

**Clinical trial results:****A phase II, multicenter, single-arm study of oral LDK378 in crizotinib naïve adult patients with ALK-activated non-small cell lung cancer****Summary**

|                          |                      |
|--------------------------|----------------------|
| EudraCT number           | 2012-003474-36       |
| Trial protocol           | IT ES GB SE DE NO BE |
| Global end of trial date | 22 January 2018      |

**Results information**

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 07 February 2019 |
| First version publication date | 07 February 2019 |

**Trial information****Trial identification**

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CLDK378A2203 |
|-----------------------|--------------|

**Additional study identifiers**

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01685138 |
| WHO universal trial number (UTN)   | -           |

Notes:

**Sponsors**

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Novartis Pharma, AG   |
| Sponsor organisation address | CH-4002, Basel, Switzerland,  |
| Public contact               | Clinical Disclosure Office, Novartis Parma, AG, +41 613241111, novartis.email@novartis.com  |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma, AG, +41 613241111, novartis.email@novartis.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                       | 22 January 2018 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 22 January 2018 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate the antitumor activity of ceritinib, as measured by overall response rate (ORR) by Investigator assessment.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 20 December 2012 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | France: 1              |
| Country: Number of subjects enrolled | Australia: 3           |
| Country: Number of subjects enrolled | Belgium: 3             |
| Country: Number of subjects enrolled | Hong Kong: 3           |
| Country: Number of subjects enrolled | Italy: 8               |
| Country: Number of subjects enrolled | Japan: 19              |
| Country: Number of subjects enrolled | Korea, Republic of: 18 |
| Country: Number of subjects enrolled | New Zealand: 5         |
| Country: Number of subjects enrolled | Norway: 2              |
| Country: Number of subjects enrolled | Russian Federation: 15 |
| Country: Number of subjects enrolled | Singapore: 4           |
| Country: Number of subjects enrolled | Spain: 13              |
| Country: Number of subjects enrolled | Sweden: 3              |
| Country: Number of subjects enrolled | Taiwan: 22             |
| Country: Number of subjects enrolled | Thailand: 3            |
| Country: Number of subjects enrolled | United States: 2       |
| Worldwide total number of subjects   | 124                    |
| EEA total number of subjects         | 30                     |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| 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)                      | 94 |
| From 65 to 84 years                       | 30 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Approximately 105 patients were planned to be enrolled. A total of 124 patients were enrolled and treated with ceritinib.

### Pre-assignment

Screening details:

Approximately 105 patients were planned to be enrolled. A total of 124 patients were enrolled and treated with ceritinib.

### Period 1

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

### Arms

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | LDK378 (Ceritinib) |
|------------------|--------------------|

Arm description:

Participants on this arm took oral LDK378 750 mg once daily.

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Ceritinib     |
| Investigational medicinal product code | LDK378        |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

Dosage and administration details:

Ceritinib/LDK378 was supplied as 150 mg hard gelatin capsules and administered orally, once-daily at a dose of 750 mg on a continuous dosing schedule (5 x 150 mg capsules).

| <b>Number of subjects in period 1</b> | LDK378 (Ceritinib) |
|---------------------------------------|--------------------|
| Started                               | 124                |
| Discontinued from treatment phase     | 124                |
| Entered post-treatment efficacy f/up  | 10 <sup>[1]</sup>  |
| Entered survival follow-up            | 63                 |
| Discontinued from study               | 51                 |
| Completed                             | 32                 |
| Not completed                         | 92                 |
| Adverse event, serious fatal          | 10                 |
| Physician decision                    | 6                  |
| Adverse event, non-fatal              | 18                 |
| Lost to follow-up                     | 1                  |
| Progressive disease                   | 53                 |
| No longer requires treatment          | 1                  |

|                           |   |
|---------------------------|---|
| Subject/guardian decision | 2 |
| Protocol deviation        | 1 |

---

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Subjects dropped off at various time points during the course of the study.

## Baseline characteristics

### Reporting groups

Reporting group title LDK378 (Ceritinib)

Reporting group description:

Participants on this arm took oral LDK378 750 mg once daily.

| Reporting group values                        | LDK378 (Ceritinib) | Total |  |
|---|--------------------|-------|--|
| Number of subjects                            | 124                | 124   |  |
| Age categorical<br>Units: Subjects            |                    |       |  |
| Adults (18-64 years)                          | 94                 | 94    |  |
| From 65-84 years                              | 30                 | 30    |  |
| Age Continuous<br>Units: Years                |                    |       |  |
| arithmetic mean                               | 54.8               |       |  |
| standard deviation                            | ± 12.16            | -     |  |
| Sex: Female, Male<br>Units: Subjects          |                    |       |  |
| Female  | 74                 | 74    |  |
| Male  | 50                 | 50    |  |
| Race/Ethnicity, Customized<br>Units: Subjects |                    |       |  |
| Asian   | 74                 | 74    |  |
| Caucasian                                     | 48                 | 48    |  |
| Black   | 1                  | 1     |  |
| Other   | 1                  | 1     |  |

## End points

### End points reporting groups

|  |                    |
|--|--------------------|
| Reporting group title  | LDK378 (Ceritinib) |
| Reporting group description:<br>Participants on this arm took oral LDK378 750 mg once daily. |                    |

### Primary: Overall response rate (ORR) by Investigator assessment

|  |   |
|--|---|
| End point title  | Overall response rate (ORR) by Investigator assessment <sup>[1]</sup> |
| End point description:<br>ORR per RECIST 1.1 calculated as the percentage of participants with a best overall response (BOR) defined as complete response (CR) or partial response (PR) as assessed by the investigator.<br>CR: Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm. PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters. |   |
| End point type   | Primary   |
| End point timeframe:<br>every 8 weeks (i.e. every 2 cycles; cycle = 28 days), starting from the first day of treatment with LDK378 until permanent discontinuation of study drug   |   |

Notes:

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

Justification: No statistical analysis was planned for this endpoint

|                                   |                     |  |  |  |
|-----------------------------------|---------------------|--|--|--|
| <b>End point values</b>           | LDK378 (Ceritinib)  |  |  |  |
| Subject group type                | Reporting group     |  |  |  |
| Number of subjects analysed       | 124                 |  |  |  |
| Units: Percentage of participants |                     |  |  |  |
| number (confidence interval 95%)  | 67.7 (58.8 to 75.9) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: ORR by Blinded Independent Review Committee (BIRC)

|   |  |
|---|--|
| End point title   | ORR by Blinded Independent Review Committee (BIRC) |
| End point description:<br>ORR per RECIST 1.1 calculated as the percentage of participants with a best overall response (BOR) defined as complete response (CR) or partial response (PR) as assessed by the BIRC. CR: Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm. PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters. |  |
| End point type  | Secondary  |
| End point timeframe:<br>every 8 weeks (i.e. every 2 cycles; cycle = 28 days), starting from the first day of treatment with LDK378 until permanent discontinuation of study drug  |  |

|                                   |                        |  |  |  |
|-----------------------------------|------------------------|--|--|--|
| <b>End point values</b>           | LDK378<br>(Ceritinib)  |  |  |  |
| Subject group type                | Reporting group        |  |  |  |
| Number of subjects analysed       | 124                    |  |  |  |
| Units: Percentage of participants |                        |  |  |  |
| number (confidence interval 95%)  | 63.7 (54.6 to<br>72.2) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of response (DOR) as per Investigator

|   |  |
|---|--|
| End point title   | Duration of response (DOR) as per Investigator |
| End point description:  |  |
| DOR, calculated as the time from the date of the first documented CR or PR to the first documented progression or death due to any cause, by investigator assessment per RECIST 1.1. CR: Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm. PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters. |  |
| End point type  | Secondary                                      |
| End point timeframe:  |  |
| every 8 weeks (i.e. every 2 cycles; cycle = 28 days), starting from the first day of treatment with LDK378 until permanent discontinuation of study drug  |  |

|                                  |                        |  |  |  |
|----------------------------------|------------------------|--|--|--|
| <b>End point values</b>          | LDK378<br>(Ceritinib)  |  |  |  |
| Subject group type               | Reporting group        |  |  |  |
| Number of subjects analysed      | 84                     |  |  |  |
| Units: Months                    |                        |  |  |  |
| median (confidence interval 95%) | 24.0 (14.8 to<br>37.5) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of response (DOR) as per BIRC

|  |  |
|--|--|
| End point title  | Duration of response (DOR) as per BIRC |
| End point description:   |  |
| DOR, calculated as the time from the date of the first documented CR or PR to the first documented progression or death due to any cause, by BIRC assessment per RECIST 1.1. CR: Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 |  |

mm. PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters. Discontinuation: permanent discontinuation of study drug for patients who experienced progressive disease (PD), or until PD was assessed by investigator if patients discontinued in the absence of PD.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| every 8 weeks (i.e. every 2 cycles; cycle = 28 days), starting from the first day of treatment with LDK378 until permanent discontinuation of study drug |           |

|                                  |                       |  |  |  |
|----------------------------------|-----------------------|--|--|--|
| <b>End point values</b>          | LDK378<br>(Ceritinib) |  |  |  |
| Subject group type               | Reporting group       |  |  |  |
| Number of subjects analysed      | 79                    |  |  |  |
| Units: Months                    |                       |  |  |  |
| median (confidence interval 95%) | 27.3 (16.6 to 44.3)   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Disease Control Rate (DCR) as per Investigator and BIRC

|  |   |  |  |  |
|--|---|--|--|--|
| End point title  | Disease Control Rate (DCR) as per Investigator and BIRC |  |  |  |
| End point description:   |   |  |  |  |
| DCR per RECIST 1.1 is percentage of participants with best overall response of CR, PR, stable disease (SD) or Non-CR/Non-PD as per Investigator and BIRC. CR: Disappearance of all non-nodal target lesions. Also, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm. PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters. SD: Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions that would qualify for PD. PD: At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm. |   |  |  |  |
| End point type   | Secondary   |  |  |  |
| End point timeframe:   |   |  |  |  |
| every 8 weeks (i.e. every 2 cycles; cycle = 28 days), starting from the first day of treatment with LDK378 until permanent discontinuation of study drug   |   |  |  |  |

|                                   |                       |  |  |  |
|-----------------------------------|-----------------------|--|--|--|
| <b>End point values</b>           | LDK378<br>(Ceritinib) |  |  |  |
| Subject group type                | Reporting group       |  |  |  |
| Number of subjects analysed       | 124                   |  |  |  |
| Units: Percentage of participants |                       |  |  |  |
| number (confidence interval 95%)  |                       |  |  |  |
| DCR per Investigator              | 90.3 (83.7 to 94.9)   |  |  |  |
| DCR per BIRC                      | 86.3 (79.0 to 91.8)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Response (TTR) as per Investigator

|                 |  |
|-----------------|--|
| End point title | Time to Response (TTR) as per Investigator |
|-----------------|--|

End point description:

TTR, calculated as the time from first dose of LDK378 to first documented response (CR+PR), by investigator assessment. This was only on participants with confirmed CR or PR. CR: Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm. PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.

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

End point timeframe:

every 8 weeks (i.e. every 2 cycles; cycle = 28 days), starting from the first day of treatment with LDK378 until permanent discontinuation of study drug

| End point values                     | LDK378 (Ceritinib) |  |  |  |
|--------------------------------------|--------------------|--|--|--|
| Subject group type                   | Reporting group    |  |  |  |
| Number of subjects analysed          | 84                 |  |  |  |
| Units: Months                        |                    |  |  |  |
| arithmetic mean (standard deviation) | 2.5 (± 2.66)       |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Response (TTR) as per BIRC

|                 |                                    |
|-----------------|------------------------------------|
| End point title | Time to Response (TTR) as per BIRC |
|-----------------|------------------------------------|

End point description:

TTR, calculated as the time from first dose of LDK378 to first documented response (CR+PR), by BIRC assessment. This was only on participants with confirmed CR or PR. CR: Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm. PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.

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

End point timeframe:

every 8 weeks (i.e. every 2 cycles; cycle = 28 days), starting from the first day of treatment with LDK378 until permanent discontinuation of study drug

|                                      |                       |  |  |  |
|--------------------------------------|-----------------------|--|--|--|
| <b>End point values</b>              | LDK378<br>(Ceritinib) |  |  |  |
| Subject group type                   | Reporting group       |  |  |  |
| Number of subjects analysed          | 79                    |  |  |  |
| Units: Months                        |                       |  |  |  |
| arithmetic mean (standard deviation) | 2.2 ( $\pm$ 1.22)     |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall intracranial response rate (OIRR) as per Investigator

|                 |   |
|-----------------|---|
| End point title | Overall intracranial response rate (OIRR) as per Investigator |
|-----------------|---|

End point description:

OIRR calculated as the ORR (CR+PR) of lesions in the brain for patients who have measurable disease in the brain at baseline by investigator.

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

End point timeframe:

every 8 weeks (i.e. every 2 cycles; cycle = 28 days), starting from the first day of treatment with LDK378 until permanent discontinuation of study drug

|                                   |                       |  |  |  |
|-----------------------------------|-----------------------|--|--|--|
| <b>End point values</b>           | LDK378<br>(Ceritinib) |  |  |  |
| Subject group type                | Reporting group       |  |  |  |
| Number of subjects analysed       | 10                    |  |  |  |
| Units: Percentage of participants |                       |  |  |  |
| number (confidence interval 95%)  | 20.0 (2.5 to 55.6)    |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall intracranial response rate (OIRR) as per BIRC

|                 |   |
|-----------------|---|
| End point title | Overall intracranial response rate (OIRR) as per BIRC |
|-----------------|---|

End point description:

OIRR calculated as the ORR (CR+PR) of lesions in the brain for patients who have measurable disease in the brain at baseline by BIRC.

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

End point timeframe:

every 8 weeks (i.e. every 2 cycles; cycle = 28 days), starting from the first day of treatment with LDK378 until permanent discontinuation of study drug

|                                   |                       |  |  |  |
|-----------------------------------|-----------------------|--|--|--|
| <b>End point values</b>           | LDK378<br>(Ceritinib) |  |  |  |
| Subject group type                | Reporting group       |  |  |  |
| Number of subjects analysed       | 13                    |  |  |  |
| Units: Percentage of participants |                       |  |  |  |
| number (confidence interval 95%)  | 61.5 (31.6 to 86.1)   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression-free survival (PFS) as per Investigator and BIRC

|                 |  |
|-----------------|--|
| End point title | Progression-free survival (PFS) as per Investigator and BIRC |
|-----------------|--|

End point description:

PFS, defined as time from first dose of LDK378 to progression or death due to any cause, as assessed by investigator and BIRC assessment

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

End point timeframe:

every 8 weeks (i.e. every 2 cycles; cycle = 28 days), starting from the first day of treatment with LDK378 until permanent discontinuation of study drug

|                                  |                       |  |  |  |
|----------------------------------|-----------------------|--|--|--|
| <b>End point values</b>          | LDK378<br>(Ceritinib) |  |  |  |
| Subject group type               | Reporting group       |  |  |  |
| Number of subjects analysed      | 124                   |  |  |  |
| Units: Months                    |                       |  |  |  |
| median (confidence interval 95%) |                       |  |  |  |
| PFS per Investigator             | 16.6 (11.0 to 23.2)   |  |  |  |
| PFS per BIRC                     | 19.4 (10.9 to 29.3)   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall survival (OS)

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

End point description:

OS, defined as time from first dose of LDK378 to death due to any cause

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

---

End point timeframe:

Time from the date of first dose of LDK378 to the date of death due to any cause up to 5 years

---

|                                  |                        |  |  |  |
|----------------------------------|------------------------|--|--|--|
| <b>End point values</b>          | LDK378<br>(Ceritinib)  |  |  |  |
| Subject group type               | Reporting group        |  |  |  |
| Number of subjects analysed      | 124                    |  |  |  |
| Units: Months                    |                        |  |  |  |
| median (confidence interval 95%) | 51.3 (42.7 to<br>55.3) |  |  |  |

---

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse Events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 20.1   |

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | LDK378 750 mg |
|-----------------------|---------------|

Reporting group description:

LDK378 750 mg

| Reporting group title   | LDK378 750 mg     |  |  |
|---|-------------------|--|--|
| <b>Serious adverse events</b>                                       | LDK378 750 mg     |  |  |
| Total subjects affected by serious adverse events                   |                   |  |  |
| subjects affected / exposed   | 50 / 124 (40.32%) |  |  |
| number of deaths (all causes)                                       | 56                |  |  |
| number of deaths resulting from adverse events                      | 1                 |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |  |  |
| Brain neoplasm  |                   |  |  |
| subjects affected / exposed   | 1 / 124 (0.81%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1             |  |  |
| deaths causally related to treatment / all                          | 0 / 0             |  |  |
| Chordoma  |                   |  |  |
| subjects affected / exposed   | 1 / 124 (0.81%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1             |  |  |
| deaths causally related to treatment / all                          | 0 / 0             |  |  |
| Metastases to central nervous system                                |                   |  |  |
| subjects affected / exposed   | 1 / 124 (0.81%)   |  |  |
| 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                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Fatigue   |                 |  |  |
| subjects affected / exposed                     | 2 / 124 (1.61%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pain  |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pyrexia   |                 |  |  |
| subjects affected / exposed                     | 2 / 124 (1.61%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Acute pulmonary oedema                          |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Dyspnoea  |                 |  |  |
| subjects affected / exposed                     | 3 / 124 (2.42%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pleural effusion                                |                 |  |  |
| subjects affected / exposed                     | 2 / 124 (1.61%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pleurisy  |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Pneumonia aspiration                            |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Pneumothorax                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pulmonary embolism                              |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pulmonary oedema                                |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory failure                             |                 |  |  |
| subjects affected / exposed                     | 2 / 124 (1.61%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Psychiatric disorders                           |                 |  |  |
| Depression                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Investigations                                  |                 |  |  |
| Alanine aminotransferase increased              |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Weight decreased                                |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Injury, poisoning and procedural complications  |                 |  |  |
| Fall  |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Joint dislocation                               |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Radiation oesophagitis                          |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Toxicity to various agents                      |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Tracheal haemorrhage                            |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Congenital, familial and genetic disorders      |                 |  |  |
| Tracheo-oesophageal fistula                     |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac disorders                               |                 |  |  |
| Cardiac tamponade                               |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Pericardial effusion                            |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Pericarditis                                    |                 |  |  |
| subjects affected / exposed                     | 4 / 124 (3.23%) |  |  |
| occurrences causally related to treatment / all | 4 / 4           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nervous system disorders                        |                 |  |  |
| Altered state of consciousness                  |                 |  |  |
| subjects affected / exposed                     | 2 / 124 (1.61%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 1 / 1           |  |  |
| Cognitive disorder                              |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Dizziness                                       |                 |  |  |
| subjects affected / exposed                     | 3 / 124 (2.42%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Encephalopathy                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Headache  |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Parkinson's disease                             |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Partial seizures                                |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Radicular pain</b>                           |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Seizure</b>                                  |                 |  |  |
| subjects affected / exposed                     | 2 / 124 (1.61%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Blood and lymphatic system disorders</b>     |                 |  |  |
| <b>Neutropenia</b>                              |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Ear and labyrinth disorders</b>              |                 |  |  |
| <b>Vertigo</b>                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Eye disorders</b>                            |                 |  |  |
| <b>Cataract</b>                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Gastrointestinal disorders</b>               |                 |  |  |
| <b>Abdominal pain</b>                           |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Anal inflammation</b>                        |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Diarrhoea</b>                                |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Faecaloma</b>                                |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Nausea</b>                                   |                 |  |  |
| subjects affected / exposed                     | 5 / 124 (4.03%) |  |  |
| occurrences causally related to treatment / all | 4 / 5           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Oesophageal stenosis</b>                     |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Pancreatitis</b>                             |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Stomatitis</b>                               |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Vomiting</b>                                 |                 |  |  |
| subjects affected / exposed                     | 3 / 124 (2.42%) |  |  |
| occurrences causally related to treatment / all | 2 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Hepatobiliary disorders</b>                  |                 |  |  |
| Hepatitis                                       |                 |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                            | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all        | 0 / 1           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Endocrine disorders</b>                             |                 |  |  |
| <b>Adrenal insufficiency</b>                           |                 |  |  |
| subjects affected / exposed                            | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all        | 0 / 1           |  |  |
| deaths causally related to treatment / all             | 0 / 1           |  |  |
| <b>Musculoskeletal and connective tissue disorders</b> |                 |  |  |
| <b>Arthralgia</b>                                      |                 |  |  |
| subjects affected / exposed                            | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all        | 0 / 1           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Back pain</b>                                       |                 |  |  |
| subjects affected / exposed                            | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all        | 0 / 1           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Bone pain</b>                                       |                 |  |  |
| subjects affected / exposed                            | 2 / 124 (1.61%) |  |  |
| occurrences causally related to treatment / all        | 0 / 2           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Muscular weakness</b>                               |                 |  |  |
| subjects affected / exposed                            | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all        | 0 / 1           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Infections and infestations</b>                     |                 |  |  |
| <b>Appendicitis</b>                                    |                 |  |  |
| subjects affected / exposed                            | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all        | 0 / 1           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Atypical pneumonia</b>                              |                 |  |  |
| subjects affected / exposed                            | 2 / 124 (1.61%) |  |  |
| occurrences causally related to treatment / all        | 0 / 2           |  |  |
| deaths causally related to treatment / all             | 0 / 1           |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| Bronchitis                                      |                 |  |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Epididymitis                                    |                 |  |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Escherichia bacteraemia                         |                 |  |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Infection                                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Lower respiratory tract infection               |                 |  |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Lung infection                                  |                 |  |  |  |
| subjects affected / exposed                     | 4 / 124 (3.23%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 4           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Nosocomial infection                            |                 |  |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Parvovirus infection                            |                 |  |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pneumocystis jirovecii pneumonia                |                 |  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Pneumonia</b>                                |                 |  |  |
| subjects affected / exposed                     | 5 / 124 (4.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 6           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Post procedural infection</b>                |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Respiratory tract infection</b>              |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Sepsis</b>                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Sinusitis</b>                                |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Metabolism and nutrition disorders</b>       |                 |  |  |
| <b>Dehydration</b>                              |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Diabetes mellitus</b>                        |                 |  |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Diabetic ketosis</b>                         |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 124 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hyperglycaemia                                  |                 |  |  |
| subjects affected / exposed                     | 3 / 124 (2.42%) |  |  |
| occurrences causally related to treatment / all | 1 / 4           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

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

|   |                    |  |  |
|---|--------------------|--|--|
| <b>Non-serious adverse events</b>                     | LDK378 750 mg      |  |  |
| Total subjects affected by non-serious adverse events |                    |  |  |
| subjects affected / exposed                           | 123 / 124 (99.19%) |  |  |
| Investigations  |                    |  |  |
| Alanine aminotransferase increased                    |                    |  |  |
| subjects affected / exposed                           | 65 / 124 (52.42%)  |  |  |
| occurrences (all)                                     | 144                |  |  |
| Amylase increased                                     |                    |  |  |
| subjects affected / exposed                           | 14 / 124 (11.29%)  |  |  |
| occurrences (all)                                     | 20                 |  |  |
| Aspartate aminotransferase increased                  |                    |  |  |
| subjects affected / exposed                           | 58 / 124 (46.77%)  |  |  |
| occurrences (all)                                     | 105                |  |  |
| Blood alkaline phosphatase increased                  |                    |  |  |
| subjects affected / exposed                           | 29 / 124 (23.39%)  |  |  |
| occurrences (all)                                     | 34                 |  |  |
| Blood creatinine increased                            |                    |  |  |
| subjects affected / exposed                           | 33 / 124 (26.61%)  |  |  |
| occurrences (all)                                     | 67                 |  |  |
| Creatinine renal clearance decreased                  |                    |  |  |
| subjects affected / exposed                           | 8 / 124 (6.45%)    |  |  |
| occurrences (all)                                     | 13                 |  |  |
| Electrocardiogram QT prolonged                        |                    |  |  |
| subjects affected / exposed                           | 20 / 124 (16.13%)  |  |  |
| occurrences (all)                                     | 44                 |  |  |

|  |                   |  |  |
|--|-------------------|--|--|
| Gamma-glutamyltransferase increased                  |                   |  |  |
| subjects affected / exposed                          | 36 / 124 (29.03%) |  |  |
| occurrences (all)                                    | 49                |  |  |
| Lipase increased                                     |                   |  |  |
| subjects affected / exposed                          | 9 / 124 (7.26%)   |  |  |
| occurrences (all)                                    | 16                |  |  |
| Weight decreased                                     |                   |  |  |
| subjects affected / exposed                          | 47 / 124 (37.90%) |  |  |
| occurrences (all)                                    | 58                |  |  |
| Weight increased                                     |                   |  |  |
| subjects affected / exposed                          | 8 / 124 (6.45%)   |  |  |
| occurrences (all)                                    | 8                 |  |  |
| White blood cell count decreased                     |                   |  |  |
| subjects affected / exposed                          | 9 / 124 (7.26%)   |  |  |
| occurrences (all)                                    | 16                |  |  |
| Nervous system disorders                             |                   |  |  |
| Dizziness  |                   |  |  |
| subjects affected / exposed                          | 21 / 124 (16.94%) |  |  |
| occurrences (all)                                    | 28                |  |  |
| Headache   |                   |  |  |
| subjects affected / exposed                          | 31 / 124 (25.00%) |  |  |
| occurrences (all)                                    | 52                |  |  |
| Paraesthesia   |                   |  |  |
| subjects affected / exposed                          | 8 / 124 (6.45%)   |  |  |
| occurrences (all)                                    | 8                 |  |  |
| Blood and lymphatic system disorders                 |                   |  |  |
| Anaemia  |                   |  |  |
| subjects affected / exposed                          | 13 / 124 (10.48%) |  |  |
| occurrences (all)                                    | 18                |  |  |
| Neutropenia  |                   |  |  |
| subjects affected / exposed                          | 11 / 124 (8.87%)  |  |  |
| occurrences (all)                                    | 23                |  |  |
| General disorders and administration site conditions |                   |  |  |
| Asthenia   |                   |  |  |
| subjects affected / exposed                          | 19 / 124 (15.32%) |  |  |
| occurrences (all)                                    | 27                |  |  |

|                             |                    |  |  |
|-----------------------------|--------------------|--|--|
| Chest discomfort            |                    |  |  |
| subjects affected / exposed | 9 / 124 (7.26%)    |  |  |
| occurrences (all)           | 12                 |  |  |
| Fatigue                     |                    |  |  |
| subjects affected / exposed | 47 / 124 (37.90%)  |  |  |
| occurrences (all)           | 69                 |  |  |
| Malaise                     |                    |  |  |
| subjects affected / exposed | 9 / 124 (7.26%)    |  |  |
| occurrences (all)           | 14                 |  |  |
| Non-cardiac chest pain      |                    |  |  |
| subjects affected / exposed | 19 / 124 (15.32%)  |  |  |
| occurrences (all)           | 25                 |  |  |
| Pyrexia                     |                    |  |  |
| subjects affected / exposed | 23 / 124 (18.55%)  |  |  |
| occurrences (all)           | 38                 |  |  |
| Gastrointestinal disorders  |                    |  |  |
| Abdominal distension        |                    |  |  |
| subjects affected / exposed | 7 / 124 (5.65%)    |  |  |
| occurrences (all)           | 8                  |  |  |
| Abdominal pain              |                    |  |  |
| subjects affected / exposed | 51 / 124 (41.13%)  |  |  |
| occurrences (all)           | 73                 |  |  |
| Abdominal pain upper        |                    |  |  |
| subjects affected / exposed | 19 / 124 (15.32%)  |  |  |
| occurrences (all)           | 23                 |  |  |
| Constipation                |                    |  |  |
| subjects affected / exposed | 35 / 124 (28.23%)  |  |  |
| occurrences (all)           | 42                 |  |  |
| Diarrhoea                   |                    |  |  |
| subjects affected / exposed | 106 / 124 (85.48%) |  |  |
| occurrences (all)           | 370                |  |  |
| Dyspepsia                   |                    |  |  |
| subjects affected / exposed | 15 / 124 (12.10%)  |  |  |
| occurrences (all)           | 16                 |  |  |
| Gastrointestinal pain       |                    |  |  |

|  |                          |  |  |
|--|--------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                       | 9 / 124 (7.26%)<br>14    |  |  |
| Haemorrhoids<br>subjects affected / exposed<br>occurrences (all)       | 7 / 124 (5.65%)<br>7     |  |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)             | 97 / 124 (78.23%)<br>163 |  |  |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)         | 14 / 124 (11.29%)<br>16  |  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)           | 89 / 124 (71.77%)<br>199 |  |  |
| Respiratory, thoracic and mediastinal disorders                        |                          |  |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)              | 29 / 124 (23.39%)<br>50  |  |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)           | 31 / 124 (25.00%)<br>40  |  |  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all) | 8 / 124 (6.45%)<br>11    |  |  |
| Productive cough<br>subjects affected / exposed<br>occurrences (all)   | 15 / 124 (12.10%)<br>24  |  |  |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)        | 9 / 124 (7.26%)<br>16    |  |  |
| Skin and subcutaneous tissue disorders                                 |                          |  |  |
| Dry skin<br>subjects affected / exposed<br>occurrences (all)           | 12 / 124 (9.68%)<br>12   |  |  |
| Pruritus   |                          |  |  |

|   |                         |  |  |
|---|-------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)  | 18 / 124 (14.52%)<br>25 |  |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)  | 28 / 124 (22.58%)<br>37 |  |  |
| Rash maculo-papular<br>subjects affected / exposed<br>occurrences (all)   | 7 / 124 (5.65%)<br>8    |  |  |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)                             | 11 / 124 (8.87%)<br>12  |  |  |
| Renal and urinary disorders<br>Dysuria<br>subjects affected / exposed<br>occurrences (all)                        | 7 / 124 (5.65%)<br>8    |  |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 25 / 124 (20.16%)<br>32 |  |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)   | 32 / 124 (25.81%)<br>37 |  |  |
| Bone pain<br>subjects affected / exposed<br>occurrences (all)   | 7 / 124 (5.65%)<br>7    |  |  |
| Muscular weakness<br>subjects affected / exposed<br>occurrences (all)   | 7 / 124 (5.65%)<br>8    |  |  |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)  | 21 / 124 (16.94%)<br>25 |  |  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)   | 8 / 124 (6.45%)<br>11   |  |  |
| Neck pain   |                         |  |  |

|  |                          |  |  |
|--|--------------------------|--|--|
| subjects affected / exposed<br>occurrences (all) | 9 / 124 (7.26%)<br>9     |  |  |
| <b>Infections and infestations</b>               |                          |  |  |
| <b>Influenza</b>                                 |                          |  |  |
| subjects affected / exposed<br>occurrences (all) | 8 / 124 (6.45%)<br>9     |  |  |
| <b>Nasopharyngitis</b>                           |                          |  |  |
| subjects affected / exposed<br>occurrences (all) | 18 / 124 (14.52%)<br>30  |  |  |
| <b>Pneumonia</b>                                 |                          |  |  |
| subjects affected / exposed<br>occurrences (all) | 8 / 124 (6.45%)<br>11    |  |  |
| <b>Upper respiratory tract infection</b>         |                          |  |  |
| subjects affected / exposed<br>occurrences (all) | 25 / 124 (20.16%)<br>41  |  |  |
| <b>Urinary tract infection</b>                   |                          |  |  |
| subjects affected / exposed<br>occurrences (all) | 10 / 124 (8.06%)<br>29   |  |  |
| <b>Metabolism and nutrition disorders</b>        |                          |  |  |
| <b>Decreased appetite</b>                        |                          |  |  |
| subjects affected / exposed<br>occurrences (all) | 69 / 124 (55.65%)<br>117 |  |  |
| <b>Hyperglycaemia</b>                            |                          |  |  |
| subjects affected / exposed<br>occurrences (all) | 15 / 124 (12.10%)<br>20  |  |  |
| <b>Hyperkalaemia</b>                             |                          |  |  |
| subjects affected / exposed<br>occurrences (all) | 7 / 124 (5.65%)<br>10    |  |  |
| <b>Hypokalaemia</b>                              |                          |  |  |
| subjects affected / exposed<br>occurrences (all) | 14 / 124 (11.29%)<br>28  |  |  |
| <b>Hyponatraemia</b>                             |                          |  |  |
| subjects affected / exposed<br>occurrences (all) | 7 / 124 (5.65%)<br>10    |  |  |
| <b>Hypophosphataemia</b>                         |                          |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 9 / 124 (7.26%) |  |  |
| occurrences (all)           | 21              |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date           | Amendment   |
|----------------|---|
| 27 March 2013  | <p>At the time this amendment was issued 5 patients had been screened for enrollment and 3 patients had been treated with ceritinib. The amendment reflected the availability of new toxicity data, addressed requests from health authorities, and clarified sections of the protocol where additional guidance was required:</p> <ul style="list-style-type: none"><li>•Addition of an ECG assessment for all patients 6 hours after first dose</li><li>•Provided general guidance on dose modification</li><li>•Provided guidance on dose modification in response to QTc prolongation</li><li>•Provided guidance for treatment of hypophosphatemia</li><li>•Clarified tumor sample collection requirements</li></ul>  |
| 27 August 2013 | <p>At the time this amendment was issued 57 patients had been screened for enrollment and 45 patients had been treated with ceritinib. The amendment addressed the availability of new safety data as represented in the latest Investigator Brochure and clarified sections of the protocol where additional guidance was required:</p> <ul style="list-style-type: none"><li>•Addition of a secondary endpoint of OIRR for patients with measurable brain lesions at baseline to conduct a preliminary assessment of ceritinib activity in the brain.</li><li>•Allowing pre-screening during prior chemotherapy treatment and prior to progression of disease.</li><li>•Allowing the enrolment of chemotherapy-naive patients to target the ALK-inhibitors-naive population regardless of previous chemotherapy.</li><li>•Update of safety data in the protocol and associated ICF to match the Investigator Brochure Edition 4 (released on 28-Jun-2013).</li><li>•An exclusion criterion for patients with pneumonitis was added. Further, dose-modification criteria were added for patients who experience pneumonitis during the course of the study.</li><li>•The definition of DOR was changed from time from first documented response (PR or CR) to the date of first documented disease progression or death due to underlying cancer to time from first documented response (PR or CR) to the date of first documented disease progression or death due to any cause. The change, was done due to a request from the FDA and is further justifiable given that in an advanced cancer study it is difficult to ascertain whether a death is due to underlying cancer.</li></ul> |
| 26 May 2015    | <p>As of the release date of this amendment, the recruitment had been completed. One hundred and thirty two patients were screened and 124 patients were treated with ceritinib. This amendment was implemented to include availability of new safety data as presented in the Investigator's Brochure and to clarify sections of the protocol where additional guidance was required:</p> <ul style="list-style-type: none"><li>•Updated safety data in the protocol to match the Investigator's Brochure Edition 7 (released on 12-Jun-2014). The associated Informed Consent Form (ICF) was also updated separately to this protocol</li><li>•Ceritinib dose modification and follow up of toxicities guidance was updated to handle elevations of pancreatic enzymes (lipase and/or amylase) based on available safety data. Pancreatic enzyme elevations (lipase and/or amylase) occurred in patients treated with ceritinib. Clinical data suggested that a small proportion (&lt;1%) of patients treated with ceritinib could develop clinical pancreatitis, and the causal role of ceritinib in these cases couldn't be ruled out. The protocol was amended to include additional dose modification and follow up monitoring language for patients who may experience this event.</li><li>•An evaluation of the anticipated benefits and risks were added to the protocol to comply with EU clinical trial regulations.</li><li>•Sections related to study discontinuation were revised to bring clarification and provide additional guidance regarding study treatment discontinuation and withdrawal of consent.</li></ul>   |

|                  |   |
|------------------|---|
| 11 December 2015 | As of the release date of this amendment, the recruitment had been completed. In all, 132 patients were screened and 124 patients were treated with ceritinib. The amendment reflected the availability of new safety data, and updated sections of the protocol where additional guidance was required: <ul style="list-style-type: none"><li>•Protocol was updated to include follow up evaluations for hepatic toxicities and management guidelines for potential drug induced liver injury (DILI) cases in order to optimize patient safety.</li><li>•Dose guidance modification for QTcF text was updated to provide clarification on monitoring procedure.</li><li>•Updated the guidance related to corticosteroid use</li><li>•Updated of the definition of the End of Study</li></ul> |
|------------------|---|

Notes:

---

### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported