 20/Day 1) (N=223) | -2.4 (± 13.6)  |  |  |  |
| Haemoptysis (Cycle 21/Day 1) (N=342) | -2.5 (± 11.5)  |  |  |  |
| Haemoptysis (Cycle 22/Day 1) (N=182) | -2.9 (± 11.2)  |  |  |  |
| Haemoptysis (Cycle 23/Day 1) (N=309) | -2.7 (± 12.5)  |  |  |  |
| Haemoptysis (Cycle 24/Day 1) (N=156) | -2.4 (± 12)    |  |  |  |
| Haemoptysis (Cycle 25/Day 1) (N=294) | -2.8 (± 12.4)  |  |  |  |
| Haemoptysis (Cycle 26/Day 1) (N=126) | -3.2 (± 12.9)  |  |  |  |
| Haemoptysis (Cycle 27/Day 1) (N=272) | -2.9 (± 11.4)  |  |  |  |

|                                                     |                |  |  |  |
|-----------------------------------------------------|----------------|--|--|--|
| Haemoptysis (Cycle 28/Day 1) (N=119)                | -3.1 (± 12.3)  |  |  |  |
| Haemoptysis (Cycle 29/Day 1) (N=248)                | -1.7 (± 12.1)  |  |  |  |
| Haemoptysis (Cycle 30/Day 1) (N=107)                | -2.8 (± 11.3)  |  |  |  |
| Haemoptysis (End of treatment)<br>(N=451)           | -1.4 (± 15.9)  |  |  |  |
| Pain in Arm or Shoulder (Cycle 2/Day 1)<br>(N=926)  | -9.6 (± 26.9)  |  |  |  |
| Pain in Arm or Shoulder (Cycle 3/Day 1)<br>(N=876)  | -12.2 (± 27)   |  |  |  |
| Pain in Arm or Shoulder (Cycle 4/Day 1)<br>(N=832)  | -12.5 (± 28.2) |  |  |  |
| Pain in Arm or Shoulder (Cycle 5/Day 1)<br>(N=807)  | -11.7 (± 27.1) |  |  |  |
| Pain in Arm or Shoulder (Cycle 6/Day 1)<br>(N=773)  | -11.6 (± 26.3) |  |  |  |
| Pain in Arm or Shoulder (Cycle 7/Day 1)<br>(N=738)  | -11.3 (± 28.1) |  |  |  |
| Pain in Arm or Shoulder (Cycle 8/Day 1)<br>(N=702)  | -11.7 (± 28.5) |  |  |  |
| Pain in Arm or Shoulder (Cycle 9/Day 1)<br>(N=669)  | -11.9 (± 28.5) |  |  |  |
| Pain in Arm or Shoulder (Cycle 10/Day<br>1) (N=635) | -11.3 (± 28)   |  |  |  |
| Pain in Arm or Shoulder (Cycle 11/Day<br>1) (N=576) | -12.1 (± 27.3) |  |  |  |
| Pain in Arm or Shoulder (Cycle 12/Day<br>1) (N=414) | -11 (± 27.7)   |  |  |  |
| Pain in Arm or Shoulder (Cycle 13/Day<br>1) (N=513) | -10.9 (± 27.2) |  |  |  |
| Pain in Arm or Shoulder (Cycle 14/Day<br>1) (N=355) | -11.3 (± 27.3) |  |  |  |
| Pain in Arm or Shoulder (Cycle 15/Day<br>1) (N=461) | -10.3 (± 25.6) |  |  |  |
| Pain in Arm or Shoulder (Cycle 16/Day<br>1) (N=293) | -9.9 (± 28)    |  |  |  |
| Pain in Arm or Shoulder (Cycle 17/Day<br>1) (N=421) | -8.2 (± 26.5)  |  |  |  |
| Pain in Arm or Shoulder (Cycle 18/Day<br>1) (N=249) | -9.4 (± 27.6)  |  |  |  |
| Pain in Arm or Shoulder (Cycle 19/Day<br>1) (N=379) | -9.1 (± 26.5)  |  |  |  |
| Pain in Arm or Shoulder (Cycle 20/Day<br>1) (N=222) | -7.4 (± 27.3)  |  |  |  |
| Pain in Arm or Shoulder (Cycle 21/Day<br>1) (N=344) | -9 (± 27)      |  |  |  |
| Pain in Arm or Shoulder (Cycle 22/Day<br>1) (N=182) | -9 (± 29.1)    |  |  |  |
| Pain in Arm or Shoulder (Cycle 23/Day<br>1) (N=311) | -8.9 (± 25.5)  |  |  |  |
| Pain in Arm or Shoulder (Cycle 24/Day<br>1) (N=155) | -9.7 (± 30.6)  |  |  |  |
| Pain in Arm or Shoulder (Cycle 25/Day<br>1) (N=295) | -9.2 (± 26)    |  |  |  |
| Pain in Arm or Shoulder (Cycle 26/Day<br>1) (N=126) | -10.8 (± 33.7) |  |  |  |
| Pain in Arm or Shoulder (Cycle 27/Day<br>1) (N=274) | -8.6 (± 26.5)  |  |  |  |
| Pain in Arm or Shoulder (Cycle 28/Day<br>1) (N=119) | -8.7 (± 29.6)  |  |  |  |
| Pain in Arm or Shoulder (Cycle 29/Day<br>1) (N=248) | -7.9 (± 27.2)  |  |  |  |

|                                                   |                |  |  |  |
|---------------------------------------------------|----------------|--|--|--|
| Pain in Arm or Shoulder (Cycle 30/Day 1) (N=107)  | -8.1 (± 30.3)  |  |  |  |
| Pain in Arm or Shoulder (End of treatment)(N=445) | -5.8 (± 30.7)  |  |  |  |
| Pain in Chest (Cycle 2/Day 1) (N=928)             | -9.5 (± 23.4)  |  |  |  |
| Pain in Chest (Cycle 3/Day 1) (N=875)             | -11.9 (± 25.1) |  |  |  |
| Pain in Chest (Cycle 4/Day 1) (N=833)             | -12.1 (± 26.1) |  |  |  |
| Pain in Chest (Cycle 5/Day 1) (N=808)             | -11.8 (± 25.8) |  |  |  |
| Pain in Chest (Cycle 6/Day 1) (N=774)             | -12.1 (± 25.3) |  |  |  |
| Pain in Chest (Cycle 7/Day 1) (N=735)             | -12.6 (± 25.4) |  |  |  |
| Pain in Chest (Cycle 8/Day 1) (N=703)             | -13.2 (± 25)   |  |  |  |
| Pain in Chest (Cycle 9/Day 1) (N=665)             | -13.1 (± 25.8) |  |  |  |
| Pain in Chest (Cycle 10/Day 1) (N=633)            | -12.9 (± 26)   |  |  |  |
| Pain in Chest (Cycle 11/Day 1) (N=574)            | -12 (± 25.5)   |  |  |  |
| Pain in Chest (Cycle 12/Day 1) (N=414)            | -10.7 (± 25.5) |  |  |  |
| Pain in Chest (Cycle 13/Day 1) (N=513)            | -12.6 (± 24.5) |  |  |  |
| Pain in Chest (Cycle 14/Day 1) (N=355)            | -11.5 (± 24.4) |  |  |  |
| Pain in Chest (Cycle 15/Day 1) (N=462)            | -11.9 (± 24.7) |  |  |  |
| Pain in Chest (Cycle 16/Day 1) (N=294)            | -11 (± 23.4)   |  |  |  |
| Pain in Chest (Cycle 17/Day 1) (N=421)            | -11.6 (± 23.8) |  |  |  |
| Pain in Chest (Cycle 18/Day 1) (N=249)            | -8 (± 23.1)    |  |  |  |
| Pain in Chest (Cycle 19/Day 1) (N=378)            | -11.2 (± 23.8) |  |  |  |
| Pain in Chest (Cycle 20/Day 1) (N=222)            | -9.4 (± 24.3)  |  |  |  |
| Pain in Chest (Cycle 21/Day 1) (N=343)            | -11.9 (± 23.5) |  |  |  |
| Pain in Chest (Cycle 22/Day 1) (N=182)            | -10.1 (± 21.9) |  |  |  |
| Pain in Chest (Cycle 23/Day 1) (N=308)            | -10.8 (± 24)   |  |  |  |
| Pain in Chest (Cycle 24/Day 1) (N=156)            | -7.1 (± 26.8)  |  |  |  |
| Pain in Chest (Cycle 25/Day 1) (N=293)            | -10.2 (± 22.3) |  |  |  |
| Pain in Chest (Cycle 26/Day 1) (N=126)            | -10.6 (± 25.2) |  |  |  |
| Pain in Chest (Cycle 27/Day 1) (N=272)            | -9.2 (± 22)    |  |  |  |
| Pain in Chest (Cycle 28/Day 1) (N=120)            | -9.4 (± 26.7)  |  |  |  |
| Pain in Chest (Cycle 29/Day 1) (N=248)            | -9.5 (± 24.4)  |  |  |  |
| Pain in Chest (Cycle 30/Day 1) (N=107)            | -5.3 (± 26.8)  |  |  |  |
| Pain in Chest (End of treatment) (N=451)          | -6.7 (± 28)    |  |  |  |
| Pain in Other Parts (Cycle 2/Day 1) (N=893)       | -10 (± 31.3)   |  |  |  |
| Pain in Other Parts (Cycle 3/Day 1) (N=854)       | -12 (± 31.9)   |  |  |  |
| Pain in Other Parts (Cycle 4/Day 1) (N=806)       | -13.5 (± 31)   |  |  |  |
| Pain in Other Parts (Cycle 5/Day 1) (N=793)       | -12.2 (± 30.2) |  |  |  |
| Pain in Other Parts (Cycle 6/Day 1) (N=752)       | -12.5 (± 30.9) |  |  |  |
| Pain in Other Parts (Cycle 7/Day 1) (N=715)       | -11.8 (± 30.3) |  |  |  |
| Pain in Other Parts (Cycle 8/Day 1) (N=680)       | -11.7 (± 30.5) |  |  |  |
| Pain in Other Parts (Cycle 9/Day 1) (N=650)       | -13.1 (± 29.9) |  |  |  |
| Pain in Other Parts (Cycle 10/Day 1) (N=616)      | -12.1 (± 30.4) |  |  |  |
| Pain in Other Parts (Cycle 11/Day 1) (N=562)      | -10.8 (± 29.3) |  |  |  |

|                                                   |                |  |  |  |
|---------------------------------------------------|----------------|--|--|--|
| Pain in Other Parts (Cycle 12/Day 1)<br>(N=399)   | -11.6 (± 30.9) |  |  |  |
| Pain in Other Parts (Cycle 13/Day 1)<br>(N=499)   | -9.9 (± 30)    |  |  |  |
| Pain in Other Parts (Cycle 14/Day 1)<br>(N=342)   | -11.5 (± 31.3) |  |  |  |
| Pain in Other Parts (Cycle 15/Day 1)<br>(N=451)   | -10.1 (± 28.9) |  |  |  |
| Pain in Other Parts (Cycle 16/Day 1)<br>(N=282)   | -9.6 (± 30.3)  |  |  |  |
| Pain in Other Parts (Cycle 17/Day 1)<br>(N=411)   | -8.8 (± 28.1)  |  |  |  |
| Pain in Other Parts (Cycle 18/Day 1)<br>(N=239)   | -8.6 (± 31)    |  |  |  |
| Pain in Other Parts (Cycle 19/Day 1)<br>(N=370)   | -8.8 (± 29)    |  |  |  |
| Pain in Other Parts (Cycle 20/Day 1)<br>(N=210)   | -9.4 (± 31.3)  |  |  |  |
| Pain in Other Parts (Cycle 21/Day 1)<br>(N=337)   | -8.2 (± 28.6)  |  |  |  |
| Pain in Other Parts (Cycle 22/Day 1)<br>(N=176)   | -10.4 (± 30.2) |  |  |  |
| Pain in Other Parts (Cycle 23/Day 1)<br>(N=300)   | -6.6 (± 29.2)  |  |  |  |
| Pain in Other Parts (Cycle 24/Day 1)<br>(N=149)   | -7.8 (± 35.2)  |  |  |  |
| Pain in Other Parts (Cycle 25/Day 1)<br>(N=286)   | -7.2 (± 30.2)  |  |  |  |
| Pain in Other Parts (Cycle 26/Day 1)<br>(N=121)   | -8.8 (± 34.6)  |  |  |  |
| Pain in Other Parts (Cycle 27/Day 1)<br>(N=267)   | -5.9 (± 29.5)  |  |  |  |
| Pain in Other Parts (Cycle 28/Day 1)<br>(N=116)   | -3.2 (± 34.6)  |  |  |  |
| Pain in Other Parts (Cycle 29/Day 1)<br>(N=242)   | -6.3 (± 27.1)  |  |  |  |
| Pain in Other Parts (Cycle 30/Day 1)<br>(N=102)   | -6.5 (± 34.8)  |  |  |  |
| Pain in Other Parts (End of treatment)<br>(N=427) | -4.6 (± 34.8)  |  |  |  |
| Peripheral Neuropathy (Cycle 2/Day 1)<br>(N=925)  | 0.6 (± 25.3)   |  |  |  |
| Peripheral Neuropathy (Cycle 3/Day 1)<br>(N=876)  | -0.4 (± 25.6)  |  |  |  |
| Peripheral Neuropathy (Cycle 4/Day 1)<br>(N=833)  | -1.7 (± 26.5)  |  |  |  |
| Peripheral Neuropathy (Cycle 5/Day 1)<br>(N=807)  | -1.2 (± 26.3)  |  |  |  |
| Peripheral Neuropathy (Cycle 6/Day 1)<br>(N=775)  | -1.4 (± 26.5)  |  |  |  |
| Peripheral Neuropathy (Cycle 7/Day 1)<br>(N=737)  | -2.6 (± 27.2)  |  |  |  |
| Peripheral Neuropathy (Cycle 8/Day 1)<br>(N=703)  | -2.1 (± 25.6)  |  |  |  |
| Peripheral Neuropathy (Cycle 9/Day 1)<br>(N=668)  | -1.8 (± 27.2)  |  |  |  |
| Peripheral Neuropathy (Cycle 10/Day 1)<br>(N=635) | -1 (± 26.4)    |  |  |  |
| Peripheral Neuropathy (Cycle 11/Day 1)<br>(N=575) | -1.6 (± 27.5)  |  |  |  |
| Peripheral Neuropathy (Cycle 12/Day 1)<br>(N=413) | -0.8 (± 27.3)  |  |  |  |

|                                                     |               |  |  |  |
|-----------------------------------------------------|---------------|--|--|--|
| Peripheral Neuropathy (Cycle 13/Day 1)<br>(N=512)   | -1.5 (± 27)   |  |  |  |
| Peripheral Neuropathy (Cycle 14/Day 1)<br>(N=354)   | -2.1 (± 28.6) |  |  |  |
| Peripheral Neuropathy (Cycle 15/Day 1)<br>(N=462)   | -0.7 (± 27.5) |  |  |  |
| Peripheral Neuropathy (Cycle 16/Day 1)<br>(N=294)   | -1.5 (± 29.9) |  |  |  |
| Peripheral Neuropathy (Cycle 17/Day 1)<br>(N=418)   | -0.3 (± 28.3) |  |  |  |
| Peripheral Neuropathy (Cycle 18/Day 1)<br>(N=249)   | -0.7 (± 28.3) |  |  |  |
| Peripheral Neuropathy (Cycle 19/Day 1)<br>(N=378)   | -1.5 (± 23.9) |  |  |  |
| Peripheral Neuropathy (Cycle 20/Day 1)<br>(N=221)   | 0 (± 28.1)    |  |  |  |
| Peripheral Neuropathy (Cycle 21/Day 1)<br>(N=342)   | 0.2 (± 27.6)  |  |  |  |
| Peripheral Neuropathy (Cycle 22/Day 1)<br>(N=182)   | -3.7 (± 27.6) |  |  |  |
| Peripheral Neuropathy (Cycle 23/Day 1)<br>(N=310)   | -1 (± 26.2)   |  |  |  |
| Peripheral Neuropathy (Cycle 24/Day 1)<br>(N=156)   | -1.7 (± 26.4) |  |  |  |
| Peripheral Neuropathy (Cycle 25/Day 1)<br>(N=295)   | 2.3 (± 25.5)  |  |  |  |
| Peripheral Neuropathy (Cycle 26/Day 1)<br>(N=126)   | -1.6 (± 24.9) |  |  |  |
| Peripheral Neuropathy (Cycle 27/Day 1)<br>(N=274)   | 2.1 (± 27.1)  |  |  |  |
| Peripheral Neuropathy (Cycle 28/Day 1)<br>(N=119)   | -0.6 (± 27.1) |  |  |  |
| Peripheral Neuropathy (Cycle 29/Day 1)<br>(N=249)   | 1.5 (± 26.3)  |  |  |  |
| Peripheral Neuropathy (Cycle 30/Day 1)<br>(N=107)   | -0.6 (± 28.2) |  |  |  |
| Peripheral Neuropathy (End of<br>treatment) (N=451) | -0.6 (± 26.6) |  |  |  |
| Sore Mouth (Cycle 2/Day 1) (N=928)                  | 1 (± 20)      |  |  |  |
| Sore Mouth (Cycle 3/Day 1) (N=879)                  | -0.2 (± 19.8) |  |  |  |
| Sore Mouth (Cycle 4/Day 1) (N=834)                  | -0.6 (± 19.1) |  |  |  |
| Sore Mouth (Cycle 5/Day 1) (N=808)                  | -1.3 (± 17.9) |  |  |  |
| Sore Mouth (Cycle 6/Day 1) (N=776)                  | -1.8 (± 17.1) |  |  |  |
| Sore Mouth (Cycle 7/Day 1) (N=738)                  | -1.2 (± 18.3) |  |  |  |
| Sore Mouth (Cycle 8/Day 1) (N=704)                  | -2.2 (± 17)   |  |  |  |
| Sore Mouth (Cycle 9/Day 1) (N=669)                  | -2.1 (± 18.3) |  |  |  |
| Sore Mouth (Cycle 10/Day 1) (N=636)                 | -1.7 (± 19.1) |  |  |  |
| Sore Mouth (Cycle 11/Day 1) (N=577)                 | -1.8 (± 17.2) |  |  |  |
| Sore Mouth (Cycle 12/Day 1) (N=414)                 | -1.9 (± 17.1) |  |  |  |
| Sore Mouth (Cycle 13/Day 1) (N=514)                 | -1.5 (± 18)   |  |  |  |
| Sore Mouth (Cycle 14/Day 1) (N=354)                 | -1.3 (± 14.8) |  |  |  |
| Sore Mouth (Cycle 15/Day 1) (N=463)                 | -0.9 (± 16.1) |  |  |  |
| Sore Mouth (Cycle 16/Day 1) (N=294)                 | 0.1 (± 16.6)  |  |  |  |
| Sore Mouth (Cycle 17/Day 1) (N=422)                 | -1.4 (± 17.6) |  |  |  |
| Sore Mouth (Cycle 18/Day 1) (N=249)                 | -0.9 (± 18)   |  |  |  |
| Sore Mouth (Cycle 19/Day 1) (N=379)                 | -0.9 (± 17.3) |  |  |  |
| Sore Mouth (Cycle 20/Day 1) (N=223)                 | -1.3 (± 17.7) |  |  |  |
| Sore Mouth (Cycle 21/Day 1) (N=344)                 | -0.6 (± 18)   |  |  |  |

|                                       |               |  |  |  |
|---------------------------------------|---------------|--|--|--|
| Sore Mouth (Cycle 22/Day 1) (N=182)   | -1.1 (± 14.8) |  |  |  |
| Sore Mouth (Cycle 23/Day 1) (N=311)   | 0.3 (± 17.7)  |  |  |  |
| Sore Mouth (Cycle 24/Day 1) (N=156)   | 2.6 (± 17.2)  |  |  |  |
| Sore Mouth (Cycle 25/Day 1) (N=294)   | -1.6 (± 17.6) |  |  |  |
| Sore Mouth (Cycle 26/Day 1) (N=126)   | -2.4 (± 14.7) |  |  |  |
| Sore Mouth (Cycle 27/Day 1) (N=274)   | -0.6 (± 18.4) |  |  |  |
| Sore Mouth (Cycle 28/Day 1) (N=120)   | -0.3 (± 15.3) |  |  |  |
| Sore Mouth (Cycle 29/Day 1) (N=249)   | -1.7 (± 16.4) |  |  |  |
| Sore Mouth (Cycle 30/Day 1) (N=107)   | -1.2 (± 12.9) |  |  |  |
| Sore Mouth (End of treatment) (N=451) | -0.4 (± 20)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Patient reported outcomes (PROs) of health-related quality of life (HRQoL): Mean change from baseline of EQ-5D Visual Analog Score (VAS) Scale

|                 |                                                                                                                                                |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Patient reported outcomes (PROs) of health-related quality of life (HRQoL): Mean change from baseline of EQ-5D Visual Analog Score (VAS) Scale |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The EQ-5D descriptive system measured a patient's health state on 5 dimensions which included: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The respondent's self-rated health was assessed on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state) by the EQ-VAS. "n" is the number of participants who completed the scale at baseline and at the respective Cycles. The PRO evaluable population was defined as the participants from the SA population who completed a baseline assessment and at least one post-baseline assessment

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: | 5 years   |

| End point values                     | Crizotinib 250 mg BID |  |  |  |
|--------------------------------------|-----------------------|--|--|--|
| Subject group type                   | Reporting group       |  |  |  |
| Number of subjects analysed          | 974                   |  |  |  |
| Units: Units on a scale              |                       |  |  |  |
| arithmetic mean (standard deviation) |                       |  |  |  |
| CYCLE 2/DAY 1 (N=926)                | 5.72 (± 17.51)        |  |  |  |
| CYCLE 3/DAY 1 (N=875)                | 8.57 (± 18.82)        |  |  |  |
| CYCLE 4/DAY 1 (N=836)                | 10.01 (± 19.73)       |  |  |  |
| CYCLE 5/DAY 1 (N=804)                | 10.38 (± 19.85)       |  |  |  |
| CYCLE 6/DAY 1 (N=771)                | 10.17 (± 20.38)       |  |  |  |
| CYCLE 7/DAY 1 (N=728)                | 10.17 (± 20.38)       |  |  |  |
| CYCLE 8/DAY 1 (N=693)                | 10.35 (± 19.22)       |  |  |  |
| CYCLE 9/DAY 1 (N=667)                | 10.69 (± 19.82)       |  |  |  |

|                          |                 |  |  |  |
|--------------------------|-----------------|--|--|--|
| CYCLE 10/DAY 1 (N=633)   | 10.34 (± 19.15) |  |  |  |
| CYCLE 11/DAY 1 (N=573)   | 10.09 (± 19.72) |  |  |  |
| CYCLE 12/DAY 1 (N=409)   | 9.69 (± 18.81)  |  |  |  |
| CYCLE 13/DAY 1 (N=512)   | 9.74 (± 19.64)  |  |  |  |
| CYCLE 14/DAY 1 (N=351)   | 10.93 (± 18.67) |  |  |  |
| CYCLE 15/DAY 1 (N=461)   | 8.71 (± 20.53)  |  |  |  |
| CYCLE 16/DAY 1 (N=289)   | 8.47 (± 20.66)  |  |  |  |
| CYCLE 17/DAY 1 (N=417)   | 7.99 (± 20.8)   |  |  |  |
| CYCLE 18/DAY 1 (N=244)   | 7.62 (± 19.86)  |  |  |  |
| CYCLE 19/DAY 1 (N=372)   | 8.17 (± 18.92)  |  |  |  |
| CYCLE 20/DAY 1 (N=219)   | 8.03 (± 18.45)  |  |  |  |
| CYCLE 21/DAY 1 (N=339)   | 6.96 (± 18.71)  |  |  |  |
| CYCLE 22/DAY 1 (N=179)   | 6.59 (± 18.97)  |  |  |  |
| CYCLE 23/DAY 1 (N=310)   | 5.53 (± 19.5)   |  |  |  |
| CYCLE 24/DAY 1 (N=154)   | 7.61 (± 19.58)  |  |  |  |
| CYCLE 25/DAY 1 (N=299)   | 4.97 (± 17.98)  |  |  |  |
| CYCLE 26/DAY 1 (N=128)   | 8.54 (± 18.97)  |  |  |  |
| CYCLE 27/DAY 1 (N=272)   | 5.24 (± 17.61)  |  |  |  |
| CYCLE 28/DAY 1 (N=120)   | 7.93 (± 19.53)  |  |  |  |
| CYCLE 29/DAY 1 (N=249)   | 5.05 (± 17.07)  |  |  |  |
| CYCLE 30/DAY 1 (N=108)   | 8.07 (± 19.95)  |  |  |  |
| End of Treatment (N=450) | 0.09 (± 23.92)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of participants with Visual Symptom Assessment Questionnaire (VSAQ-ALK)

|                 |                                                                                    |
|-----------------|------------------------------------------------------------------------------------|
| End point title | Percentage of participants with Visual Symptom Assessment Questionnaire (VSAQ-ALK) |
|-----------------|------------------------------------------------------------------------------------|

End point description:

The participants who responded to the question: "Have you experienced any visual disturbances?" Only the participants who answered yes were instructed to complete the rest of the questionnaire. "n" is the number of participants who completed the first question. The safety analysis population included all participants who were enrolled and received at least 1 dose of study medication (excluding day-7 pharmacokinetic [PK] dosing).

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

End point timeframe:

5 years

| End point values                  | Crizotinib 250 mg BID |  |  |  |
|-----------------------------------|-----------------------|--|--|--|
| Subject group type                | Reporting group       |  |  |  |
| Number of subjects analysed       | 1066                  |  |  |  |
| Units: Percentage of participants |                       |  |  |  |
| number (not applicable)           |                       |  |  |  |
| Cycle 2/Day 1 (Yes) (N=798)       | 64.5                  |  |  |  |
| Cycle 2/Day 1 (No) (N=798)        | 35.5                  |  |  |  |
| Cycle 3/Day 1 (Yes) (N=768)       | 56.5                  |  |  |  |
| Cycle 3/Day 1 (No) (N=768)        | 43.5                  |  |  |  |
| Cycle 4/Day 1 (Yes) (N=754)       | 52.3                  |  |  |  |
| Cycle 4/Day 1 (No) (N=754)        | 47.7                  |  |  |  |
| Cycle 5/Day 1 (Yes) (N=743)       | 49.1                  |  |  |  |
| Cycle 5/Day 1 (No) (N=743)        | 50.9                  |  |  |  |
| Cycle 6/Day 1 (Yes) (N=731)       | 48.8                  |  |  |  |
| Cycle 6/Day 1 (No) (N=731)        | 51.2                  |  |  |  |
| Cycle 7/Day 1 (Yes) (N=699)       | 45.8                  |  |  |  |
| Cycle 7/Day 1 (No) (N=699)        | 54.2                  |  |  |  |
| Cycle 8/Day 1 (Yes) (N=670)       | 43.7                  |  |  |  |
| Cycle 8/Day 1 (No) (N=670)        | 56.3                  |  |  |  |
| Cycle 9/Day 1 (Yes) (N=653)       | 43.5                  |  |  |  |
| Cycle 9/Day 1 (No) (N=653)        | 56.5                  |  |  |  |
| Cycle 10/Day 1 (Yes) (N=621)      | 42.7                  |  |  |  |
| Cycle 10/Day 1 (No) (N=621)       | 57.3                  |  |  |  |
| Cycle 11/Day 1 (Yes) (N=565)      | 40.2                  |  |  |  |
| Cycle 11/Day 1 (No) (N=565)       | 59.8                  |  |  |  |
| Cycle 12/Day 1 (Yes) (N=403)      | 42.9                  |  |  |  |
| Cycle 12/Day 1 (No) (N=403)       | 57.1                  |  |  |  |
| Cycle 13/Day 1 (Yes) (N=507)      | 41.2                  |  |  |  |
| Cycle 13/Day 1 (No) (N=507)       | 58.8                  |  |  |  |
| Cycle 14/Day 1 (Yes) (N=354)      | 41.5                  |  |  |  |
| Cycle 14/Day 1 (No) (N=354)       | 58.5                  |  |  |  |
| Cycle 15/Day 1 (Yes) (N=468)      | 39.1                  |  |  |  |
| Cycle 15/Day 1 (No) (N=468)       | 60.9                  |  |  |  |
| Cycle 16/Day 1 (Yes) (N=296)      | 43.6                  |  |  |  |
| Cycle 16/Day 1 (No) (N=296)       | 56.4                  |  |  |  |
| Cycle 17/Day 1 (Yes) (N=418)      | 37.3                  |  |  |  |
| Cycle 17/Day 1 (No) (N=418)       | 62.7                  |  |  |  |
| Cycle 18/Day 1 (Yes) (N=249)      | 40.2                  |  |  |  |
| Cycle 18/Day 1 (No) (N=249)       | 59.8                  |  |  |  |
| Cycle 19/Day 1 (Yes) (N=378)      | 36.8                  |  |  |  |
| Cycle 19/Day 1 (No) (N=378)       | 63.2                  |  |  |  |
| Cycle 20/Day 1 (Yes) (N=221)      | 38.9                  |  |  |  |
| Cycle 20/Day 1 (No) (N=221)       | 61.1                  |  |  |  |
| Cycle 21/Day 1 (Yes) (N=344)      | 39                    |  |  |  |
| Cycle 21/Day 1 (No) (N=344)       | 61                    |  |  |  |
| Cycle 22/Day 1 (Yes) (N=181)      | 39.2                  |  |  |  |
| Cycle 22/Day 1 (No) (N=181)       | 60.8                  |  |  |  |
| Cycle 23/Day 1 (Yes) (N=312)      | 34.9                  |  |  |  |
| Cycle 23/Day 1 (No) (N=312)       | 65.1                  |  |  |  |
| Cycle 24/Day 1 (Yes) (N=155)      | 34.8                  |  |  |  |
| Cycle 24/Day 1 (No) (N=155)       | 65.2                  |  |  |  |

|                                |      |  |  |  |
|--------------------------------|------|--|--|--|
| Cycle 25/Day 1 (Yes) (N=302)   | 35.8 |  |  |  |
| Cycle 25/Day 1 (No) (N=302)    | 64.2 |  |  |  |
| Cycle 26/Day 1 (Yes) (N=130)   | 30.8 |  |  |  |
| Cycle 26/Day 1 (No) (N=130)    | 69.2 |  |  |  |
| Cycle 27/Day 1 (Yes) (N=276)   | 32.6 |  |  |  |
| Cycle 27/Day 1 (No) (N=276)    | 67.4 |  |  |  |
| Cycle 28/Day 1 (Yes) (N=118)   | 31.4 |  |  |  |
| Cycle 28/Day 1 (No) (N=118)    | 68.6 |  |  |  |
| Cycle 29/Day 1 (Yes) (N=249)   | 30.5 |  |  |  |
| Cycle 29/Day 1 (No) (N=249)    | 69.5 |  |  |  |
| Cycle 30/Day 1 (Yes) (N=106)   | 27.4 |  |  |  |
| Cycle 30/Day 1 (No) (N=106)    | 72.6 |  |  |  |
| End of Treatment (Yes) (N=428) | 39.3 |  |  |  |
| End of Treatment (No) (N=428)  | 60.7 |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma concentrations of crizotinib (PF-02341066) and its metabolite PF-06260182

|                 |                                                                                  |
|-----------------|----------------------------------------------------------------------------------|
| End point title | Plasma concentrations of crizotinib (PF-02341066) and its metabolite PF-06260182 |
|-----------------|----------------------------------------------------------------------------------|

End point description:

Plasma concentration of crizotinib (PF-02341066) and its metabolite PF-06260182. The method of dispersion is % coefficient of variation. All participants who have  $\geq 1$  measurement of PF-02341066 or PF-06260182 at the time of reporting are included in PK analysis. Pre-dose concentrations of PF-02341066 and PF-06260182 were performed in only Chinese sub study participants for Cycle 1 and steady state concentrations in those who received at least 14 continuous days of 250 mg BID dosing.

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

End point timeframe:

5 years

| End point values                                    | Crizotinib 250 mg BID | PF-06260182          |  |  |
|-----------------------------------------------------|-----------------------|----------------------|--|--|
| Subject group type                                  | Reporting group       | Subject analysis set |  |  |
| Number of subjects analysed                         | 906                   | 904                  |  |  |
| Units: ng/mL                                        |                       |                      |  |  |
| geometric mean (geometric coefficient of variation) |                       |                      |  |  |
| Cycle 1 (N= 13, 13)                                 | 1.95 ( $\pm$ 55)      | 0.00601 ( $\pm$ 167) |  |  |
| Cycle 2 (N=447, 431)                                | 279 ( $\pm$ 46)       | 76.2 ( $\pm$ 79)     |  |  |
| Cycle 3 (N=398, 385)                                | 297 ( $\pm$ 44)       | 80.8 ( $\pm$ 58)     |  |  |
| Cycle 5 (N=297, 290)                                | 294 ( $\pm$ 48)       | 81.4 ( $\pm$ 61)     |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Molecular Profiling (ALK Status) Descriptive Statistics for ALK Percentage of Positive Cells by Central Laboratory Test (SA [ALK positive by IUO] Population)

|                 |                                                                                                                                                               |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Molecular Profiling (ALK Status) Descriptive Statistics for ALK Percentage of Positive Cells by Central Laboratory Test (SA [ALK positive by IUO] Population) |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Molecular profiling outcomes included: Types of EML4-ALK fusion variants and ALK protein expression; Protein expression of identified biomarkers in serial tumor samples from surgery or biopsy, when available. The safety analysis population included all participants who received at least 1 dose of study medication (excluding day-7 pharmacokinetic [PK] dosing) and were ALK positive by IUO (SA-ALK positive by IUO population).

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

End point timeframe:

5 years

|                               |                       |  |  |  |
|-------------------------------|-----------------------|--|--|--|
| <b>End point values</b>       | Crizotinib 250 mg BID |  |  |  |
| Subject group type            | Reporting group       |  |  |  |
| Number of subjects analysed   | 908                   |  |  |  |
| Units: Number                 |                       |  |  |  |
| median (full range (min-max)) | 60 (15 to 100)        |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Genotypes of alleles possibly associated with adverse hepatic drug reactions (Pharmacogenomic evaluable population)

|                 |                                                                                                                     |
|-----------------|---------------------------------------------------------------------------------------------------------------------|
| End point title | Genotypes of alleles possibly associated with adverse hepatic drug reactions (Pharmacogenomic evaluable population) |
|-----------------|---------------------------------------------------------------------------------------------------------------------|

End point description:

Frequency of candidate gene alleles, HLA-DQA1\*02:01, HLA-DQB1\*02:02, HLA-DRB1\*07:01 and TNXB/rs12153855, were measured in alanine transaminase (ALT) Cases and Controls to evaluate if there were statistically significant associations that would support/suggest any predictive (ie, diagnostic) value of these markers in identifying participants at increased risk for hepatic toxicity. Frequency of 2 additional HLA gene alleles, HLA-B\*57:01 and HLA-DRB1\*15:01, were also measured in ALT Cases and Controls. ALT Cases are participants with baseline ALT  $\leq 1 \times \text{ULN}$  and at least one on-treatment ALT assessment  $> 3 \times$  upper limit of normal (ULN); and ALT Controls are those with baseline and on-treatment assessments of ALT  $\leq 1 \times \text{ULN}$ . All Genotyped Population was all participants in safety analysis population who had at least 1 genotype result. Pharmacogenomic Evaluable (PE) Population was participants in All Genotyped Population who had an HLA genotype result and were designated as ALT Case or Control.

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

End point timeframe:

5 years

| End point values                  | Crizotinib 250 mg BID-ALT cases | Crizotinib 250 mg BID-ALT controls |  |  |
|-----------------------------------|---------------------------------|------------------------------------|--|--|
| Subject group type                | Subject analysis set            | Subject analysis set               |  |  |
| Number of subjects analysed       | 74                              | 115                                |  |  |
| Units: Percentage of participants |                                 |                                    |  |  |
| number (not applicable)           |                                 |                                    |  |  |
| HLA-DQA1*02:01                    | 20.3                            | 20                                 |  |  |
| HLA-DQB1*02:02                    | 17.6                            | 16.5                               |  |  |
| HLA-DRB1*07:01                    | 20.3                            | 20                                 |  |  |
| TNXB/rs12153855                   | 10.8                            | 16.5                               |  |  |
| HLA-B*57:01                       | 2.7                             | 4.3                                |  |  |
| HLA-DRB1*15:01                    | 17.6                            | 20.9                               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: QTc prolongation in participants

|                                                                                                                                                                                                                                                                                                                                             |                                  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                             | QTc prolongation in participants |
| End point description:                                                                                                                                                                                                                                                                                                                      |                                  |
| The number and percentage of participants with maximum post-dose QTcF/QTcB (<450, 450 - <480, 480 - <500, and ≥500 msec) were evaluated. Participants from the SA population who had a Baseline (last ECG [electrocardiogram] prior to Cycle 1 Day 1 dose) and ≥1 post Baseline ECG measurement and were not included in the ECG sub-study. |                                  |
| End point type                                                                                                                                                                                                                                                                                                                              | Secondary                        |
| End point timeframe:                                                                                                                                                                                                                                                                                                                        |                                  |
| 5 years                                                                                                                                                                                                                                                                                                                                     |                                  |

| End point values                   | Crizotinib 250 mg BID |  |  |  |
|------------------------------------|-----------------------|--|--|--|
| Subject group type                 | Reporting group       |  |  |  |
| Number of subjects analysed        | 999                   |  |  |  |
| Units: Percentage                  |                       |  |  |  |
| number (not applicable)            |                       |  |  |  |
| Maximum QTcF Interval (<450)       | 89.8                  |  |  |  |
| Maximum QTcF Interval (450-<480)   | 7.7                   |  |  |  |
| Maximum QTcF Interval (480 - <500) | 1                     |  |  |  |
| Maximum QTcF Interval (≥500)       | 1.5                   |  |  |  |
| Maximum QTcB Interval (<450)       | 74.2                  |  |  |  |
| Maximum QTcB Interval (450-<480)   | 21.4                  |  |  |  |
| Maximum QTcB Interval (480-<500)   | 2.4                   |  |  |  |
| Maximum QTcB Interval (≥500)       | 2.1                   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival (OS)

|                 |                       |
|-----------------|-----------------------|
| End point title | Overall Survival (OS) |
|-----------------|-----------------------|

End point description:

OS was defined as the time from the Cycle 1 Day 1 dose to the date of death due to any cause. OS (in months) was calculated as (date of death – date of Cycle 1 Day 1 dose + 1)/30.4. The safety analysis populations included all participants who received at least 1 dose of study medication (excluding day-7 pharmacokinetic [PK] dosing), and were ALK positive either by IUO (SA-ALK positive by IUO population) or by non-IUO (SA-ALK positive by non-IUO population), respectively.

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

End point timeframe:

5 years

|                                  |                       |  |  |  |
|----------------------------------|-----------------------|--|--|--|
| <b>End point values</b>          | Crizotinib 250 mg BID |  |  |  |
| Subject group type               | Reporting group       |  |  |  |
| Number of subjects analysed      | 1066                  |  |  |  |
| Units: Months                    |                       |  |  |  |
| median (confidence interval 95%) |                       |  |  |  |
| ALK-positive by IUO (N= 908)     | 21.8 (19.4 to 24)     |  |  |  |
| ALK-positive by non-IUO (N= 158) | 16.9 (13.4 to 21.5)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Probability of Survival

|                 |                         |
|-----------------|-------------------------|
| End point title | Probability of Survival |
|-----------------|-------------------------|

End point description:

Six-month and 1-year survival probabilities were defined as the probabilities of survival at 6 months and 1 year, respectively, after the date of the Cycle 1 Day 1 dose based on the Kaplan-Meier estimate. The safety analysis populations included all participants who received at least 1 dose of study medication (excluding day-7 pharmacokinetic [PK] dosing), and were ALK positive either by IUO (SA-ALK positive by IUO population) or by non-IUO (SA-ALK positive by non-IUO population), respectively.

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

End point timeframe:

5 years

|                                      |                       |  |  |  |
|--------------------------------------|-----------------------|--|--|--|
| <b>End point values</b>              | Crizotinib 250 mg BID |  |  |  |
| Subject group type                   | Reporting group       |  |  |  |
| Number of subjects analysed          | 1066                  |  |  |  |
| Units: Percentage                    |                       |  |  |  |
| number (confidence interval 95%)     |                       |  |  |  |
| ALK positive by IUO at 6 Months      | 81.7 (79 to 84)       |  |  |  |
| ALK positive by non IUO at 6 Months  | 77.5 (70.1 to 83.3)   |  |  |  |
| ALK positive by IUO at 12 Months     | 66.5 (63.3 to 69.5)   |  |  |  |
| ALK positive by non IUO at 12 Months | 62.4 (54.3 to 69.6)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Active reporting period is from the time of informed consent until at least 28 days after study treatment last dose. For Serious adverse events: those with the possibility of being related to study drug must be reported as minimum thereafter.

Adverse event reporting additional description:

All causality (serious and non-serious) adverse events have been reported. Non-serious adverse events above the 5% threshold are reported herein. 15 fatalities causally related to crizotinib have been reported.

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

### Reporting groups

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | Crizotinib 250 mg BID |
|-----------------------|-----------------------|

Reporting group description:

Participants were administered crizotinib at a starting dose of 250 mg orally, BID on a continuous dosing period as two 100-mg tablets and one 50-mg tablet at approximately 12 hours apart the same time each day.

| Serious adverse events                                              | Crizotinib 250 mg BID |  |  |
|---------------------------------------------------------------------|-----------------------|--|--|
| Total subjects affected by serious adverse events                   |                       |  |  |
| subjects affected / exposed                                         | 533 / 1066 (50.00%)   |  |  |
| number of deaths (all causes)                                       | 241                   |  |  |
| number of deaths resulting from adverse events                      | 15                    |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                       |  |  |
| Basal cell carcinoma                                                |                       |  |  |
| subjects affected / exposed                                         | 1 / 1066 (0.09%)      |  |  |
| occurrences causally related to treatment / all                     | 1 / 1                 |  |  |
| deaths causally related to treatment / all                          | 0 / 0                 |  |  |
| Breast cancer                                                       |                       |  |  |
| subjects affected / exposed                                         | 1 / 1066 (0.09%)      |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                 |  |  |
| deaths causally related to treatment / all                          | 0 / 0                 |  |  |
| Gallbladder cancer                                                  |                       |  |  |
| subjects affected / exposed                                         | 1 / 1066 (0.09%)      |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                 |  |  |
| deaths causally related to treatment / all                          | 0 / 1                 |  |  |

|                                                 |                  |  |  |  |
|-------------------------------------------------|------------------|--|--|--|
| Malignant melanoma                              |                  |  |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Metastases to meninges                          |                  |  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Neoplasm malignant                              |                  |  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Neuroendocrine tumour                           |                  |  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Pancreatic carcinoma                            |                  |  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Plasma cell myeloma                             |                  |  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Prostate cancer                                 |                  |  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Small cell lung cancer                          |                  |  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Squamous cell carcinoma of skin                 |                  |  |  |  |

|                                                 |                   |  |  |
|-------------------------------------------------|-------------------|--|--|
| subjects affected / exposed                     | 2 / 1066 (0.19%)  |  |  |
| occurrences causally related to treatment / all | 2 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Vascular disorders                              |                   |  |  |
| Deep vein thrombosis                            |                   |  |  |
| subjects affected / exposed                     | 14 / 1066 (1.31%) |  |  |
| occurrences causally related to treatment / all | 4 / 15            |  |  |
| deaths causally related to treatment / all      | 1 / 1             |  |  |
| Embolism                                        |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Haematoma                                       |                   |  |  |
| subjects affected / exposed                     | 3 / 1066 (0.28%)  |  |  |
| occurrences causally related to treatment / all | 1 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hypotension                                     |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hypovolaemic shock                              |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Orthostatic hypotension                         |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Peripheral arterial occlusive disease           |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Peripheral embolism                             |                   |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Phlebitis                                       |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Superior vena cava syndrome                     |                  |  |  |
| subjects affected / exposed                     | 4 / 1066 (0.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 5            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Thrombophlebitis                                |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Thrombosis                                      |                  |  |  |
| subjects affected / exposed                     | 5 / 1066 (0.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 5            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Vasculitis                                      |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Vena cava thrombosis                            |                  |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Venous thrombosis                               |                  |  |  |
| subjects affected / exposed                     | 4 / 1066 (0.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Surgical and medical procedures                 |                  |  |  |
| Pleural decortication                           |                  |  |  |

|                                                      |                  |  |  |
|------------------------------------------------------|------------------|--|--|
| subjects affected / exposed                          | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1            |  |  |
| deaths causally related to treatment / all           | 0 / 0            |  |  |
| General disorders and administration site conditions |                  |  |  |
| Asthenia                                             |                  |  |  |
| subjects affected / exposed                          | 7 / 1066 (0.66%) |  |  |
| occurrences causally related to treatment / all      | 0 / 9            |  |  |
| deaths causally related to treatment / all           | 0 / 0            |  |  |
| Chest discomfort                                     |                  |  |  |
| subjects affected / exposed                          | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all      | 0 / 2            |  |  |
| deaths causally related to treatment / all           | 0 / 0            |  |  |
| Chest pain                                           |                  |  |  |
| subjects affected / exposed                          | 5 / 1066 (0.47%) |  |  |
| occurrences causally related to treatment / all      | 1 / 6            |  |  |
| deaths causally related to treatment / all           | 0 / 0            |  |  |
| Chills                                               |                  |  |  |
| subjects affected / exposed                          | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1            |  |  |
| deaths causally related to treatment / all           | 0 / 0            |  |  |
| Condition aggravated                                 |                  |  |  |
| subjects affected / exposed                          | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all      | 0 / 2            |  |  |
| deaths causally related to treatment / all           | 0 / 0            |  |  |
| Death                                                |                  |  |  |
| subjects affected / exposed                          | 8 / 1066 (0.75%) |  |  |
| occurrences causally related to treatment / all      | 6 / 8            |  |  |
| deaths causally related to treatment / all           | 6 / 8            |  |  |
| Device dislocation                                   |                  |  |  |
| subjects affected / exposed                          | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1            |  |  |
| deaths causally related to treatment / all           | 0 / 0            |  |  |
| Disease progression                                  |                  |  |  |

|                                                    |                        |  |  |  |
|----------------------------------------------------|------------------------|--|--|--|
| subjects affected / exposed                        | 135 / 1066<br>(12.66%) |  |  |  |
| occurrences causally related to<br>treatment / all | 0 / 136                |  |  |  |
| deaths causally related to<br>treatment / all      | 0 / 133                |  |  |  |
| Fatigue                                            |                        |  |  |  |
| subjects affected / exposed                        | 4 / 1066 (0.38%)       |  |  |  |
| occurrences causally related to<br>treatment / all | 1 / 4                  |  |  |  |
| deaths causally related to<br>treatment / all      | 0 / 0                  |  |  |  |
| Gait disturbance                                   |                        |  |  |  |
| subjects affected / exposed                        | 1 / 1066 (0.09%)       |  |  |  |
| occurrences causally related to<br>treatment / all | 0 / 1                  |  |  |  |
| deaths causally related to<br>treatment / all      | 0 / 0                  |  |  |  |
| General physical health deterioration              |                        |  |  |  |
| subjects affected / exposed                        | 9 / 1066 (0.84%)       |  |  |  |
| occurrences causally related to<br>treatment / all | 1 / 11                 |  |  |  |
| deaths causally related to<br>treatment / all      | 0 / 3                  |  |  |  |
| Generalised oedema                                 |                        |  |  |  |
| subjects affected / exposed                        | 3 / 1066 (0.28%)       |  |  |  |
| occurrences causally related to<br>treatment / all | 2 / 3                  |  |  |  |
| deaths causally related to<br>treatment / all      | 0 / 0                  |  |  |  |
| Mass                                               |                        |  |  |  |
| subjects affected / exposed                        | 1 / 1066 (0.09%)       |  |  |  |
| occurrences causally related to<br>treatment / all | 1 / 1                  |  |  |  |
| deaths causally related to<br>treatment / all      | 0 / 0                  |  |  |  |
| Multi-organ failure                                |                        |  |  |  |
| subjects affected / exposed                        | 1 / 1066 (0.09%)       |  |  |  |
| occurrences causally related to<br>treatment / all | 0 / 1                  |  |  |  |
| deaths causally related to<br>treatment / all      | 0 / 1                  |  |  |  |
| Oedema peripheral                                  |                        |  |  |  |
| subjects affected / exposed                        | 7 / 1066 (0.66%)       |  |  |  |
| occurrences causally related to<br>treatment / all | 5 / 8                  |  |  |  |
| deaths causally related to<br>treatment / all      | 0 / 0                  |  |  |  |
| Pain                                               |                        |  |  |  |

|                                                 |                   |  |  |
|-------------------------------------------------|-------------------|--|--|
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Pyrexia                                         |                   |  |  |
| subjects affected / exposed                     | 18 / 1066 (1.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 19            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Thrombosis in device                            |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Immune system disorders                         |                   |  |  |
| Contrast media allergy                          |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Reproductive system and breast disorders        |                   |  |  |
| Benign prostatic hyperplasia                    |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Pelvic pain                                     |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Respiratory, thoracic and mediastinal disorders |                   |  |  |
| Acute respiratory distress syndrome             |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Acute respiratory failure                       |                   |  |  |

|                                                 |                   |  |  |  |
|-------------------------------------------------|-------------------|--|--|--|
| subjects affected / exposed                     | 3 / 1066 (0.28%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 5             |  |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |  |
| Alveolitis                                      |                   |  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |  |
| occurrences causally related to treatment / all | 1 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Asphyxia                                        |                   |  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |  |
| Atelectasis                                     |                   |  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Bronchial hyperreactivity                       |                   |  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Chronic obstructive pulmonary disease           |                   |  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |  |
| Cough                                           |                   |  |  |  |
| subjects affected / exposed                     | 3 / 1066 (0.28%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Dyspnoea                                        |                   |  |  |  |
| subjects affected / exposed                     | 39 / 1066 (3.66%) |  |  |  |
| occurrences causally related to treatment / all | 8 / 46            |  |  |  |
| deaths causally related to treatment / all      | 2 / 8             |  |  |  |
| Epistaxis                                       |                   |  |  |  |

|                                                 |                   |  |  |
|-------------------------------------------------|-------------------|--|--|
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Haemoptysis                                     |                   |  |  |
| subjects affected / exposed                     | 3 / 1066 (0.28%)  |  |  |
| occurrences causally related to treatment / all | 1 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hypoxia                                         |                   |  |  |
| subjects affected / exposed                     | 4 / 1066 (0.38%)  |  |  |
| occurrences causally related to treatment / all | 0 / 5             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Interstitial lung disease                       |                   |  |  |
| subjects affected / exposed                     | 3 / 1066 (0.28%)  |  |  |
| occurrences causally related to treatment / all | 1 / 4             |  |  |
| deaths causally related to treatment / all      | 1 / 2             |  |  |
| Lung disorder                                   |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Lung infiltration                               |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Oropharyngeal pain                              |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Pleural effusion                                |                   |  |  |
| subjects affected / exposed                     | 13 / 1066 (1.22%) |  |  |
| occurrences causally related to treatment / all | 1 / 15            |  |  |
| deaths causally related to treatment / all      | 0 / 2             |  |  |
| Pleuritic pain                                  |                   |  |  |

|                                                 |                   |  |  |
|-------------------------------------------------|-------------------|--|--|
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Pneumonia aspiration                            |                   |  |  |
| subjects affected / exposed                     | 4 / 1066 (0.38%)  |  |  |
| occurrences causally related to treatment / all | 0 / 5             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Pneumonitis                                     |                   |  |  |
| subjects affected / exposed                     | 16 / 1066 (1.50%) |  |  |
| occurrences causally related to treatment / all | 17 / 20           |  |  |
| deaths causally related to treatment / all      | 4 / 4             |  |  |
| Pneumothorax                                    |                   |  |  |
| subjects affected / exposed                     | 8 / 1066 (0.75%)  |  |  |
| occurrences causally related to treatment / all | 0 / 9             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Pulmonary arterial hypertension                 |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Pulmonary artery thrombosis                     |                   |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Pulmonary embolism                              |                   |  |  |
| subjects affected / exposed                     | 26 / 1066 (2.44%) |  |  |
| occurrences causally related to treatment / all | 5 / 30            |  |  |
| deaths causally related to treatment / all      | 1 / 7             |  |  |
| Pulmonary haemorrhage                           |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Pulmonary oedema                                |                   |  |  |

|                                                 |                   |  |  |
|-------------------------------------------------|-------------------|--|--|
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Pulmonary thrombosis                            |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Rales                                           |                   |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Respiratory failure                             |                   |  |  |
| subjects affected / exposed                     | 17 / 1066 (1.59%) |  |  |
| occurrences causally related to treatment / all | 1 / 23            |  |  |
| deaths causally related to treatment / all      | 0 / 10            |  |  |
| Thoracic haemorrhage                            |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Psychiatric disorders                           |                   |  |  |
| Completed suicide                               |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Confusional state                               |                   |  |  |
| subjects affected / exposed                     | 7 / 1066 (0.66%)  |  |  |
| occurrences causally related to treatment / all | 1 / 7             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Depression                                      |                   |  |  |
| subjects affected / exposed                     | 3 / 1066 (0.28%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Disorientation                                  |                   |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Mania                                           |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Mental status changes                           |                  |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Suicide attempt                                 |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Investigations                                  |                  |  |  |
| Alanine aminotransferase increased              |                  |  |  |
| subjects affected / exposed                     | 4 / 1066 (0.38%) |  |  |
| occurrences causally related to treatment / all | 5 / 5            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Blood albumin decreased                         |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Blood bilirubin increased                       |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Blood creatinine increased                      |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Blood lactate dehydrogenase increased           |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| C-reactive protein increased                    |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Electrocardiogram QT prolonged                  |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hepatic enzyme increased                        |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Troponin I increased                            |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Injury, poisoning and procedural complications  |                  |  |  |
| Ankle fracture                                  |                  |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Bone fissure                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Craniocerebral injury                           |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Dislocation of vertebra                         |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Fall                                            |                  |  |  |
| subjects affected / exposed                     | 6 / 1066 (0.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Femoral neck fracture                           |                  |  |  |
| subjects affected / exposed                     | 4 / 1066 (0.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 5            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Femur fracture                                  |                  |  |  |
| subjects affected / exposed                     | 4 / 1066 (0.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hip fracture                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Humerus fracture                                |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Joint dislocation                               |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Lower limb fracture                             |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Overdose                                        |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pelvic fracture                                 |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Radiation necrosis                              |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Radiation pneumonitis                           |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Radius fracture                                 |                  |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Road traffic accident                           |                  |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Spinal compression fracture                     |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Subdural haemorrhage                            |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Traumatic haematoma                             |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Upper limb fracture                             |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cardiac disorders                               |                  |  |  |
| Acute myocardial infarction                     |                  |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Angina pectoris                                 |                  |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Atrial fibrillation                             |                  |  |  |
| subjects affected / exposed                     | 3 / 1066 (0.28%) |  |  |
| occurrences causally related to treatment / all | 1 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Bradycardia                                     |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cardiac arrest                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Cardiac failure                                 |                  |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Cardiac failure congestive                      |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Cardiac tamponade                               |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Coronary artery stenosis                        |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cyanosis                                        |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Left ventricular failure                        |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Myocardial infarction                           |                  |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 2            |  |  |
| Myocarditis                                     |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Palpitations                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pericardial effusion                            |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 7 / 1066 (0.66%) |  |  |
| occurrences causally related to treatment / all | 0 / 7            |  |  |
| deaths causally related to treatment / all      | 0 / 2            |  |  |
| Pericarditis                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Supraventricular tachycardia                    |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Syncope                                         |                  |  |  |
| subjects affected / exposed                     | 6 / 1066 (0.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Tachycardia                                     |                  |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Nervous system disorders                        |                  |  |  |
| Aphasia                                         |                  |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ataxia                                          |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Brain oedema                                    |                  |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cerebellar infarction                           |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cerebral haemorrhage                            |                  |  |  |
| subjects affected / exposed                     | 4 / 1066 (0.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 4            |  |  |
| Cerebral infarction                             |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Cerebrovascular accident                        |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Chorea                                          |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Coma                                            |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Depressed level of consciousness                |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Dizziness                                       |                  |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Dysarthria                                      |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Generalised tonic-clonic seizure                |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Haemorrhage intracranial                        |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Headache                                        |                  |  |  |
| subjects affected / exposed                     | 4 / 1066 (0.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Intracranial pressure increased                 |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ischaemic stroke                                |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Nervous system disorder                         |                  |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Neurological decompensation                     |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Paraplegia                                      |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Peripheral motor neuropathy                     |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Peripheral sensorimotor neuropathy              |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Peripheral sensory neuropathy                   |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pyramidal tract syndrome                        |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Seizure                                         |                  |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 3 / 11           |  |  |
| deaths causally related to treatment / all      | 0 / 2            |  |  |
| Spinal cord compression                         |                  |  |  |
| subjects affected / exposed                     | 3 / 1066 (0.28%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Transient ischaemic attack                      |                  |  |  |
| subjects affected / exposed                     | 3 / 1066 (0.28%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Tremor                                          |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Vocal cord paralysis                            |                  |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Blood and lymphatic system disorders            |                  |  |  |
| Anaemia                                         |                  |  |  |
| subjects affected / exposed                     | 4 / 1066 (0.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Basophilia                                      |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Eosinophilia                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Febrile neutropenia                             |                  |  |  |
| subjects affected / exposed                     | 6 / 1066 (0.56%) |  |  |
| occurrences causally related to treatment / all | 4 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Leukocytosis                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Monocytosis                                     |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Thrombocytopenia                                |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Thrombocytosis                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Eye disorders                                   |                  |  |  |
| Cataract                                        |                  |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Glaucoma                                        |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Optic atrophy                                   |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Vision blurred                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Retinal detachment                              |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Vitreous haemorrhage                            |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastrointestinal disorders                      |                  |  |  |

|                                                 |                  |  |  |  |
|-------------------------------------------------|------------------|--|--|--|
| Abdominal pain                                  |                  |  |  |  |
| subjects affected / exposed                     | 6 / 1066 (0.56%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 6            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Abdominal wall haematoma                        |                  |  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Colitis                                         |                  |  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Ascites                                         |                  |  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Constipation                                    |                  |  |  |  |
| subjects affected / exposed                     | 3 / 1066 (0.28%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 3            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Diarrhoea                                       |                  |  |  |  |
| subjects affected / exposed                     | 4 / 1066 (0.38%) |  |  |  |
| occurrences causally related to treatment / all | 2 / 4            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Dysphagia                                       |                  |  |  |  |
| subjects affected / exposed                     | 6 / 1066 (0.56%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 7            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Diarrhoea haemorrhagic                          |                  |  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Gastric ulcer                                   |                  |  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastritis                                       |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastrointestinal haemorrhage                    |                  |  |  |
| subjects affected / exposed                     | 3 / 1066 (0.28%) |  |  |
| occurrences causally related to treatment / all | 4 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Intestinal obstruction                          |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ileus                                           |                  |  |  |
| subjects affected / exposed                     | 3 / 1066 (0.28%) |  |  |
| occurrences causally related to treatment / all | 1 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Intestinal perforation                          |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Nausea                                          |                  |  |  |
| subjects affected / exposed                     | 9 / 1066 (0.84%) |  |  |
| occurrences causally related to treatment / all | 4 / 10           |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Oesophagitis                                    |                  |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Oesophageal stenosis                            |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pancreatic atrophy                              |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pancreatitis acute                              |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pancreatitis                                    |                  |  |  |
| subjects affected / exposed                     | 3 / 1066 (0.28%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Peritoneal disorder                             |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Peptic ulcer haemorrhage                        |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Retroperitoneal haemorrhage                     |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Small intestinal obstruction                    |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Subileus                                        |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Upper gastrointestinal haemorrhage              |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Vomiting                                        |                  |  |  |
| subjects affected / exposed                     | 6 / 1066 (0.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hepatobiliary disorders                         |                  |  |  |
| Cholecystitis                                   |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Drug-induced liver injury                       |                  |  |  |
| subjects affected / exposed                     | 3 / 1066 (0.28%) |  |  |
| occurrences causally related to treatment / all | 4 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hepatic failure                                 |                  |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |
| deaths causally related to treatment / all      | 1 / 1            |  |  |
| Hepatitis                                       |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hepatocellular injury                           |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hepatotoxicity                                  |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 3 / 1066 (0.28%) |  |  |
| occurrences causally related to treatment / all | 3 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Skin and subcutaneous tissue disorders          |                  |  |  |
| Paraneoplastic pemphigus                        |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Rash                                            |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Renal and urinary disorders                     |                  |  |  |
| Acute kidney injury                             |                  |  |  |
| subjects affected / exposed                     | 4 / 1066 (0.38%) |  |  |
| occurrences causally related to treatment / all | 3 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Dysuria                                         |                  |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Haematuria                                      |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hydronephrosis                                  |                  |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Nephrolithiasis                                 |                  |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Renal cyst                                      |                  |  |  |

|                                                 |                   |  |  |
|-------------------------------------------------|-------------------|--|--|
| subjects affected / exposed                     | 13 / 1066 (1.22%) |  |  |
| occurrences causally related to treatment / all | 20 / 20           |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Renal cyst haemorrhage                          |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Renal failure                                   |                   |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Ureteral polyp                                  |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Urinary retention                               |                   |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Urinary tract obstruction                       |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Musculoskeletal and connective tissue disorders |                   |  |  |
| Arthralgia                                      |                   |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Back pain                                       |                   |  |  |
| subjects affected / exposed                     | 5 / 1066 (0.47%)  |  |  |
| occurrences causally related to treatment / all | 0 / 5             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Bursitis                                        |                   |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Chest wall mass                                 |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Joint swelling                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Lumbar spinal stenosis                          |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Muscular weakness                               |                  |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Musculoskeletal pain                            |                  |  |  |
| subjects affected / exposed                     | 3 / 1066 (0.28%) |  |  |
| occurrences causally related to treatment / all | 1 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Myalgia                                         |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Myopathy                                        |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Neck pain                                       |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Osteoarthritis                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pain in extremity                               |                  |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pathological fracture                           |                  |  |  |
| subjects affected / exposed                     | 5 / 1066 (0.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 5            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Spinal column stenosis                          |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Spondylolisthesis                               |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Systemic lupus erythematosus                    |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Infections and infestations                     |                  |  |  |
| Abdominal abscess                               |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 2 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Abscess limb                                    |                  |  |  |

|                                                 |                   |  |  |
|-------------------------------------------------|-------------------|--|--|
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Appendicitis                                    |                   |  |  |
| subjects affected / exposed                     | 8 / 1066 (0.75%)  |  |  |
| occurrences causally related to treatment / all | 0 / 8             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Bacteraemia                                     |                   |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Bone abscess                                    |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Bronchitis                                      |                   |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Candiduria                                      |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cellulitis                                      |                   |  |  |
| subjects affected / exposed                     | 12 / 1066 (1.13%) |  |  |
| occurrences causally related to treatment / all | 4 / 15            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Chest wall abscess                              |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Clostridium difficile infection                 |                   |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cystitis                                        |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Diverticulitis                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Empyema                                         |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastroenteritis                                 |                  |  |  |
| subjects affected / exposed                     | 6 / 1066 (0.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Herpes zoster                                   |                  |  |  |
| subjects affected / exposed                     | 3 / 1066 (0.28%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Infection                                       |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Infectious pleural effusion                     |                  |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Infective spondylitis                           |                  |  |  |

|                                                 |                   |  |  |
|-------------------------------------------------|-------------------|--|--|
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Lower respiratory tract infection               |                   |  |  |
| subjects affected / exposed                     | 3 / 1066 (0.28%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Lung abscess                                    |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Lung infection                                  |                   |  |  |
| subjects affected / exposed                     | 14 / 1066 (1.31%) |  |  |
| occurrences causally related to treatment / all | 3 / 20            |  |  |
| deaths causally related to treatment / all      | 2 / 5             |  |  |
| Meningitis                                      |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Metapneumovirus infection                       |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Oesophageal candidiasis                         |                   |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Osteomyelitis chronic                           |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Peritonitis                                     |                   |  |  |

|                                                 |                   |  |  |
|-------------------------------------------------|-------------------|--|--|
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Pneumonia                                       |                   |  |  |
| subjects affected / exposed                     | 74 / 1066 (6.94%) |  |  |
| occurrences causally related to treatment / all | 7 / 99            |  |  |
| deaths causally related to treatment / all      | 4 / 20            |  |  |
| Pneumonia bacterial                             |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Pneumonia fungal                                |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Pneumonia staphylococcal                        |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Pyelonephritis                                  |                   |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Renal abscess                                   |                   |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%)  |  |  |
| occurrences causally related to treatment / all | 1 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Renal cyst infection                            |                   |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%)  |  |  |
| occurrences causally related to treatment / all | 2 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Respiratory tract infection                     |                   |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 5 / 1066 (0.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Sepsis                                          |                  |  |  |
| subjects affected / exposed                     | 8 / 1066 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 11           |  |  |
| deaths causally related to treatment / all      | 0 / 4            |  |  |
| Septic shock                                    |                  |  |  |
| subjects affected / exposed                     | 4 / 1066 (0.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 5            |  |  |
| deaths causally related to treatment / all      | 0 / 4            |  |  |
| Skin infection                                  |                  |  |  |
| subjects affected / exposed                     | 4 / 1066 (0.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Soft tissue infection                           |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Staphylococcal sepsis                           |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Urinary tract infection                         |                  |  |  |
| subjects affected / exposed                     | 7 / 1066 (0.66%) |  |  |
| occurrences causally related to treatment / all | 0 / 8            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Upper respiratory tract infection               |                  |  |  |
| subjects affected / exposed                     | 7 / 1066 (0.66%) |  |  |
| occurrences causally related to treatment / all | 0 / 8            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Urinary tract infection bacterial               |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Viral upper respiratory tract infection         |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Viral infection                                 |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Wound infection                                 |                  |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Metabolism and nutrition disorders              |                  |  |  |
| Decreased appetite                              |                  |  |  |
| subjects affected / exposed                     | 3 / 1066 (0.28%) |  |  |
| occurrences causally related to treatment / all | 1 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Dehydration                                     |                  |  |  |
| subjects affected / exposed                     | 4 / 1066 (0.38%) |  |  |
| occurrences causally related to treatment / all | 2 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Failure to thrive                               |                  |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Fluid retention                                 |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hypercalcaemia                                  |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hyperglycaemia                                  |                  |  |  |
| subjects affected / exposed                     | 2 / 1066 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hyperkalaemia                                   |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hypoalbuminaemia                                |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hypocalcaemia                                   |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hypoglycaemia                                   |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hypokalaemia                                    |                  |  |  |
| subjects affected / exposed                     | 5 / 1066 (0.47%) |  |  |
| occurrences causally related to treatment / all | 1 / 5            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hypomagnesaemia                                 |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hyponatraemia                                   |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 4 / 1066 (0.38%) |  |  |
| occurrences causally related to treatment / all | 4 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hypophosphataemia                               |                  |  |  |
| subjects affected / exposed                     | 1 / 1066 (0.09%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |

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

| <b>Non-serious adverse events</b>                     | Crizotinib 250 mg<br>BID |  |  |
|-------------------------------------------------------|--------------------------|--|--|
| Total subjects affected by non-serious adverse events |                          |  |  |
| subjects affected / exposed                           | 1038 / 1066<br>(97.37%)  |  |  |
| General disorders and administration site conditions  |                          |  |  |
| Asthenia                                              |                          |  |  |
| subjects affected / exposed                           | 155 / 1066<br>(14.54%)   |  |  |
| occurrences (all)                                     | 240                      |  |  |
| Chest pain                                            |                          |  |  |
| subjects affected / exposed                           | 104 / 1066 (9.76%)       |  |  |
| occurrences (all)                                     | 121                      |  |  |
| Fatigue                                               |                          |  |  |
| subjects affected / exposed                           | 323 / 1066<br>(30.30%)   |  |  |
| occurrences (all)                                     | 524                      |  |  |
| Oedema                                                |                          |  |  |
| subjects affected / exposed                           | 95 / 1066 (8.91%)        |  |  |
| occurrences (all)                                     | 124                      |  |  |
| Oedema peripheral                                     |                          |  |  |
| subjects affected / exposed                           | 444 / 1066<br>(41.65%)   |  |  |
| occurrences (all)                                     | 744                      |  |  |
| Pyrexia                                               |                          |  |  |
| subjects affected / exposed                           | 181 / 1066<br>(16.98%)   |  |  |
| occurrences (all)                                     | 284                      |  |  |
| Respiratory, thoracic and mediastinal disorders       |                          |  |  |

|                                                                                                          |                               |  |  |
|----------------------------------------------------------------------------------------------------------|-------------------------------|--|--|
| Cough<br>subjects affected / exposed<br>occurrences (all)                                                | 256 / 1066<br>(24.02%)<br>362 |  |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)                                             | 221 / 1066<br>(20.73%)<br>312 |  |  |
| Haemoptysis<br>subjects affected / exposed<br>occurrences (all)                                          | 55 / 1066 (5.16%)<br>68       |  |  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)                                   | 76 / 1066 (7.13%)<br>89       |  |  |
| Productive cough<br>subjects affected / exposed<br>occurrences (all)                                     | 71 / 1066 (6.66%)<br>99       |  |  |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)                     | 76 / 1066 (7.13%)<br>82       |  |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                                             | 137 / 1066<br>(12.85%)<br>172 |  |  |
| Investigations<br>Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all) | 300 / 1066<br>(28.14%)<br>715 |  |  |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)                 | 232 / 1066<br>(21.76%)<br>479 |  |  |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all)                 | 75 / 1066 (7.04%)<br>112      |  |  |
| Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all)                           | 103 / 1066 (9.66%)<br>158     |  |  |

|                                                                                                            |                            |  |  |
|------------------------------------------------------------------------------------------------------------|----------------------------|--|--|
| Blood lactate dehydrogenase increased<br>subjects affected / exposed<br>occurrences (all)                  | 59 / 1066 (5.53%)<br>79    |  |  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                                       | 109 / 1066 (10.23%)<br>212 |  |  |
| Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all)                             | 84 / 1066 (7.88%)<br>263   |  |  |
| Weight increased<br>subjects affected / exposed<br>occurrences (all)                                       | 98 / 1066 (9.19%)<br>203   |  |  |
| White blood cell count decreased<br>subjects affected / exposed<br>occurrences (all)                       | 98 / 1066 (9.19%)<br>277   |  |  |
| Injury, poisoning and procedural complications<br>Fall<br>subjects affected / exposed<br>occurrences (all) | 58 / 1066 (5.44%)<br>69    |  |  |
| Cardiac disorders<br>Bradycardia<br>subjects affected / exposed<br>occurrences (all)                       | 92 / 1066 (8.63%)<br>113   |  |  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)                  | 262 / 1066 (24.58%)<br>342 |  |  |
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)                                              | 213 / 1066 (19.98%)<br>253 |  |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)                                               | 214 / 1066 (20.08%)<br>322 |  |  |
| Hypoaesthesia                                                                                              |                            |  |  |

|                                      |                     |  |  |
|--------------------------------------|---------------------|--|--|
| subjects affected / exposed          | 64 / 1066 (6.00%)   |  |  |
| occurrences (all)                    | 80                  |  |  |
| Paraesthesia                         |                     |  |  |
| subjects affected / exposed          | 83 / 1066 (7.79%)   |  |  |
| occurrences (all)                    | 99                  |  |  |
| Blood and lymphatic system disorders |                     |  |  |
| Anaemia                              |                     |  |  |
| subjects affected / exposed          | 136 / 1066 (12.76%) |  |  |
| occurrences (all)                    | 276                 |  |  |
| Leukopenia                           |                     |  |  |
| subjects affected / exposed          | 101 / 1066 (9.47%)  |  |  |
| occurrences (all)                    | 353                 |  |  |
| Lymphopenia                          |                     |  |  |
| subjects affected / exposed          | 71 / 1066 (6.66%)   |  |  |
| occurrences (all)                    | 159                 |  |  |
| Neutropenia                          |                     |  |  |
| subjects affected / exposed          | 178 / 1066 (16.70%) |  |  |
| occurrences (all)                    | 749                 |  |  |
| Eye disorders                        |                     |  |  |
| Photopsia                            |                     |  |  |
| subjects affected / exposed          | 96 / 1066 (9.01%)   |  |  |
| occurrences (all)                    | 113                 |  |  |
| Vision blurred                       |                     |  |  |
| subjects affected / exposed          | 80 / 1066 (7.50%)   |  |  |
| occurrences (all)                    | 103                 |  |  |
| Visual impairment                    |                     |  |  |
| subjects affected / exposed          | 459 / 1066 (43.06%) |  |  |
| occurrences (all)                    | 536                 |  |  |
| Gastrointestinal disorders           |                     |  |  |
| Abdominal pain                       |                     |  |  |
| subjects affected / exposed          | 118 / 1066 (11.07%) |  |  |
| occurrences (all)                    | 148                 |  |  |
| Abdominal pain upper                 |                     |  |  |
| subjects affected / exposed          | 104 / 1066 (9.76%)  |  |  |
| occurrences (all)                    | 134                 |  |  |
| Constipation                         |                     |  |  |

|                                                 |                        |  |  |
|-------------------------------------------------|------------------------|--|--|
| subjects affected / exposed                     | 475 / 1066<br>(44.56%) |  |  |
| occurrences (all)                               | 693                    |  |  |
| Diarrhoea                                       |                        |  |  |
| subjects affected / exposed                     | 548 / 1066<br>(51.41%) |  |  |
| occurrences (all)                               | 1015                   |  |  |
| Dyspepsia                                       |                        |  |  |
| subjects affected / exposed                     | 80 / 1066 (7.50%)      |  |  |
| occurrences (all)                               | 94                     |  |  |
| Dysphagia                                       |                        |  |  |
| subjects affected / exposed                     | 54 / 1066 (5.07%)      |  |  |
| occurrences (all)                               | 69                     |  |  |
| Nausea                                          |                        |  |  |
| subjects affected / exposed                     | 603 / 1066<br>(56.57%) |  |  |
| occurrences (all)                               | 1074                   |  |  |
| Vomiting                                        |                        |  |  |
| subjects affected / exposed                     | 564 / 1066<br>(52.91%) |  |  |
| occurrences (all)                               | 1223                   |  |  |
| Skin and subcutaneous tissue disorders          |                        |  |  |
| Alopecia                                        |                        |  |  |
| subjects affected / exposed                     | 67 / 1066 (6.29%)      |  |  |
| occurrences (all)                               | 75                     |  |  |
| Pruritus                                        |                        |  |  |
| subjects affected / exposed                     | 84 / 1066 (7.88%)      |  |  |
| occurrences (all)                               | 103                    |  |  |
| Rash                                            |                        |  |  |
| subjects affected / exposed                     | 132 / 1066<br>(12.38%) |  |  |
| occurrences (all)                               | 170                    |  |  |
| Musculoskeletal and connective tissue disorders |                        |  |  |
| Arthralgia                                      |                        |  |  |
| subjects affected / exposed                     | 129 / 1066<br>(12.10%) |  |  |
| occurrences (all)                               | 184                    |  |  |
| Back pain                                       |                        |  |  |
| subjects affected / exposed                     | 184 / 1066<br>(17.26%) |  |  |
| occurrences (all)                               | 245                    |  |  |

|                                                                                       |                               |  |  |
|---------------------------------------------------------------------------------------|-------------------------------|--|--|
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)                     | 79 / 1066 (7.41%)<br>103      |  |  |
| Muscular weakness<br>subjects affected / exposed<br>occurrences (all)                 | 57 / 1066 (5.35%)<br>71       |  |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)                 | 73 / 1066 (6.85%)<br>84       |  |  |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)              | 137 / 1066<br>(12.85%)<br>182 |  |  |
| Infections and infestations                                                           |                               |  |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                   | 114 / 1066<br>(10.69%)<br>185 |  |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 142 / 1066<br>(13.32%)<br>227 |  |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)           | 62 / 1066 (5.82%)<br>86       |  |  |
| Metabolism and nutrition disorders                                                    |                               |  |  |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)                    | 55 / 1066 (5.16%)<br>107      |  |  |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)                | 324 / 1066<br>(30.39%)<br>494 |  |  |
| Hypoalbuminaemia<br>subjects affected / exposed<br>occurrences (all)                  | 96 / 1066 (9.01%)<br>219      |  |  |
| Hypocalcaemia<br>subjects affected / exposed<br>occurrences (all)                     | 96 / 1066 (9.01%)<br>194      |  |  |
| Hypokalaemia                                                                          |                               |  |  |

|                             |                   |  |  |
|-----------------------------|-------------------|--|--|
| subjects affected / exposed | 77 / 1066 (7.22%) |  |  |
| occurrences (all)           | 129               |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 12 August 2009    | Participants who were ineligible to enroll in Study A8081007 because they were treated with docetaxel as part of their platinum-based prior chemotherapy, yet had NSCLC that was predominantly squamous-cell carcinoma, and thus, were not eligible to be dosed with pemetrexed, were allowed to enroll in this study.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 27 August 2009    | The RECIST version was modified to Version 1.1, and participants with spinal cord compression, carcinomatous meningitis, or leptomeningeal disease were no longer excluded.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 21 December 2009  | The NCI CTCAE version was modified to version 4.0, the primary endpoint was modified to add safety as a co-primary endpoint, timing of tumor measurements was modified from a per cycle basis to a calendar basis, and the administration of crizotinib was allowed to be administered without regards to meals.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 22 June 2010      | The patient-reported VSAQ-ALK was included, additional ECG monitoring was added for participants with QTc >500 msec, modifications of the eligibility criteria (which included cutoffs for hemoglobin and platelet counts) were included, washout period for cardiovascular (CV) or cerebrovascular events was decreased, hypertension exclusion criteria was deleted, all available scans were required to be reviewed by a third-party radiology laboratory, a treatment delay to up to 42 days without requiring discontinuation was now allowed; and metabolites of crizotinib were to be evaluated, if possible.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 05 August 2010    | Additional safety monitoring for the potential AEs of pneumonitis were added and an exclusion criterion to exclude patients with known interstitial fibrosis or interstitial lung disease was added.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 12 January 2011   | Entry criteria changed to allow A8081007 eligible participants to enroll into this protocol once enrollment is closed in a specific country and approved by a site's IRB/IEC. Other entry criteria changed or updated: non-measurable disease now allowed, washout for palliative radiation changed, criteria for known brain metastases clarified, other ALK testing may be allowed after Sponsor review and approval. ECG substudy was added; sample size increased; dose modifications for PF-02341066 updated; PK analysis updated; endpoint descriptions updated; safety guidelines for potential cases of drug-induced liver injury added.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 21 September 2011 | Increase the number of participants to 800 in order to better evaluate possible genetic associations in patients with significant toxicities, especially those related to liver and kidney. Study objective and related endpoint for evaluation of pharmacogenetic markers of adverse hepatic and renal drug reactions were added. Monitoring guidance for the potential adverse hepatic and renal drug reactions were added. Entry criteria changed or updated: entry of participants with ALT/AST abnormalities expanded to x 5 ULN after agreement with Sponsor; entry of participants ineligible for Study A8081007 allowed if due to ECOG PS; once enrollment of the phase 3 A8081007 is closed, entry of participants receiving only one prior treatment for advanced NSCLC allowed. Dose administration modality as a oral solution allowed in participants unable to swallow the tablets, with agreement by the Sponsor. Visit frequency reduced for participants on study after 10 cycles; PK sampling collection not required any longer in participants newly enrolled; follow-up of visual symptoms, if present at end of treatment, added. Text modified is some sections following compliance with the Sponsor protocol template. |

|                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 26 April 2012    | The total number of participants enrolled was revised to manage country-specific regulatory requirements. Entry criteria changed to allow participants from the comparator arm of study A8081007 to enroll into this protocol once the study A8081007 has met the primary endpoint. Background safety information was updated. Dose modification rules were revised based on the updated safety information. Required imaging frequency was clarified. PK sampling collection required for ECG subgroup participants was clarified. Adverse event guidelines were updated to be consistent with Sponsor standards. Editing errors from prior Amendment were rectified.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 18 December 2012 | Inclusion criterion and related language elsewhere was modified to comply with the FDA requirement for all participants in the chemotherapy arm of Study A8081007 to have disease progression confirmed by independent radiology review (IRR) before they are allowed to cross over to receive crizotinib on Study A8081005. Detailed description of participants of childbearing potential language as an inclusion criterion and detailed contraception guidelines were introduced to ensure consistency with updated Pfizer protocol template. Text was added or replaced to ensure consistency with updated Pfizer protocol template language especially with respect to medication error, and serious adverse event reporting for Oncology studies after the active safety reporting period was clarified. Use of prophylactic antiemetics, prohibited medications by topical administration, and concomitant acetaminophen/paracetamol was clarified. Pregnancy testing in response to IRBs/IECs and/or local regulations was clarified. Reporting of local cardiologist manual ECG overread was clarified. Requirements for data retention were revised in consistency with the updated Pfizer protocol template language. Corrections of typographical errors and other administrative inconsistencies were made throughout the protocol. |
| 26 November 2014 | Blood samples for hematology and blood chemistries will now be collected also during the non-visit cycles after Cycle 10 to ensure consistency with the Investigator's Brochure. Dose modification and adverse event management guidances were revised for QTc prolongation, bradycardia, and pneumonitis based on the updated safety information for PF-02341066. Reduced Schedule of Activities was introduced for participants still ongoing after the Primary Completion Date. Text was added or replaced to ensure consistency with updated Pfizer protocol template language, especially with respect to contraception guidelines, pregnancy testing, and serious adverse event reporting for Oncology studies after permanent discontinuation of PF- 02341066 treatment. Corrections of typographical errors and other administrative inconsistencies were made throughout the protocol.                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

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

Pharmacogenetic analysis of renal adverse events was not performed as no gene alleles have been identified with sufficient supportive data establishing an association with renal toxicity to support a case-control candidate gene assessment.

Notes: