



## Clinical trial results:

**A phase II, multi-center, open-label study of AUY922 administered i.v. on a once weekly schedule in patients with advanced non-small-cell lung cancer (NSCLC) who have received at least two lines of prior chemotherapy.**

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

## Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2010-020116-11 |
| Trial protocol           | NL ES FR DE    |
| Global end of trial date | 12 August 2014 |

## Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 27 May 2016  |
| First version publication date | 27 May 2016  |

## Trial information

### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CAUY922A2206 |
|-----------------------|--------------|

### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01124864 |
| 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 Pharma AG, 41 613241111,                                         |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, trialandresults.registries@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                       | 12 August 2014 |
| Is this the analysis of the primary completion data? | No             |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 12 August 2014 |
| Was the trial ended prematurely?                     | No             |

Notes:

## General information about the trial

Main objective of the trial:

To estimate efficacy for each study strata at 18 weeks as assessed by Response Evaluation Criteria in Solid Tumors (RECIST).

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                          | 27 October 2010 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Canada: 3              |
| Country: Number of subjects enrolled | France: 25             |
| Country: Number of subjects enrolled | Netherlands: 12        |
| Country: Number of subjects enrolled | Norway: 5              |
| Country: Number of subjects enrolled | Singapore: 3           |
| Country: Number of subjects enrolled | Spain: 41              |
| Country: Number of subjects enrolled | United States: 32      |
| Country: Number of subjects enrolled | Germany: 3             |
| Country: Number of subjects enrolled | Korea, Republic of: 29 |
| Worldwide total number of subjects   | 153                    |
| EEA total number of subjects         | 86                     |

Notes:

### Subjects enrolled per age group

|                                           |   |
|-------------------------------------------|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |

|                                          |     |
|------------------------------------------|-----|
| Infants and toddlers (28 days-23 months) | 0   |
| Children (2-11 years)                    | 0   |
| Adolescents (12-17 years)                | 0   |
| Adults (18-64 years)                     | 108 |
| From 65 to 84 years                      | 45  |
| 85 years and over                        | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Two patients who were ongoing at the data cut-off of 30-Jul-2013 are considered as 'completed' in this study.

### Pre-assignment

Screening details:

All patients were to receive weekly i.v. administrations of AUY922 at a dose of 70 mg/m<sup>2</sup>. However, patients were also stratified to one of the following five groups based on the molecular etiology of their baseline tumors: EGFR mutant, KRAS mutant, EML4-ALK translocations, EGFR and KRAS wild type, and modified EGFR mutant.

### Period 1

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

### Arms

|                              |                      |
|------------------------------|----------------------|
| Are arms mutually exclusive? | Yes                  |
| <b>Arm title</b>             | Kras mutant patients |

Arm description:

Patients with KRAS mutant tumors. Patients received AUY922 at 70 mg/m<sup>2</sup> weekly infusions.

|                                        |                 |
|----------------------------------------|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | AUY922          |
| Investigational medicinal product code | AUY922          |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

Dosage and administration details:

Investigational treatment consisted of AUY922. This was supplied by Novartis in individual

|                  |                      |
|------------------|----------------------|
| <b>Arm title</b> | EGFR mutant patients |
|------------------|----------------------|

Arm description:

Patients with EGFR activating mutation tumors (Note: These patients must have progressed on one prior EGFR TKI containing regimen unless they have documented T790M activating mutation). Patients received AUY922 at 70 mg/m<sup>2</sup> weekly infusions.

|                                        |                 |
|----------------------------------------|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | AUY922          |
| Investigational medicinal product code | AUY922          |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

Dosage and administration details:

Investigational treatment consisted of AUY922. This was supplied by Novartis in individual

|                  |                                  |
|------------------|----------------------------------|
| <b>Arm title</b> | EGFR and Kras wild type patients |
|------------------|----------------------------------|

Arm description:

Patients exhibiting both mutations were stratified to the KRAS mutation stratum. Patients received AUY922 at 70 mg/m<sup>2</sup> weekly infusions.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|                                                                                            |                                      |
|--------------------------------------------------------------------------------------------|--------------------------------------|
| Investigational medicinal product name                                                     | AUY922                               |
| Investigational medicinal product code                                                     | AUY922                               |
| Other name                                                                                 |                                      |
| Pharmaceutical forms                                                                       | Infusion                             |
| Routes of administration                                                                   | Intravenous use                      |
| Dosage and administration details:                                                         |                                      |
| Investigational treatment consisted of AUY922. This was supplied by Novartis in individual |                                      |
| <b>Arm title</b>                                                                           | Patients with EML4-ALK translocation |

Arm description:

Patients with NSCLC who have tumors with an inversion in the short arm of chromosome 2 that results in the fusion of the echinoderm microtubule-associated protein-like 4 (EML4) gene with the ALK gene leading to the production of an EML4-ALK fusion tyrosine kinase. ALK is a transmembrane protein, which has a kinase domain and is not usually expressed in the lung. EML4 mediate ligand-independent dimerization, and therefore constitutive activity of the ALK tyrosine kinase domain. Patients received AUY922 at 70 mg/m<sup>2</sup> weekly infusions.

|                                                                                            |                               |
|--------------------------------------------------------------------------------------------|-------------------------------|
| Arm type                                                                                   | Experimental                  |
| Investigational medicinal product name                                                     | AUY922                        |
| Investigational medicinal product code                                                     | AUY922                        |
| Other name                                                                                 |                               |
| Pharmaceutical forms                                                                       | Infusion                      |
| Routes of administration                                                                   | Intravenous use               |
| Dosage and administration details:                                                         |                               |
| Investigational treatment consisted of AUY922. This was supplied by Novartis in individual |                               |
| <b>Arm title</b>                                                                           | Modified EGFR mutant patients |

Arm description:

The modified EGFR stratum was defined as patients less heavily pretreated who had received one or two lines of prior therapy, with a documented response to a EGFR tyrosine kinase inhibitor (TKI) (complete response (CR), partial response (PR) or stable disease (SD) for  $\geq 6$  months), unless the patient had de novo resistance to EGFR TKI. Patients received AUY922 at 70 mg/m<sup>2</sup> weekly infusions.

|                                                                                            |                 |
|--------------------------------------------------------------------------------------------|-----------------|
| Arm type                                                                                   | Experimental    |
| Investigational medicinal product name                                                     | AUY922          |
| Investigational medicinal product code                                                     | AUY922          |
| Other name                                                                                 |                 |
| Pharmaceutical forms                                                                       | Infusion        |
| Routes of administration                                                                   | Intravenous use |
| Dosage and administration details:                                                         |                 |
| Investigational treatment consisted of AUY922. This was supplied by Novartis in individual |                 |
| <b>Arm title</b>                                                                           | Unknown         |

Arm description:

For some patients, it was not possible to determine their genotype, and hence their stratum membership could not be determined. Patients received AUY922 at 70 mg/m<sup>2</sup> weekly infusions.

|                                        |                 |
|----------------------------------------|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | AUY922          |
| Investigational medicinal product code | AUY922          |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

Dosage and administration details:

Investigational treatment consisted of AUY922. This was supplied by Novartis in individual

| <b>Number of subjects in period 1</b>     | Kras mutant patients | EGFR mutant patients | EGFR and Kras wild type patients |
|-------------------------------------------|----------------------|----------------------|----------------------------------|
| Started                                   | 28                   | 35                   | 34                               |
| Completed                                 | 0                    | 0                    | 0                                |
| Not completed                             | 28                   | 35                   | 34                               |
| Adverse event, serious fatal              | 6                    | 9                    | 6                                |
| Consent withdrawn by subject              | 2                    | 3                    | 4                                |
| Follow up phase completed as per protocol | 18                   | 22                   | 24                               |
| Lost to follow-up                         | 1                    | 1                    | -                                |
| Protocol deviation                        | 1                    | -                    | -                                |

| <b>Number of subjects in period 1</b>     | Patients with EML4-ALK translocation | Modified EGFR mutant patients | Unknown |
|-------------------------------------------|--------------------------------------|-------------------------------|---------|
| Started                                   | 22                                   | 31                            | 3       |
| Completed                                 | 1                                    | 1                             | 0       |
| Not completed                             | 21                                   | 30                            | 3       |
| Adverse event, serious fatal              | 2                                    | 1                             | -       |
| Consent withdrawn by subject              | -                                    | 2                             | 1       |
| Follow up phase completed as per protocol | 18                                   | 26                            | 2       |
| Lost to follow-up                         | 1                                    | -                             | -       |
| Protocol deviation                        | -                                    | 1                             | -       |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                      |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Kras mutant patients                 |
| Reporting group description:<br>Patients with KRAS mutant tumors. Patients received AUY922 at 70 mg/m <sup>2</sup> weekly infusions.                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                      |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | EGFR mutant patients                 |
| Reporting group description:<br>Patients with EGFR activating mutation tumors (Note: These patients must have progressed on one prior EGFR TKI containing regimen unless they have documented T790M activating mutation). Patients received AUY922 at 70 mg/m <sup>2</sup> weekly infusions.                                                                                                                                                                                                                                                                                                         |                                      |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | EGFR and Kras wild type patients     |
| Reporting group description:<br>Patients exhibiting both mutations were stratified to the KRAS mutation stratum. Patients received AUY922 at 70 mg/m <sup>2</sup> weekly infusions.                                                                                                                                                                                                                                                                                                                                                                                                                  |                                      |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Patients with EML4-ALK translocation |
| Reporting group description:<br>Patients with NSCLC who have tumors with an inversion in the short arm of chromosome 2 that results in the fusion of the echinoderm microtubule-associated protein-like 4 (EML4) gene with the ALK gene leading to the production of an EML4-ALK fusion tyrosine kinase. ALK is a transmembrane protein, which has a kinase domain and is not usually expressed in the lung. EML4 mediate ligand-independent dimerization, and therefore constitutive activity of the ALK tyrosine kinase domain. Patients received AUY922 at 70 mg/m <sup>2</sup> weekly infusions. |                                      |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Modified EGFR mutant patients        |
| Reporting group description:<br>The modified EGFR stratum was defined as patients less heavily pretreated who had received one or two lines of prior therapy, with a documented response to a EGFR tyrosine kinase inhibitor (TKI) (complete response (CR), partial response (PR) or stable disease (SD) for ≥ 6 months), unless the patient had de novo resistance to EGFR TKI. Patients received AUY922 at 70 mg/m <sup>2</sup> weekly infusions.                                                                                                                                                  |                                      |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Unknown                              |
| Reporting group description:<br>For some patients, it was not possible to determine their genotype, and hence their stratum membership could not be determined. Patients received AUY922 at 70 mg/m <sup>2</sup> weekly infusions.                                                                                                                                                                                                                                                                                                                                                                   |                                      |

| Reporting group values                             | Kras mutant patients | EGFR mutant patients | EGFR and Kras wild type patients |
|----------------------------------------------------|----------------------|----------------------|----------------------------------|
| Number of subjects                                 | 28                   | 35                   | 34                               |
| 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)                               | 20                   | 21                   | 23                               |
| From 65-84 years                                   | 8                    | 14                   | 11                               |
| 85 years and over                                  | 0                    | 0                    | 0                                |
| Gender, Male/Female<br>Units: Participants         |                      |                      |                                  |
| Female                                             | 11                   | 25                   | 18                               |
| Male                                               | 17                   | 10                   | 16                               |

| Reporting group values                             | Patients with EML4-ALK translocation | Modified EGFR mutant patients | Unknown |
|----------------------------------------------------|--------------------------------------|-------------------------------|---------|
| Number of subjects                                 | 22                                   | 31                            | 3       |
| 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)                               | 18                                   | 25                            | 1       |
| From 65-84 years                                   | 4                                    | 6                             | 2       |
| 85 years and over                                  | 0                                    | 0                             | 0       |
| Gender, Male/Female<br>Units: Participants         |                                      |                               |         |
| Female                                             | 15                                   | 19                            | 0       |
| Male                                               | 7                                    | 12                            | 3       |

| Reporting group values                             | Total |  |  |
|----------------------------------------------------|-------|--|--|
| Number of subjects                                 | 153   |  |  |
| Age categorical<br>Units: Subjects                 |       |  |  |
| In utero                                           | 0     |  |  |
| Preterm newborn infants (gestational age < 37 wks) | 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)                               | 108   |  |  |
| From 65-84 years                                   | 45    |  |  |
| 85 years and over                                  | 0     |  |  |
| Gender, Male/Female<br>Units: Participants         |       |  |  |
| Female                                             | 88    |  |  |
| Male                                               | 65    |  |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                      |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Kras mutant patients                 |
| Reporting group description:<br>Patients with KRAS mutant tumors. Patients received AUY922 at 70 mg/m <sup>2</sup> weekly infusions.                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                      |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | EGFR mutant patients                 |
| Reporting group description:<br>Patients with EGFR activating mutation tumors (Note: These patients must have progressed on one prior EGFR TKI containing regimen unless they have documented T790M activating mutation). Patients received AUY922 at 70 mg/m <sup>2</sup> weekly infusions.                                                                                                                                                                                                                                                                                                         |                                      |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | EGFR and Kras wild type patients     |
| Reporting group description:<br>Patients exhibiting both mutations were stratified to the KRAS mutation stratum. Patients received AUY922 at 70 mg/m <sup>2</sup> weekly infusions.                                                                                                                                                                                                                                                                                                                                                                                                                  |                                      |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Patients with EML4-ALK translocation |
| Reporting group description:<br>Patients with NSCLC who have tumors with an inversion in the short arm of chromosome 2 that results in the fusion of the echinoderm microtubule-associated protein-like 4 (EML4) gene with the ALK gene leading to the production of an EML4-ALK fusion tyrosine kinase. ALK is a transmembrane protein, which has a kinase domain and is not usually expressed in the lung. EML4 mediate ligand-independent dimerization, and therefore constitutive activity of the ALK tyrosine kinase domain. Patients received AUY922 at 70 mg/m <sup>2</sup> weekly infusions. |                                      |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Modified EGFR mutant patients        |
| Reporting group description:<br>The modified EGFR stratum was defined as patients less heavily pretreated who had received one or two lines of prior therapy, with a documented response to a EGFR tyrosine kinase inhibitor (TKI) (complete response (CR), partial response (PR) or stable disease (SD) for ≥ 6 months), unless the patient had de novo resistance to EGFR TKI. Patients received AUY922 at 70 mg/m <sup>2</sup> weekly infusions.                                                                                                                                                  |                                      |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Unknown                              |
| Reporting group description:<br>For some patients, it was not possible to determine their genotype, and hence their stratum membership could not be determined. Patients received AUY922 at 70 mg/m <sup>2</sup> weekly infusions.                                                                                                                                                                                                                                                                                                                                                                   |                                      |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | AUY922                               |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Full analysis                        |
| Subject analysis set description:<br>AUY922 Plasma Concentration                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                      |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | BJP762                               |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Full analysis                        |
| Subject analysis set description:<br>AUY Metabolite                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                      |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | AUY922                               |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Intention-to-treat                   |
| Subject analysis set description:<br>AUY922 Plasma Concentration                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                      |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | BJP762                               |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Intention-to-treat                   |
| Subject analysis set description:<br>AUY Metabolite                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                      |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | AUY922                               |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Safety analysis                      |
| Subject analysis set description:<br>AUY922 Plasma Concentration                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                      |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | BJP762                               |

|                                   |                 |
|-----------------------------------|-----------------|
| Subject analysis set type         | Safety analysis |
| Subject analysis set description: |                 |
| AUY Metabolite                    |                 |

### Primary: Response assessment by study stratum - per Investigator assessment

|                 |                                                                                   |
|-----------------|-----------------------------------------------------------------------------------|
| End point title | Response assessment by study stratum - per Investigator assessment <sup>[1]</sup> |
|-----------------|-----------------------------------------------------------------------------------|

End point description:

The primary endpoint of the study was the investigator assessment of efficacy at 18 weeks in terms of response complete response (CR)/partial response (PR), stable disease (SD), or non clinical benefit (NCB) as assessed by response evaluation criteria in solid tumors (RECIST) version 1.0. ORR = patients with confirmed complete or partial response. Stable disease at 18 weeks = patients without response and with no assessment of progressive disease up to 18 weeks, but with an assessment of stable disease or better either within 2 weeks prior to the 18 week time point, or at the next non-missing assessment after the 18 week time point. No clinical benefit = all other patients.

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

End point timeframe:

18 weeks

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: There was no statistical analysis done to compare the arms.

| End point values             | Kras mutant patients | EGFR mutant patients | EGFR and Kras wild type patients | Patients with EML4-ALK translocation |
|------------------------------|----------------------|----------------------|----------------------------------|--------------------------------------|
| Subject group type           | Reporting group      | Reporting group      | Reporting group                  | Reporting group                      |
| Number of subjects analysed  | 28                   | 35                   | 34                               | 22                                   |
| Units: Participants          |                      |                      |                                  |                                      |
| Overall response rate (ORR)  | 0                    | 6                    | 3                                | 7                                    |
| Stable disease for ≥18 weeks | 2                    | 3                    | 3                                | 2                                    |
| No clinical benefit          | 26                   | 26                   | 28                               | 13                                   |

| End point values             | Modified EGFR mutant patients | Unknown         |  |  |
|------------------------------|-------------------------------|-----------------|--|--|
| Subject group type           | Reporting group               | Reporting group |  |  |
| Number of subjects analysed  | 31                            | 3               |  |  |
| Units: Participants          |                               |                 |  |  |
| Overall response rate (ORR)  | 3                             | 1               |  |  |
| Stable disease for ≥18 weeks | 7                             | 0               |  |  |
| No clinical benefit          | 21                            | 2               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival rate using Kaplan Meier estimates - per Investigator radiological review

|                 |                                                          |
|-----------------|----------------------------------------------------------|
| End point title | Overall Survival rate using Kaplan Meier estimates - per |
|-----------------|----------------------------------------------------------|

End point description:

Overall survival (OS) is defined as the time from date of randomization/start of treatment to date of death due to any cause. If a patient is not known to have died, survival was censored at the date of last contact.

End point type Secondary

End point timeframe:

Week 12, Week 18

| End point values                  | Kras mutant patients | EGFR mutant patients | EGFR and Kras wild type patients | Patients with EML4-ALK translocation |
|-----------------------------------|----------------------|----------------------|----------------------------------|--------------------------------------|
| Subject group type                | Reporting group      | Reporting group      | Reporting group                  | Reporting group                      |
| Number of subjects analysed       | 28                   | 35                   | 34                               | 22                                   |
| Units: Percentage of participants |                      |                      |                                  |                                      |
| number (not applicable)           |                      |                      |                                  |                                      |
| 12 weeks                          | 68.7                 | 77                   | 78.6                             | 90.7                                 |
| 18 weeks                          | 55.9                 | 74.1                 | 72.3                             | 71.6                                 |

| End point values                  | Modified EGFR mutant patients | Unknown         |  |  |
|-----------------------------------|-------------------------------|-----------------|--|--|
| Subject group type                | Reporting group               | Reporting group |  |  |
| Number of subjects analysed       | 31                            | 3               |  |  |
| Units: Percentage of participants |                               |                 |  |  |
| number (not applicable)           |                               |                 |  |  |
| 12 weeks                          | 96.7                          | 66.7            |  |  |
| 18 weeks                          | 93.3                          | 33.3            |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Progression Free Survival (PFS) rate as per Investigator using Kaplan Meier estimates - per Investigator radiological review

End point title Progression Free Survival (PFS) rate as per Investigator using Kaplan Meier estimates - per Investigator radiological review

End point description:

Progression-free survival (PFS) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient did not have an event, progression-free survival was censored at the date of last adequate tumor assessment. A Novartis modified response evaluation criteria in solid tumors RECIST 1.1 criteria was applied to CT/MRI imaging data when assessing any responses to AUY922 treatment. All images were evaluated locally by the investigator. All complete or partial responses were confirmed by a second assessment at least 4 weeks later.

End point type Secondary

End point timeframe:

Week 12, Week 18

| <b>End point values</b>           | Kras mutant patients | EGFR mutant patients | EGFR and Kras wild type patients | Patients with EML4-ALK translocation |
|-----------------------------------|----------------------|----------------------|----------------------------------|--------------------------------------|
| Subject group type                | Reporting group      | Reporting group      | Reporting group                  | Reporting group                      |
| Number of subjects analysed       | 28                   | 35                   | 34                               | 22                                   |
| Units: Percentage of participants |                      |                      |                                  |                                      |
| number (not applicable)           |                      |                      |                                  |                                      |
| 12 weeks                          | 31.5                 | 44.4                 | 31.5                             | 45.5                                 |
| 18 weeks                          | 9                    | 27.7                 | 24                               | 36.4                                 |

| <b>End point values</b>           | Modified EGFR mutant patients | Unknown         |  |  |
|-----------------------------------|-------------------------------|-----------------|--|--|
| Subject group type                | Reporting group               | Reporting group |  |  |
| Number of subjects analysed       | 31                            | 3               |  |  |
| Units: Percentage of participants |                               |                 |  |  |
| number (not applicable)           |                               |                 |  |  |
| 12 weeks                          | 56.4                          | 33.3            |  |  |
| 18 weeks                          | 37.8                          | 33.3            |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacokinetics (PK) of plasma concentration of AUY922 and its metabolite BJP762: AUCinf

|                 |                                                                                           |
|-----------------|-------------------------------------------------------------------------------------------|
| End point title | Pharmacokinetics (PK) of plasma concentration of AUY922 and its metabolite BJP762: AUCinf |
|-----------------|-------------------------------------------------------------------------------------------|

End point description:

Summary of PK parameters for all patients one hour post 70 mg/m<sup>2</sup> AUY922 infusion for area under the curve infinity. There are discrepancies between sample numbers and study population because PK samples were not collected from all study subjects and thus were not analyzed.

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

End point timeframe:

1 hour after infusion

| End point values                     | AUY922               | BJP762                 |  |  |
|--------------------------------------|----------------------|------------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set   |  |  |
| Number of subjects analysed          | 119                  | 117                    |  |  |
| Units: h*ng/mL                       |                      |                        |  |  |
| arithmetic mean (standard deviation) | 2101.27 (± 990.32)   | 13963.07 (± 13006.537) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacokinetics (PK) of plasma concentration of AUY922 and its metabolite BJP762: AUClast

|                 |                                                                                            |
|-----------------|--------------------------------------------------------------------------------------------|
| End point title | Pharmacokinetics (PK) of plasma concentration of AUY922 and its metabolite BJP762: AUClast |
|-----------------|--------------------------------------------------------------------------------------------|

End point description:

Summary of PK parameters for all patients one hour post 70 mg/m<sup>2</sup> AUY922 infusion for area under the curve last. There are discrepancies between sample numbers and study population because PK samples were not collected from all study subjects and thus were not analyzed.

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

End point timeframe:

1 hour after infusion

| End point values                     | AUY922               | BJP762                 |  |  |
|--------------------------------------|----------------------|------------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set   |  |  |
| Number of subjects analysed          | 139                  | 142                    |  |  |
| Units: h*ng/mL                       |                      |                        |  |  |
| arithmetic mean (standard deviation) | 1997.04 (± 894.903)  | 12496.75 (± 12035.525) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacokinetics (PK) of plasma concentration of AUY922 and its metabolite BJP762: Cmax

|                 |                                                                                         |
|-----------------|-----------------------------------------------------------------------------------------|
| End point title | Pharmacokinetics (PK) of plasma concentration of AUY922 and its metabolite BJP762: Cmax |
|-----------------|-----------------------------------------------------------------------------------------|

End point description:

Summary of PK parameters for all patients one hour post 70 mg/m<sup>2</sup> AUY922 infusion for concentration max. There are discrepancies between sample numbers and study population because PK samples were not collected from all study subjects and thus were not analyzed.

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

End point timeframe:

1 hour after infusion

| <b>End point values</b>              | AUY922                   | BJP762                   |  |  |
|--------------------------------------|--------------------------|--------------------------|--|--|
| Subject group type                   | Subject analysis set     | Subject analysis set     |  |  |
| Number of subjects analysed          | 144                      | 144                      |  |  |
| Units: ng/mL                         |                          |                          |  |  |
| arithmetic mean (standard deviation) | 1130.59 ( $\pm$ 705.177) | 2332.86 ( $\pm$ 1377.35) |  |  |

### 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 | 17.1 |
|--------------------|------|

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | KRAS mutant |
|-----------------------|-------------|

Reporting group description:

Patients with KRAS mutant tumors. Patients received AUY922 at 70 mg/m<sup>2</sup> weekly infusions.

|                       |             |
|-----------------------|-------------|
| Reporting group title | EGFR mutant |
|-----------------------|-------------|

Reporting group description:

Patients with EGFR activating mutation tumors (Note: These patients must have progressed on one prior EGFR TKI containing regimen unless they have documented T790M activating mutation). Patients received AUY922 at 70 mg/m<sup>2</sup> weekly infusions.

|                       |         |
|-----------------------|---------|
| Reporting group title | Unknown |
|-----------------------|---------|

Reporting group description:

For some patients, it was not possible to determine their genotype, and hence their stratum membership could not be determined. Patients received AUY922 at 70 mg/m<sup>2</sup> weekly infusions.

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | EML4-ALK translocation |
|-----------------------|------------------------|

Reporting group description:

Patients with NSCLC who have tumors with an inversion in the short arm of chromosome 2 that results in the fusion of the echinoderm microtubule-associated protein-like 4 (EML4) gene with the ALK gene leading to the production of an EML4-ALK fusion tyrosine kinase. ALK is a transmembrane protein, which has a kinase domain and is not usually expressed in the lung. EML4 mediate ligand-independent dimerization, and therefore constitutive activity of the ALK tyrosine kinase domain. Patients received AUY922 at 70 mg/m<sup>2</sup> weekly infusions.

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Modified EGFR mutant |
|-----------------------|----------------------|

Reporting group description:

The modified EGFR stratum was defined as patients less heavily pretreated who had received one or two lines of prior therapy, with a documented response to a EGFR tyrosine kinase inhibitor (TKI) (complete response (CR), partial response (PR) or stable disease (SD) for ≥ 6 months), unless the patient had de novo resistance to EGFR TKI. Patients received AUY922 at 70 mg/m<sup>2</sup> weekly infusions.

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | KRAS and EGFR wild type |
|-----------------------|-------------------------|

Reporting group description:

Patients exhibiting both mutations were stratified to the KRAS mutation stratum. Patients received AUY922 at 70 mg/m<sup>2</sup> weekly infusions.

| Serious adverse events                            | KRAS mutant      | EGFR mutant      | Unknown        |
|---------------------------------------------------|------------------|------------------|----------------|
| Total subjects affected by serious adverse events |                  |                  |                |
| subjects affected / exposed                       | 17 / 28 (60.71%) | 18 / 35 (51.43%) | 2 / 3 (66.67%) |
| number of deaths (all causes)                     | 5                | 7                | 1              |

|                                                                     |                |                |               |
|---------------------------------------------------------------------|----------------|----------------|---------------|
| number of deaths resulting from adverse events                      | 0              | 0              | 0             |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                |                |               |
| Metastases To Central Nervous System                                |                |                |               |
| subjects affected / exposed                                         | 0 / 28 (0.00%) | 0 / 35 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0         |
| Metastatic Pain                                                     |                |                |               |
| subjects affected / exposed                                         | 0 / 28 (0.00%) | 1 / 35 (2.86%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0         |
| Vascular disorders                                                  |                |                |               |
| Deep Vein Thrombosis                                                |                |                |               |
| subjects affected / exposed                                         | 0 / 28 (0.00%) | 0 / 35 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0         |
| Hypertension                                                        |                |                |               |
| subjects affected / exposed                                         | 0 / 28 (0.00%) | 2 / 35 (5.71%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 2 / 2          | 0 / 0         |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0         |
| Thrombosis                                                          |                |                |               |
| subjects affected / exposed                                         | 1 / 28 (3.57%) | 1 / 35 (2.86%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 1          | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0         |
| General disorders and administration site conditions                |                |                |               |
| Asthenia                                                            |                |                |               |
| subjects affected / exposed                                         | 0 / 28 (0.00%) | 1 / 35 (2.86%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0         |
| Fatigue                                                             |                |                |               |
| subjects affected / exposed                                         | 0 / 28 (0.00%) | 0 / 35 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0         |
| General Physical Health Deterioration                               |                |                |               |

|                                                 |                 |                |               |
|-------------------------------------------------|-----------------|----------------|---------------|
| subjects affected / exposed                     | 1 / 28 (3.57%)  | 0 / 35 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0         |
| Mucosal Inflammation                            |                 |                |               |
| subjects affected / exposed                     | 0 / 28 (0.00%)  | 1 / 35 (2.86%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0         |
| Oedema Peripheral                               |                 |                |               |
| subjects affected / exposed                     | 1 / 28 (3.57%)  | 0 / 35 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0         |
| Pain                                            |                 |                |               |
| subjects affected / exposed                     | 1 / 28 (3.57%)  | 2 / 35 (5.71%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0         |
| Pyrexia                                         |                 |                |               |
| subjects affected / exposed                     | 0 / 28 (0.00%)  | 0 / 35 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0         |
| Respiratory, thoracic and mediastinal disorders |                 |                |               |
| Acute Respiratory Failure                       |                 |                |               |
| subjects affected / exposed                     | 1 / 28 (3.57%)  | 0 / 35 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0         |
| Dyspnoea                                        |                 |                |               |
| subjects affected / exposed                     | 3 / 28 (10.71%) | 2 / 35 (5.71%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 0         |
| Haemoptysis                                     |                 |                |               |
| subjects affected / exposed                     | 0 / 28 (0.00%)  | 0 / 35 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0         |
| Hypoxia                                         |                 |                |               |

|                                                 |                |                |               |
|-------------------------------------------------|----------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 28 (0.00%) | 0 / 35 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Pleural Effusion                                |                |                |               |
| subjects affected / exposed                     | 0 / 28 (0.00%) | 1 / 35 (2.86%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Pneumothorax                                    |                |                |               |
| subjects affected / exposed                     | 0 / 28 (0.00%) | 0 / 35 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Pulmonary Embolism                              |                |                |               |
| subjects affected / exposed                     | 1 / 28 (3.57%) | 3 / 35 (8.57%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 3          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Respiratory Failure                             |                |                |               |
| subjects affected / exposed                     | 0 / 28 (0.00%) | 2 / 35 (5.71%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Psychiatric disorders                           |                |                |               |
| Confusional State                               |                |                |               |
| subjects affected / exposed                     | 0 / 28 (0.00%) | 0 / 35 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Depression                                      |                |                |               |
| subjects affected / exposed                     | 0 / 28 (0.00%) | 0 / 35 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Cardiac disorders                               |                |                |               |
| Atrial Fibrillation                             |                |                |               |
| subjects affected / exposed                     | 0 / 28 (0.00%) | 1 / 35 (2.86%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Bundle Branch Block Right                       |                |                |               |

|                                                 |                |                |               |
|-------------------------------------------------|----------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 28 (0.00%) | 0 / 35 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Cardio-Respiratory Arrest                       |                |                |               |
| subjects affected / exposed                     | 1 / 28 (3.57%) | 0 / 35 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Palpitations                                    |                |                |               |
| subjects affected / exposed                     | 1 / 28 (3.57%) | 0 / 35 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Pericardial Effusion                            |                |                |               |
| subjects affected / exposed                     | 0 / 28 (0.00%) | 1 / 35 (2.86%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Tachycardia                                     |                |                |               |
| subjects affected / exposed                     | 0 / 28 (0.00%) | 1 / 35 (2.86%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Supraventricular Tachycardia                    |                |                |               |
| subjects affected / exposed                     | 1 / 28 (3.57%) | 0 / 35 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Nervous system disorders                        |                |                |               |
| Brain Compression                               |                |                |               |
| subjects affected / exposed                     | 0 / 28 (0.00%) | 0 / 35 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Balance Disorder                                |                |                |               |
| subjects affected / exposed                     | 0 / 28 (0.00%) | 0 / 35 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Nervous System Disorder                         |                |                |               |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 28 (3.57%) | 0 / 35 (0.00%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Spinal Cord Compression                         |                |                |                |
| subjects affected / exposed                     | 0 / 28 (0.00%) | 1 / 35 (2.86%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Vocal Cord Paresis                              |                |                |                |
| subjects affected / exposed                     | 1 / 28 (3.57%) | 0 / 35 (0.00%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders            |                |                |                |
| Anaemia                                         |                |                |                |
| subjects affected / exposed                     | 1 / 28 (3.57%) | 0 / 35 (0.00%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Eye disorders                                   |                |                |                |
| Night Blindness                                 |                |                |                |
| subjects affected / exposed                     | 1 / 28 (3.57%) | 0 / 35 (0.00%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |                |                |                |
| Abdominal Distension                            |                |                |                |
| subjects affected / exposed                     | 0 / 28 (0.00%) | 0 / 35 (0.00%) | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Diarrhoea                                       |                |                |                |
| subjects affected / exposed                     | 1 / 28 (3.57%) | 3 / 35 (8.57%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1          | 3 / 4          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Rectal Fissure                                  |                |                |                |
| subjects affected / exposed                     | 1 / 28 (3.57%) | 0 / 35 (0.00%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|                                                 |                |                |               |
|-------------------------------------------------|----------------|----------------|---------------|
| Proctalgia                                      |                |                |               |
| subjects affected / exposed                     | 1 / 28 (3.57%) | 0 / 35 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Vomiting                                        |                |                |               |
| subjects affected / exposed                     | 1 / 28 (3.57%) | 1 / 35 (2.86%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 1 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Hepatobiliary disorders                         |                |                |               |
| Hyperbilirubinaemia                             |                |                |               |
| subjects affected / exposed                     | 0 / 28 (0.00%) | 1 / 35 (2.86%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Cholelithiasis                                  |                |                |               |
| subjects affected / exposed                     | 0 / 28 (0.00%) | 0 / 35 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Musculoskeletal and connective tissue disorders |                |                |               |
| Bone Pain                                       |                |                |               |
| subjects affected / exposed                     | 1 / 28 (3.57%) | 1 / 35 (2.86%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Musculoskeletal Pain                            |                |                |               |
| subjects affected / exposed                     | 1 / 28 (3.57%) | 0 / 35 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Neck Pain                                       |                |                |               |
| subjects affected / exposed                     | 0 / 28 (0.00%) | 0 / 35 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Infections and infestations                     |                |                |               |
| Atypical Pneumonia                              |                |                |               |

|                                                 |                 |                |                |
|-------------------------------------------------|-----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 28 (0.00%)  | 0 / 35 (0.00%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Bronchitis                                      |                 |                |                |
| subjects affected / exposed                     | 1 / 28 (3.57%)  | 0 / 35 (0.00%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Lung Infection                                  |                 |                |                |
| subjects affected / exposed                     | 0 / 28 (0.00%)  | 0 / 35 (0.00%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Klebsiella Infection                            |                 |                |                |
| subjects affected / exposed                     | 0 / 28 (0.00%)  | 1 / 35 (2.86%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Perirectal Abscess                              |                 |                |                |
| subjects affected / exposed                     | 1 / 28 (3.57%)  | 0 / 35 (0.00%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Respiratory Tract Infection                     |                 |                |                |
| subjects affected / exposed                     | 1 / 28 (3.57%)  | 0 / 35 (0.00%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Pneumonia                                       |                 |                |                |
| subjects affected / exposed                     | 3 / 28 (10.71%) | 1 / 35 (2.86%) | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Urinary Tract Infection                         |                 |                |                |
| subjects affected / exposed                     | 0 / 28 (0.00%)  | 0 / 35 (0.00%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Metabolism and nutrition disorders              |                 |                |                |
| Decreased Appetite                              |                 |                |                |

|                                                 |                |                |               |
|-------------------------------------------------|----------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 28 (0.00%) | 0 / 35 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Failure To Thrive                               |                |                |               |
| subjects affected / exposed                     | 1 / 28 (3.57%) | 0 / 35 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Dehydration                                     |                |                |               |
| subjects affected / exposed                     | 1 / 28 (3.57%) | 1 / 35 (2.86%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Fluid Intake Reduced                            |                |                |               |
| subjects affected / exposed                     | 0 / 28 (0.00%) | 0 / 35 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Hypercalcaemia                                  |                |                |               |
| subjects affected / exposed                     | 0 / 28 (0.00%) | 0 / 35 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Hyperglycaemia                                  |                |                |               |
| subjects affected / exposed                     | 1 / 28 (3.57%) | 0 / 35 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Hyperkalaemia                                   |                |                |               |
| subjects affected / exposed                     | 1 / 28 (3.57%) | 0 / 35 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Hyponatraemia                                   |                |                |               |
| subjects affected / exposed                     | 0 / 28 (0.00%) | 0 / 35 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |

|                               |                        |                      |                         |
|-------------------------------|------------------------|----------------------|-------------------------|
| <b>Serious adverse events</b> | EML4-ALK translocation | Modified EGFR mutant | KRAS and EGFR wild type |
|-------------------------------|------------------------|----------------------|-------------------------|

|                                                                     |                 |                  |                  |
|---------------------------------------------------------------------|-----------------|------------------|------------------|
| Total subjects affected by serious adverse events                   |                 |                  |                  |
| subjects affected / exposed                                         | 6 / 22 (27.27%) | 11 / 31 (35.48%) | 22 / 34 (64.71%) |
| number of deaths (all causes)                                       | 2               | 1                | 4                |
| number of deaths resulting from adverse events                      | 0               | 0                | 0                |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                  |                  |
| Metastases To Central Nervous System                                |                 |                  |                  |
| subjects affected / exposed                                         | 0 / 22 (0.00%)  | 1 / 31 (3.23%)   | 0 / 34 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0            | 0 / 0            |
| Metastatic Pain                                                     |                 |                  |                  |
| subjects affected / exposed                                         | 0 / 22 (0.00%)  | 0 / 31 (0.00%)   | 0 / 34 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0            | 0 / 0            |
| Vascular disorders                                                  |                 |                  |                  |
| Deep Vein Thrombosis                                                |                 |                  |                  |
| subjects affected / exposed                                         | 0 / 22 (0.00%)  | 0 / 31 (0.00%)   | 1 / 34 (2.94%)   |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0            | 0 / 0            |
| Hypertension                                                        |                 |                  |                  |
| subjects affected / exposed                                         | 0 / 22 (0.00%)  | 0 / 31 (0.00%)   | 0 / 34 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0            | 0 / 0            |
| Thrombosis                                                          |                 |                  |                  |
| subjects affected / exposed                                         | 0 / 22 (0.00%)  | 0 / 31 (0.00%)   | 0 / 34 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0            | 0 / 0            |
| General disorders and administration site conditions                |                 |                  |                  |
| Asthenia                                                            |                 |                  |                  |
| subjects affected / exposed                                         | 0 / 22 (0.00%)  | 0 / 31 (0.00%)   | 2 / 34 (5.88%)   |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0            | 0 / 0            |
| Fatigue                                                             |                 |                  |                  |

|                                                 |                 |                |                |
|-------------------------------------------------|-----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 22 (0.00%)  | 1 / 31 (3.23%) | 2 / 34 (5.88%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| General Physical Health Deterioration           |                 |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%)  | 0 / 31 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Mucosal Inflammation                            |                 |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%)  | 0 / 31 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Oedema Peripheral                               |                 |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%)  | 0 / 31 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Pain                                            |                 |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%)  | 0 / 31 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Pyrexia                                         |                 |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%)  | 1 / 31 (3.23%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders |                 |                |                |
| Acute Respiratory Failure                       |                 |                |                |
| subjects affected / exposed                     | 1 / 22 (4.55%)  | 0 / 31 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Dyspnoea                                        |                 |                |                |
| subjects affected / exposed                     | 3 / 22 (13.64%) | 0 / 31 (0.00%) | 2 / 34 (5.88%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Haemoptysis                                     |                 |                |                |

|                                                 |                |                 |                |
|-------------------------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 22 (4.55%) | 0 / 31 (0.00%)  | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Hypoxia                                         |                |                 |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 31 (0.00%)  | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Pleural Effusion                                |                |                 |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 4 / 31 (12.90%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 4           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Pneumothorax                                    |                |                 |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 1 / 31 (3.23%)  | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Pulmonary Embolism                              |                |                 |                |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 0 / 31 (0.00%)  | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Respiratory Failure                             |                |                 |                |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 0 / 31 (0.00%)  | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Psychiatric disorders                           |                |                 |                |
| Confusional State                               |                |                 |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 31 (0.00%)  | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Depression                                      |                |                 |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 31 (0.00%)  | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Cardiac disorders                               |                |                 |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| Atrial Fibrillation                             |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 31 (0.00%) | 2 / 34 (5.88%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Bundle Branch Block Right                       |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 31 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardio-Respiratory Arrest                       |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 31 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Palpitations                                    |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 31 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pericardial Effusion                            |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 31 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Tachycardia                                     |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 31 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Supraventricular Tachycardia                    |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 31 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                |                |                |
| Brain Compression                               |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 31 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Balance Disorder                                |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 22 (0.00%) | 1 / 31 (3.23%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous System Disorder                         |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 31 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Spinal Cord Compression                         |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 31 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Vocal Cord Paresis                              |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 31 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders            |                |                |                |
| Anaemia                                         |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 31 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Eye disorders                                   |                |                |                |
| Night Blindness                                 |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 31 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |                |                |                |
| Abdominal Distension                            |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 31 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Diarrhoea                                       |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 1 / 31 (3.23%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| Rectal Fissure                                  |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 31 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Proctalgia                                      |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 31 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Vomiting                                        |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 31 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hepatobiliary disorders                         |                |                |                |
| Hyperbilirubinaemia                             |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 31 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cholelithiasis                                  |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 1 / 31 (3.23%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Musculoskeletal and connective tissue disorders |                |                |                |
| Bone Pain                                       |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 31 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Musculoskeletal Pain                            |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 31 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Neck Pain                                       |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 31 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|                                                                                                                                                                                   |                                  |                                  |                                  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|----------------------------------|----------------------------------|
| Infections and infestations<br>Atypical Pneumonia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | 1 / 22 (4.55%)<br>0 / 1<br>0 / 0 | 0 / 31 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 34 (0.00%)<br>0 / 0<br>0 / 0 |
| Bronchitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                        | 0 / 22 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 31 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 34 (0.00%)<br>0 / 0<br>0 / 0 |
| Lung Infection<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                    | 1 / 22 (4.55%)<br>0 / 1<br>0 / 0 | 0 / 31 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 34 (0.00%)<br>0 / 0<br>0 / 0 |
| Klebsiella Infection<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                              | 0 / 22 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 31 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 34 (0.00%)<br>0 / 0<br>0 / 0 |
| Perirectal Abscess<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                | 0 / 22 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 31 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 34 (0.00%)<br>0 / 0<br>0 / 0 |
| Respiratory Tract Infection<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                       | 1 / 22 (4.55%)<br>0 / 1<br>0 / 0 | 0 / 31 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 34 (0.00%)<br>0 / 0<br>0 / 0 |
| Pneumonia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                         | 1 / 22 (4.55%)<br>0 / 1<br>0 / 0 | 0 / 31 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 34 (2.94%)<br>0 / 1<br>0 / 0 |
| Urinary Tract Infection<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                           | 0 / 22 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 31 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 34 (2.94%)<br>0 / 1<br>0 / 0 |
| Metabolism and nutrition disorders                                                                                                                                                |                                  |                                  |                                  |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| Decreased Appetite                              |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 31 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Failure To Thrive                               |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 31 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Dehydration                                     |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 31 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Fluid Intake Reduced                            |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 1 / 31 (3.23%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hypercalcaemia                                  |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 1 / 31 (3.23%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hyperglycaemia                                  |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 31 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hyperkalaemia                                   |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 31 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hyponatraemia                                   |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 31 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

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

| <b>Non-serious adverse events</b>                                   | KRAS mutant       | EGFR mutant       | Unknown         |
|---------------------------------------------------------------------|-------------------|-------------------|-----------------|
| Total subjects affected by non-serious adverse events               |                   |                   |                 |
| subjects affected / exposed                                         | 28 / 28 (100.00%) | 35 / 35 (100.00%) | 3 / 3 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                   |                 |
| Cancer Pain                                                         |                   |                   |                 |
| subjects affected / exposed                                         | 0 / 28 (0.00%)    | 0 / 35 (0.00%)    | 1 / 3 (33.33%)  |
| occurrences (all)                                                   | 0                 | 0                 | 1               |
| Vascular disorders                                                  |                   |                   |                 |
| Deep Vein Thrombosis                                                |                   |                   |                 |
| subjects affected / exposed                                         | 0 / 28 (0.00%)    | 2 / 35 (5.71%)    | 0 / 3 (0.00%)   |
| occurrences (all)                                                   | 0                 | 2                 | 0               |
| Hot Flush                                                           |                   |                   |                 |
| subjects affected / exposed                                         | 1 / 28 (3.57%)    | 0 / 35 (0.00%)    | 0 / 3 (0.00%)   |
| occurrences (all)                                                   | 2                 | 0                 | 0               |
| Hypertension                                                        |                   |                   |                 |
| subjects affected / exposed                                         | 0 / 28 (0.00%)    | 4 / 35 (11.43%)   | 0 / 3 (0.00%)   |
| occurrences (all)                                                   | 0                 | 14                | 0               |
| Hypotension                                                         |                   |                   |                 |
| subjects affected / exposed                                         | 0 / 28 (0.00%)    | 2 / 35 (5.71%)    | 0 / 3 (0.00%)   |
| occurrences (all)                                                   | 0                 | 4                 | 0               |
| General disorders and administration site conditions                |                   |                   |                 |
| Asthenia                                                            |                   |                   |                 |
| subjects affected / exposed                                         | 13 / 28 (46.43%)  | 14 / 35 (40.00%)  | 1 / 3 (33.33%)  |
| occurrences (all)                                                   | 17                | 18                | 1               |
| Catheter Site Pain                                                  |                   |                   |                 |
| subjects affected / exposed                                         | 0 / 28 (0.00%)    | 0 / 35 (0.00%)    | 0 / 3 (0.00%)   |
| occurrences (all)                                                   | 0                 | 0                 | 0               |
| Chest Pain                                                          |                   |                   |                 |
| subjects affected / exposed                                         | 1 / 28 (3.57%)    | 2 / 35 (5.71%)    | 1 / 3 (33.33%)  |
| occurrences (all)                                                   | 1                 | 3                 | 1               |
| Pain                                                                |                   |                   |                 |
| subjects affected / exposed                                         | 1 / 28 (3.57%)    | 2 / 35 (5.71%)    | 1 / 3 (33.33%)  |
| occurrences (all)                                                   | 1                 | 2                 | 1               |
| Fatigue                                                             |                   |                   |                 |

|                                                 |                 |                  |                |
|-------------------------------------------------|-----------------|------------------|----------------|
| subjects affected / exposed                     | 7 / 28 (25.00%) | 9 / 35 (25.71%)  | 0 / 3 (0.00%)  |
| occurrences (all)                               | 7               | 14               | 0              |
| Gait Disturbance                                |                 |                  |                |
| subjects affected / exposed                     | 0 / 28 (0.00%)  | 2 / 35 (5.71%)   | 0 / 3 (0.00%)  |
| occurrences (all)                               | 0               | 2                | 0              |
| Non-Cardiac Chest Pain                          |                 |                  |                |
| subjects affected / exposed                     | 1 / 28 (3.57%)  | 0 / 35 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)                               | 1               | 0                | 0              |
| Oedema Peripheral                               |                 |                  |                |
| subjects affected / exposed                     | 2 / 28 (7.14%)  | 2 / 35 (5.71%)   | 0 / 3 (0.00%)  |
| occurrences (all)                               | 3               | 2                | 0              |
| Pyrexia                                         |                 |                  |                |
| subjects affected / exposed                     | 5 / 28 (17.86%) | 3 / 35 (8.57%)   | 2 / 3 (66.67%) |
| occurrences (all)                               | 5               | 3                | 2              |
| Reproductive system and breast disorders        |                 |                  |                |
| Pelvic Pain                                     |                 |                  |                |
| subjects affected / exposed                     | 0 / 28 (0.00%)  | 2 / 35 (5.71%)   | 0 / 3 (0.00%)  |
| occurrences (all)                               | 0               | 2                | 0              |
| Respiratory, thoracic and mediastinal disorders |                 |                  |                |
| Atelectasis                                     |                 |                  |                |
| subjects affected / exposed                     | 0 / 28 (0.00%)  | 0 / 35 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)                               | 0               | 0                | 0              |
| Cough                                           |                 |                  |                |
| subjects affected / exposed                     | 5 / 28 (17.86%) | 8 / 35 (22.86%)  | 1 / 3 (33.33%) |
| occurrences (all)                               | 7               | 12               | 1              |
| Dyspnoea                                        |                 |                  |                |
| subjects affected / exposed                     | 5 / 28 (17.86%) | 11 / 35 (31.43%) | 1 / 3 (33.33%) |
| occurrences (all)                               | 5               | 11               | 1              |
| Dysphonia                                       |                 |                  |                |
| subjects affected / exposed                     | 0 / 28 (0.00%)  | 1 / 35 (2.86%)   | 0 / 3 (0.00%)  |
| occurrences (all)                               | 0               | 1                | 0              |
| Dyspnoea Exertional                             |                 |                  |                |
| subjects affected / exposed                     | 0 / 28 (0.00%)  | 2 / 35 (5.71%)   | 0 / 3 (0.00%)  |
| occurrences (all)                               | 0               | 2                | 0              |
| Haemoptysis                                     |                 |                  |                |

|                             |                 |                 |                |
|-----------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed | 4 / 28 (14.29%) | 3 / 35 (8.57%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 5               | 3               | 0              |
| Epistaxis                   |                 |                 |                |
| subjects affected / exposed | 0 / 28 (0.00%)  | 0 / 35 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)           | 0               | 0               | 1              |
| Oropharyngeal Pain          |                 |                 |                |
| subjects affected / exposed | 0 / 28 (0.00%)  | 1 / 35 (2.86%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0               | 1               | 0              |
| Pleural Effusion            |                 |                 |                |
| subjects affected / exposed | 0 / 28 (0.00%)  | 2 / 35 (5.71%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0               | 2               | 0              |
| Wheezing                    |                 |                 |                |
| subjects affected / exposed | 0 / 28 (0.00%)  | 2 / 35 (5.71%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0               | 2               | 0              |
| Rhinorrhoea                 |                 |                 |                |
| subjects affected / exposed | 0 / 28 (0.00%)  | 2 / 35 (5.71%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0               | 2               | 0              |
| Productive Cough            |                 |                 |                |
| subjects affected / exposed | 1 / 28 (3.57%)  | 4 / 35 (11.43%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 1               | 5               | 0              |
| Psychiatric disorders       |                 |                 |                |
| Anxiety                     |                 |                 |                |
| subjects affected / exposed | 2 / 28 (7.14%)  | 2 / 35 (5.71%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 2               | 2               | 0              |
| Depressed Mood              |                 |                 |                |
| subjects affected / exposed | 0 / 28 (0.00%)  | 1 / 35 (2.86%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0               | 1               | 0              |
| Hallucination               |                 |                 |                |
| subjects affected / exposed | 0 / 28 (0.00%)  | 0 / 35 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0               | 0               | 0              |
| Insomnia                    |                 |                 |                |
| subjects affected / exposed | 0 / 28 (0.00%)  | 3 / 35 (8.57%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0               | 3               | 0              |
| Nervousness                 |                 |                 |                |
| subjects affected / exposed | 0 / 28 (0.00%)  | 0 / 35 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0               | 0               | 0              |

|                                      |                 |                 |                |
|--------------------------------------|-----------------|-----------------|----------------|
| Investigations                       |                 |                 |                |
| Alanine Aminotransferase Increased   |                 |                 |                |
| subjects affected / exposed          | 1 / 28 (3.57%)  | 2 / 35 (5.71%)  | 0 / 3 (0.00%)  |
| occurrences (all)                    | 1               | 2               | 0              |
| Blood Alkaline Phosphatase Increased |                 |                 |                |
| subjects affected / exposed          | 0 / 28 (0.00%)  | 4 / 35 (11.43%) | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0               | 5               | 0              |
| Aspartate Aminotransferase Increased |                 |                 |                |
| subjects affected / exposed          | 0 / 28 (0.00%)  | 1 / 35 (2.86%)  | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0               | 1               | 0              |
| Blood Creatinine Increased           |                 |                 |                |
| subjects affected / exposed          | 0 / 28 (0.00%)  | 0 / 35 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)                    | 0               | 0               | 1              |
| C-Reactive Protein Increased         |                 |                 |                |
| subjects affected / exposed          | 0 / 28 (0.00%)  | 0 / 35 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)                    | 0               | 0               | 1              |
| Gamma-Glutamyltransferase Increased  |                 |                 |                |
| subjects affected / exposed          | 0 / 28 (0.00%)  | 2 / 35 (5.71%)  | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0               | 2               | 0              |
| Heart Rate Increased                 |                 |                 |                |
| subjects affected / exposed          | 0 / 28 (0.00%)  | 0 / 35 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)                    | 0               | 0               | 1              |
| Hypophonesis                         |                 |                 |                |
| subjects affected / exposed          | 0 / 28 (0.00%)  | 0 / 35 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0               | 0               | 0              |
| Transaminases Increased              |                 |                 |                |
| subjects affected / exposed          | 0 / 28 (0.00%)  | 0 / 35 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0               | 0               | 0              |
| Weight Decreased                     |                 |                 |                |
| subjects affected / exposed          | 4 / 28 (14.29%) | 1 / 35 (2.86%)  | 0 / 3 (0.00%)  |
| occurrences (all)                    | 4               | 1               | 0              |
| Cardiac disorders                    |                 |                 |                |
| Tachycardia                          |                 |                 |                |
| subjects affected / exposed          | 0 / 28 (0.00%)  | 2 / 35 (5.71%)  | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0               | 2               | 0              |

|                               |                 |                 |                |
|-------------------------------|-----------------|-----------------|----------------|
| Nervous system disorders      |                 |                 |                |
| Ataxia                        |                 |                 |                |
| subjects affected / exposed   | 0 / 28 (0.00%)  | 0 / 35 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)             | 0               | 0               | 1              |
| Balance Disorder              |                 |                 |                |
| subjects affected / exposed   | 1 / 28 (3.57%)  | 0 / 35 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)             | 2               | 0               | 0              |
| Dizziness                     |                 |                 |                |
| subjects affected / exposed   | 1 / 28 (3.57%)  | 2 / 35 (5.71%)  | 1 / 3 (33.33%) |
| occurrences (all)             | 1               | 2               | 1              |
| Dysgeusia                     |                 |                 |                |
| subjects affected / exposed   | 2 / 28 (7.14%)  | 1 / 35 (2.86%)  | 0 / 3 (0.00%)  |
| occurrences (all)             | 2               | 1               | 0              |
| Headache                      |                 |                 |                |
| subjects affected / exposed   | 8 / 28 (28.57%) | 8 / 35 (22.86%) | 2 / 3 (66.67%) |
| occurrences (all)             | 10              | 25              | 3              |
| Hypoaesthesia                 |                 |                 |                |
| subjects affected / exposed   | 0 / 28 (0.00%)  | 0 / 35 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)             | 0               | 0               | 0              |
| Neuralgia                     |                 |                 |                |
| subjects affected / exposed   | 0 / 28 (0.00%)  | 3 / 35 (8.57%)  | 0 / 3 (0.00%)  |
| occurrences (all)             | 0               | 3               | 0              |
| Memory Impairment             |                 |                 |                |
| subjects affected / exposed   | 2 / 28 (7.14%)  | 0 / 35 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)             | 2               | 0               | 0              |
| Neuropathy Peripheral         |                 |                 |                |
| subjects affected / exposed   | 0 / 28 (0.00%)  | 0 / 35 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)             | 0               | 0               | 0              |
| Somnolence                    |                 |                 |                |
| subjects affected / exposed   | 1 / 28 (3.57%)  | 1 / 35 (2.86%)  | 0 / 3 (0.00%)  |
| occurrences (all)             | 1               | 1               | 0              |
| Peripheral Sensory Neuropathy |                 |                 |                |
| subjects affected / exposed   | 0 / 28 (0.00%)  | 0 / 35 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)             | 0               | 0               | 0              |
| Paraesthesia                  |                 |                 |                |

|                                                  |                     |                     |                    |
|--------------------------------------------------|---------------------|---------------------|--------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 28 (0.00%)<br>0 | 0 / 35 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0 |
| Blood and lymphatic system disorders             |                     |                     |                    |
| Lymphadenopathy                                  |                     |                     |                    |
| subjects affected / exposed                      | 0 / 28 (0.00%)      | 0 / 35 (0.00%)      | 0 / 3 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                  |
| Anaemia                                          |                     |                     |                    |
| subjects affected / exposed                      | 1 / 28 (3.57%)      | 3 / 35 (8.57%)      | 0 / 3 (0.00%)      |
| occurrences (all)                                | 1                   | 3                   | 0                  |
| Lymphopenia                                      |                     |                     |                    |
| subjects affected / exposed                      | 0 / 28 (0.00%)      | 0 / 35 (0.00%)      | 0 / 3 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                  |
| Ear and labyrinth disorders                      |                     |                     |                    |
| Ear Pain                                         |                     |                     |                    |
| subjects affected / exposed                      | 0 / 28 (0.00%)      | 1 / 35 (2.86%)      | 0 / 3 (0.00%)      |
| occurrences (all)                                | 0                   | 1                   | 0                  |
| Vertigo                                          |                     |                     |                    |
| subjects affected / exposed                      | 0 / 28 (0.00%)      | 1 / 35 (2.86%)      | 0 / 3 (0.00%)      |
| occurrences (all)                                | 0                   | 1                   | 0                  |
| Eye disorders                                    |                     |                     |                    |
| Accommodation Disorder                           |                     |                     |                    |
| subjects affected / exposed                      | 1 / 28 (3.57%)      | 2 / 35 (5.71%)      | 0 / 3 (0.00%)      |
| occurrences (all)                                | 3                   | 2                   | 0                  |
| Blepharitis                                      |                     |                     |                    |
| subjects affected / exposed                      | 1 / 28 (3.57%)      | 0 / 35 (0.00%)      | 0 / 3 (0.00%)      |
| occurrences (all)                                | 1                   | 0                   | 0                  |
| Cataract Subcapsular                             |                     |                     |                    |
| subjects affected / exposed                      | 1 / 28 (3.57%)      | 0 / 35 (0.00%)      | 0 / 3 (0.00%)      |
| occurrences (all)                                | 1                   | 0                   | 0                  |
| Lacrimation Increased                            |                     |                     |                    |
| subjects affected / exposed                      | 0 / 28 (0.00%)      | 2 / 35 (5.71%)      | 0 / 3 (0.00%)      |
| occurrences (all)                                | 0                   | 2                   | 0                  |
| Eye Pain                                         |                     |                     |                    |
| subjects affected / exposed                      | 0 / 28 (0.00%)      | 0 / 35 (0.00%)      | 0 / 3 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                  |
| Dry Eye                                          |                     |                     |                    |

|                                     |                 |                  |                |
|-------------------------------------|-----------------|------------------|----------------|
| subjects affected / exposed         | 2 / 28 (7.14%)  | 0 / 35 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)                   | 2               | 0                | 0              |
| Colour Blindness Acquired           |                 |                  |                |
| subjects affected / exposed         | 0 / 28 (0.00%)  | 3 / 35 (8.57%)   | 1 / 3 (33.33%) |
| occurrences (all)                   | 0               | 3                | 1              |
| Night Blindness                     |                 |                  |                |
| subjects affected / exposed         | 3 / 28 (10.71%) | 10 / 35 (28.57%) | 1 / 3 (33.33%) |
| occurrences (all)                   | 3               | 12               | 1              |
| Loss Of Visual Contrast Sensitivity |                 |                  |                |
| subjects affected / exposed         | 0 / 28 (0.00%)  | 0 / 35 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)                   | 0               | 0                | 0              |
| Ocular Toxicity                     |                 |                  |                |
| subjects affected / exposed         | 4 / 28 (14.29%) | 4 / 35 (11.43%)  | 1 / 3 (33.33%) |
| occurrences (all)                   | 4               | 7                | 1              |
| Photophobia                         |                 |                  |                |
| subjects affected / exposed         | 3 / 28 (10.71%) | 2 / 35 (5.71%)   | 0 / 3 (0.00%)  |
| occurrences (all)                   | 3               | 2                | 0              |
| Retinal Disorder                    |                 |                  |                |
| subjects affected / exposed         | 1 / 28 (3.57%)  | 3 / 35 (8.57%)   | 0 / 3 (0.00%)  |
| occurrences (all)                   | 1               | 4                | 0              |
| Photopsia                           |                 |                  |                |
| subjects affected / exposed         | 3 / 28 (10.71%) | 5 / 35 (14.29%)  | 0 / 3 (0.00%)  |
| occurrences (all)                   | 3               | 5                | 0              |
| Vision Blurred                      |                 |                  |                |
| subjects affected / exposed         | 5 / 28 (17.86%) | 6 / 35 (17.14%)  | 0 / 3 (0.00%)  |
| occurrences (all)                   | 5               | 7                | 0              |
| Visual Acuity Reduced               |                 |                  |                |
| subjects affected / exposed         | 1 / 28 (3.57%)  | 6 / 35 (17.14%)  | 0 / 3 (0.00%)  |
| occurrences (all)                   | 1               | 8                | 0              |
| Vitreous Floaters                   |                 |                  |                |
| subjects affected / exposed         | 1 / 28 (3.57%)  | 3 / 35 (8.57%)   | 1 / 3 (33.33%) |
| occurrences (all)                   | 1               | 3                | 1              |
| Visual Impairment                   |                 |                  |                |
| subjects affected / exposed         | 6 / 28 (21.43%) | 8 / 35 (22.86%)  | 0 / 3 (0.00%)  |
| occurrences (all)                   | 6               | 11               | 0              |
| Gastrointestinal disorders          |                 |                  |                |

|                             |                  |                  |                 |
|-----------------------------|------------------|------------------|-----------------|
| Abdominal Distension        |                  |                  |                 |
| subjects affected / exposed | 0 / 28 (0.00%)   | 0 / 35 (0.00%)   | 1 / 3 (33.33%)  |
| occurrences (all)           | 0                | 0                | 1               |
| Abdominal Pain              |                  |                  |                 |
| subjects affected / exposed | 5 / 28 (17.86%)  | 5 / 35 (14.29%)  | 0 / 3 (0.00%)   |
| occurrences (all)           | 5                | 6                | 0               |
| Abdominal Pain Upper        |                  |                  |                 |
| subjects affected / exposed | 1 / 28 (3.57%)   | 3 / 35 (8.57%)   | 0 / 3 (0.00%)   |
| occurrences (all)           | 1                | 3                | 0               |
| Dry Mouth                   |                  |                  |                 |
| subjects affected / exposed | 5 / 28 (17.86%)  | 4 / 35 (11.43%)  | 0 / 3 (0.00%)   |
| occurrences (all)           | 5                | 4                | 0               |
| Diarrhoea                   |                  |                  |                 |
| subjects affected / exposed | 25 / 28 (89.29%) | 23 / 35 (65.71%) | 3 / 3 (100.00%) |
| occurrences (all)           | 46               | 39               | 4               |
| Constipation                |                  |                  |                 |
| subjects affected / exposed | 6 / 28 (21.43%)  | 6 / 35 (17.14%)  | 0 / 3 (0.00%)   |
| occurrences (all)           | 6                | 7                | 0               |
| Dyspepsia                   |                  |                  |                 |
| subjects affected / exposed | 0 / 28 (0.00%)   | 1 / 35 (2.86%)   | 1 / 3 (33.33%)  |
| occurrences (all)           | 0                | 1                | 1               |
| Flatulence                  |                  |                  |                 |
| subjects affected / exposed | 0 / 28 (0.00%)   | 2 / 35 (5.71%)   | 0 / 3 (0.00%)   |
| occurrences (all)           | 0                | 2                | 0               |
| Nausea                      |                  |                  |                 |
| subjects affected / exposed | 16 / 28 (57.14%) | 19 / 35 (54.29%) | 1 / 3 (33.33%)  |
| occurrences (all)           | 27               | 38               | 1               |
| Oral Pain                   |                  |                  |                 |
| subjects affected / exposed | 0 / 28 (0.00%)   | 2 / 35 (5.71%)   | 0 / 3 (0.00%)   |
| occurrences (all)           | 0                | 2                | 0               |
| Rectal Haemorrhage          |                  |                  |                 |
| subjects affected / exposed | 2 / 28 (7.14%)   | 0 / 35 (0.00%)   | 0 / 3 (0.00%)   |
| occurrences (all)           | 2                | 0                | 0               |
| Stomatitis                  |                  |                  |                 |
| subjects affected / exposed | 1 / 28 (3.57%)   | 0 / 35 (0.00%)   | 0 / 3 (0.00%)   |
| occurrences (all)           | 1                | 0                | 0               |

|                                                                                |                        |                        |                     |
|--------------------------------------------------------------------------------|------------------------|------------------------|---------------------|
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                   | 13 / 28 (46.43%)<br>18 | 13 / 35 (37.14%)<br>21 | 2 / 3 (66.67%)<br>2 |
| Skin and subcutaneous tissue disorders                                         |                        |                        |                     |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)                   | 2 / 28 (7.14%)<br>2    | 1 / 35 (2.86%)<br>1    | 0 / 3 (0.00%)<br>0  |
| Pain Of Skin<br>subjects affected / exposed<br>occurrences (all)               | 0 / 28 (0.00%)<br>0    | 0 / 35 (0.00%)<br>0    | 0 / 3 (0.00%)<br>0  |
| Dry Skin<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 28 (3.57%)<br>1    | 3 / 35 (8.57%)<br>3    | 0 / 3 (0.00%)<br>0  |
| Dermatitis Acneiform<br>subjects affected / exposed<br>occurrences (all)       | 0 / 28 (0.00%)<br>0    | 0 / 35 (0.00%)<br>0    | 0 / 3 (0.00%)<br>0  |
| Rash<br>subjects affected / exposed<br>occurrences (all)                       | 2 / 28 (7.14%)<br>2    | 2 / 35 (5.71%)<br>2    | 0 / 3 (0.00%)<br>0  |
| Musculoskeletal and connective tissue disorders                                |                        |                        |                     |
| Back Pain<br>subjects affected / exposed<br>occurrences (all)                  | 8 / 28 (28.57%)<br>8   | 5 / 35 (14.29%)<br>7   | 0 / 3 (0.00%)<br>0  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 28 (3.57%)<br>2    | 4 / 35 (11.43%)<br>6   | 0 / 3 (0.00%)<br>0  |
| Musculoskeletal Chest Pain<br>subjects affected / exposed<br>occurrences (all) | 1 / 28 (3.57%)<br>1    | 2 / 35 (5.71%)<br>2    | 0 / 3 (0.00%)<br>0  |
| Muscle Spasms<br>subjects affected / exposed<br>occurrences (all)              | 2 / 28 (7.14%)<br>3    | 1 / 35 (2.86%)<br>1    | 0 / 3 (0.00%)<br>0  |
| Flank Pain<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 28 (0.00%)<br>0    | 0 / 35 (0.00%)<br>0    | 0 / 3 (0.00%)<br>0  |
| Musculoskeletal Pain                                                           |                        |                        |                     |

|                                    |                 |                 |                |
|------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed        | 3 / 28 (10.71%) | 2 / 35 (5.71%)  | 1 / 3 (33.33%) |
| occurrences (all)                  | 3               | 2               | 2              |
| Bone Pain                          |                 |                 |                |
| subjects affected / exposed        | 0 / 28 (0.00%)  | 2 / 35 (5.71%)  | 0 / 3 (0.00%)  |
| occurrences (all)                  | 0               | 2               | 0              |
| Myalgia                            |                 |                 |                |
| subjects affected / exposed        | 0 / 28 (0.00%)  | 4 / 35 (11.43%) | 1 / 3 (33.33%) |
| occurrences (all)                  | 0               | 6               | 1              |
| Neck Pain                          |                 |                 |                |
| subjects affected / exposed        | 2 / 28 (7.14%)  | 0 / 35 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)                  | 2               | 0               | 1              |
| Pain In Extremity                  |                 |                 |                |
| subjects affected / exposed        | 2 / 28 (7.14%)  | 4 / 35 (11.43%) | 0 / 3 (0.00%)  |
| occurrences (all)                  | 2               | 4               | 0              |
| Infections and infestations        |                 |                 |                |
| Conjunctivitis                     |                 |                 |                |
| subjects affected / exposed        | 0 / 28 (0.00%)  | 0 / 35 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                  | 0               | 0               | 0              |
| Influenza                          |                 |                 |                |
| subjects affected / exposed        | 0 / 28 (0.00%)  | 0 / 35 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                  | 0               | 0               | 0              |
| Nasopharyngitis                    |                 |                 |                |
| subjects affected / exposed        | 0 / 28 (0.00%)  | 0 / 35 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)                  | 0               | 0               | 1              |
| Respiratory Tract Infection        |                 |                 |                |
| subjects affected / exposed        | 0 / 28 (0.00%)  | 0 / 35 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                  | 0               | 0               | 0              |
| Upper Respiratory Tract Infection  |                 |                 |                |
| subjects affected / exposed        | 0 / 28 (0.00%)  | 2 / 35 (5.71%)  | 0 / 3 (0.00%)  |
| occurrences (all)                  | 0               | 2               | 0              |
| Urinary Tract Infection            |                 |                 |                |
| subjects affected / exposed        | 1 / 28 (3.57%)  | 2 / 35 (5.71%)  | 0 / 3 (0.00%)  |
| occurrences (all)                  | 1               | 2               | 0              |
| Metabolism and nutrition disorders |                 |                 |                |
| Decreased Appetite                 |                 |                 |                |

|                             |                  |                  |                |
|-----------------------------|------------------|------------------|----------------|
| subjects affected / exposed | 17 / 28 (60.71%) | 15 / 35 (42.86%) | 1 / 3 (33.33%) |
| occurrences (all)           | 17               | 17               | 1              |
| Dehydration                 |                  |                  |                |
| subjects affected / exposed | 1 / 28 (3.57%)   | 1 / 35 (2.86%)   | 0 / 3 (0.00%)  |
| occurrences (all)           | 1                | 1                | 0              |
| Hyperglycaemia              |                  |                  |                |
| subjects affected / exposed | 1 / 28 (3.57%)   | 0 / 35 (0.00%)   | 1 / 3 (33.33%) |
| occurrences (all)           | 1                | 0                | 1              |
| Hypokalaemia                |                  |                  |                |
| subjects affected / exposed | 2 / 28 (7.14%)   | 2 / 35 (5.71%)   | 0 / 3 (0.00%)  |
| occurrences (all)           | 3                | 5                | 0              |
| Hypomagnesaemia             |                  |                  |                |
| subjects affected / exposed | 1 / 28 (3.57%)   | 2 / 35 (5.71%)   | 0 / 3 (0.00%)  |
| occurrences (all)           | 1                | 3                | 0              |
| Hyponatraemia               |                  |                  |                |
| subjects affected / exposed | 2 / 28 (7.14%)   | 4 / 35 (11.43%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 2                | 4                | 0              |

| <b>Non-serious adverse events</b>                                      | EML4-ALK<br>translocation | Modified EGFR<br>mutant | KRAS and EGFR wild<br>type |
|------------------------------------------------------------------------|---------------------------|-------------------------|----------------------------|
| Total subjects affected by non-serious<br>adverse events               |                           |                         |                            |
| subjects affected / exposed                                            | 22 / 22 (100.00%)         | 31 / 31 (100.00%)       | 33 / 34 (97.06%)           |
| Neoplasms benign, malignant and<br>unspecified (incl cysts and polyps) |                           |                         |                            |
| Cancer Pain                                                            |                           |                         |                            |
| subjects affected / exposed                                            | 0 / 22 (0.00%)            | 0 / 31 (0.00%)          | 0 / 34 (0.00%)             |
| occurrences (all)                                                      | 0                         | 0                       | 0                          |
| Vascular disorders                                                     |                           |                         |                            |
| Deep Vein Thrombosis                                                   |                           |                         |                            |
| subjects affected / exposed                                            | 0 / 22 (0.00%)            | 0 / 31 (0.00%)          | 0 / 34 (0.00%)             |
| occurrences (all)                                                      | 0                         | 0                       | 0                          |
| Hot Flush                                                              |                           |                         |                            |
| subjects affected / exposed                                            | 2 / 22 (9.09%)            | 1 / 31 (3.23%)          | 1 / 34 (2.94%)             |
| occurrences (all)                                                      | 2                         | 1                       | 1                          |
| Hypertension                                                           |                           |                         |                            |
| subjects affected / exposed                                            | 3 / 22 (13.64%)           | 5 / 31 (16.13%)         | 3 / 34 (8.82%)             |
| occurrences (all)                                                      | 4                         | 8                       | 4                          |
| Hypotension                                                            |                           |                         |                            |

|                                                         |                     |                     |                     |
|---------------------------------------------------------|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)        | 0 / 22 (0.00%)<br>0 | 0 / 31 (0.00%)<br>0 | 0 / 34 (0.00%)<br>0 |
| General disorders and administration<br>site conditions |                     |                     |                     |
| Asthenia                                                |                     |                     |                     |
| subjects affected / exposed                             | 10 / 22 (45.45%)    | 5 / 31 (16.13%)     | 10 / 34 (29.41%)    |
| occurrences (all)                                       | 14                  | 6                   | 16                  |
| Catheter Site Pain                                      |                     |                     |                     |
| subjects affected / exposed                             | 0 / 22 (0.00%)      | 2 / 31 (6.45%)      | 0 / 34 (0.00%)      |
| occurrences (all)                                       | 0                   | 2                   | 0                   |
| Chest Pain                                              |                     |                     |                     |
| subjects affected / exposed                             | 4 / 22 (18.18%)     | 0 / 31 (0.00%)      | 0 / 34 (0.00%)      |
| occurrences (all)                                       | 8                   | 0                   | 0                   |
| Pain                                                    |                     |                     |                     |
| subjects affected / exposed                             | 0 / 22 (0.00%)      | 1 / 31 (3.23%)      | 6 / 34 (17.65%)     |
| occurrences (all)                                       | 0                   | 1                   | 8                   |
| Fatigue                                                 |                     |                     |                     |
| subjects affected / exposed                             | 3 / 22 (13.64%)     | 15 / 31 (48.39%)    | 13 / 34 (38.24%)    |
| occurrences (all)                                       | 3                   | 17                  | 17                  |
| Gait Disturbance                                        |                     |                     |                     |
| subjects affected / exposed                             | 2 / 22 (9.09%)      | 0 / 31 (0.00%)      | 2 / 34 (5.88%)      |
| occurrences (all)                                       | 2                   | 0                   | 2                   |
| Non-Cardiac Chest Pain                                  |                     |                     |                     |
| subjects affected / exposed                             | 2 / 22 (9.09%)      | 1 / 31 (3.23%)      | 2 / 34 (5.88%)      |
| occurrences (all)                                       | 2                   | 1                   | 2                   |
| Oedema Peripheral                                       |                     |                     |                     |
| subjects affected / exposed                             | 3 / 22 (13.64%)     | 3 / 31 (9.68%)      | 1 / 34 (2.94%)      |
| occurrences (all)                                       | 3                   | 3                   | 1                   |
| Pyrexia                                                 |                     |                     |                     |
| subjects affected / exposed                             | 6 / 22 (27.27%)     | 4 / 31 (12.90%)     | 4 / 34 (11.76%)     |
| occurrences (all)                                       | 7                   | 5                   | 5                   |
| Reproductive system and breast<br>disorders             |                     |                     |                     |
| Pelvic Pain                                             |                     |                     |                     |
| subjects affected / exposed                             | 0 / 22 (0.00%)      | 0 / 31 (0.00%)      | 0 / 34 (0.00%)      |
| occurrences (all)                                       | 0                   | 0                   | 0                   |
| Respiratory, thoracic and mediastinal<br>disorders      |                     |                     |                     |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| Atelectasis                 |                 |                 |                 |
| subjects affected / exposed | 0 / 22 (0.00%)  | 2 / 31 (6.45%)  | 1 / 34 (2.94%)  |
| occurrences (all)           | 0               | 2               | 1               |
| Cough                       |                 |                 |                 |
| subjects affected / exposed | 7 / 22 (31.82%) | 8 / 31 (25.81%) | 9 / 34 (26.47%) |
| occurrences (all)           | 11              | 9               | 16              |
| Dyspnoea                    |                 |                 |                 |
| subjects affected / exposed | 2 / 22 (9.09%)  | 2 / 31 (6.45%)  | 9 / 34 (26.47%) |
| occurrences (all)           | 3               | 3               | 9               |
| Dysphonia                   |                 |                 |                 |
| subjects affected / exposed | 1 / 22 (4.55%)  | 1 / 31 (3.23%)  | 2 / 34 (5.88%)  |
| occurrences (all)           | 1               | 1               | 2               |
| Dyspnoea Exertional         |                 |                 |                 |
| subjects affected / exposed | 0 / 22 (0.00%)  | 0 / 31 (0.00%)  | 2 / 34 (5.88%)  |
| occurrences (all)           | 0               | 0               | 2               |
| Haemoptysis                 |                 |                 |                 |
| subjects affected / exposed | 1 / 22 (4.55%)  | 0 / 31 (0.00%)  | 4 / 34 (11.76%) |
| occurrences (all)           | 1               | 0               | 4               |
| Epistaxis                   |                 |                 |                 |
| subjects affected / exposed | 0 / 22 (0.00%)  | 0 / 31 (0.00%)  | 1 / 34 (2.94%)  |
| occurrences (all)           | 0               | 0               | 1               |
| Oropharyngeal Pain          |                 |                 |                 |
| subjects affected / exposed | 0 / 22 (0.00%)  | 3 / 31 (9.68%)  | 1 / 34 (2.94%)  |
| occurrences (all)           | 0               | 3               | 2               |
| Pleural Effusion            |                 |                 |                 |
| subjects affected / exposed | 2 / 22 (9.09%)  | 2 / 31 (6.45%)  | 3 / 34 (8.82%)  |
| occurrences (all)           | 2               | 2               | 3               |
| Wheezing                    |                 |                 |                 |
| subjects affected / exposed | 1 / 22 (4.55%)  | 0 / 31 (0.00%)  | 0 / 34 (0.00%)  |
| occurrences (all)           | 1               | 0               | 0               |
| Rhinorrhoea                 |                 |                 |                 |
| subjects affected / exposed | 0 / 22 (0.00%)  | 0 / 31 (0.00%)  | 2 / 34 (5.88%)  |
| occurrences (all)           | 0               | 0               | 2               |
| Productive Cough            |                 |                 |                 |
| subjects affected / exposed | 2 / 22 (9.09%)  | 1 / 31 (3.23%)  | 7 / 34 (20.59%) |
| occurrences (all)           | 5               | 2               | 7               |

|                                      |                 |                 |                 |
|--------------------------------------|-----------------|-----------------|-----------------|
| Psychiatric disorders                |                 |                 |                 |
| Anxiety                              |                 |                 |                 |
| subjects affected / exposed          | 2 / 22 (9.09%)  | 2 / 31 (6.45%)  | 3 / 34 (8.82%)  |
| occurrences (all)                    | 2               | 2               | 3               |
| Depressed Mood                       |                 |                 |                 |
| subjects affected / exposed          | 2 / 22 (9.09%)  | 0 / 31 (0.00%)  | 2 / 34 (5.88%)  |
| occurrences (all)                    | 3               | 0               | 2               |
| Hallucination                        |                 |                 |                 |
| subjects affected / exposed          | 2 / 22 (9.09%)  | 0 / 31 (0.00%)  | 0 / 34 (0.00%)  |
| occurrences (all)                    | 2               | 0               | 0               |
| Insomnia                             |                 |                 |                 |
| subjects affected / exposed          | 5 / 22 (22.73%) | 4 / 31 (12.90%) | 6 / 34 (17.65%) |
| occurrences (all)                    | 6               | 4               | 6               |
| Nervousness                          |                 |                 |                 |
| subjects affected / exposed          | 2 / 22 (9.09%)  | 0 / 31 (0.00%)  | 1 / 34 (2.94%)  |
| occurrences (all)                    | 2               | 0               | 1               |
| Investigations                       |                 |                 |                 |
| Alanine Aminotransferase Increased   |                 |                 |                 |
| subjects affected / exposed          | 1 / 22 (4.55%)  | 0 / 31 (0.00%)  | 1 / 34 (2.94%)  |
| occurrences (all)                    | 1               | 0               | 1               |
| Blood Alkaline Phosphatase Increased |                 |                 |                 |
| subjects affected / exposed          | 1 / 22 (4.55%)  | 3 / 31 (9.68%)  | 1 / 34 (2.94%)  |
| occurrences (all)                    | 1               | 3               | 1               |
| Aspartate Aminotransferase Increased |                 |                 |                 |
| subjects affected / exposed          | 2 / 22 (9.09%)  | 2 / 31 (6.45%)  | 1 / 34 (2.94%)  |
| occurrences (all)                    | 2               | 3               | 1               |
| Blood Creatinine Increased           |                 |                 |                 |
| subjects affected / exposed          | 1 / 22 (4.55%)  | 1 / 31 (3.23%)  | 0 / 34 (0.00%)  |
| occurrences (all)                    | 1               | 1               | 0               |
| C-Reactive Protein Increased         |                 |                 |                 |
| subjects affected / exposed          | 0 / 22 (0.00%)  | 2 / 31 (6.45%)  | 0 / 34 (0.00%)  |
| occurrences (all)                    | 0               | 2               | 0               |
| Gamma-Glutamyltransferase Increased  |                 |                 |                 |
| subjects affected / exposed          | 0 / 22 (0.00%)  | 3 / 31 (9.68%)  | 1 / 34 (2.94%)  |
| occurrences (all)                    | 0               | 3               | 1               |

|                                                                                        |                        |                        |                       |
|----------------------------------------------------------------------------------------|------------------------|------------------------|-----------------------|
| Heart Rate Increased<br>subjects affected / exposed<br>occurrences (all)               | 0 / 22 (0.00%)<br>0    | 0 / 31 (0.00%)<br>0    | 0 / 34 (0.00%)<br>0   |
| Hypophonesis<br>subjects affected / exposed<br>occurrences (all)                       | 2 / 22 (9.09%)<br>2    | 0 / 31 (0.00%)<br>0    | 1 / 34 (2.94%)<br>1   |
| Transaminases Increased<br>subjects affected / exposed<br>occurrences (all)            | 0 / 22 (0.00%)<br>0    | 2 / 31 (6.45%)<br>2    | 0 / 34 (0.00%)<br>0   |
| Weight Decreased<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 22 (4.55%)<br>1    | 4 / 31 (12.90%)<br>4   | 3 / 34 (8.82%)<br>3   |
| Cardiac disorders<br>Tachycardia<br>subjects affected / exposed<br>occurrences (all)   | 1 / 22 (4.55%)<br>2    | 0 / 31 (0.00%)<br>0    | 1 / 34 (2.94%)<br>1   |
| Nervous system disorders<br>Ataxia<br>subjects affected / exposed<br>occurrences (all) | 0 / 22 (0.00%)<br>0    | 0 / 31 (0.00%)<br>0    | 0 / 34 (0.00%)<br>0   |
| Balance Disorder<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 22 (4.55%)<br>1    | 3 / 31 (9.68%)<br>3    | 0 / 34 (0.00%)<br>0   |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                          | 1 / 22 (4.55%)<br>1    | 3 / 31 (9.68%)<br>3    | 1 / 34 (2.94%)<br>1   |
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 22 (0.00%)<br>0    | 1 / 31 (3.23%)<br>1    | 1 / 34 (2.94%)<br>1   |
| Headache<br>subjects affected / exposed<br>occurrences (all)                           | 14 / 22 (63.64%)<br>41 | 13 / 31 (41.94%)<br>15 | 8 / 34 (23.53%)<br>13 |
| Hypoaesthesia<br>subjects affected / exposed<br>occurrences (all)                      | 2 / 22 (9.09%)<br>4    | 2 / 31 (6.45%)<br>2    | 2 / 34 (5.88%)<br>2   |
| Neuralgia                                                                              |                        |                        |                       |

|                                      |                 |                 |                 |
|--------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed          | 0 / 22 (0.00%)  | 0 / 31 (0.00%)  | 1 / 34 (2.94%)  |
| occurrences (all)                    | 0               | 0               | 1               |
| Memory Impairment                    |                 |                 |                 |
| subjects affected / exposed          | 0 / 22 (0.00%)  | 0 / 31 (0.00%)  | 1 / 34 (2.94%)  |
| occurrences (all)                    | 0               | 0               | 1               |
| Neuropathy Peripheral                |                 |                 |                 |
| subjects affected / exposed          | 0 / 22 (0.00%)  | 1 / 31 (3.23%)  | 2 / 34 (5.88%)  |
| occurrences (all)                    | 0               | 1               | 2               |
| Somnolence                           |                 |                 |                 |
| subjects affected / exposed          | 2 / 22 (9.09%)  | 0 / 31 (0.00%)  | 2 / 34 (5.88%)  |
| occurrences (all)                    | 2               | 0               | 2               |
| Peripheral Sensory Neuropathy        |                 |                 |                 |
| subjects affected / exposed          | 0 / 22 (0.00%)  | 0 / 31 (0.00%)  | 2 / 34 (5.88%)  |
| occurrences (all)                    | 0               | 0               | 2               |
| Paraesthesia                         |                 |                 |                 |
| subjects affected / exposed          | 3 / 22 (13.64%) | 3 / 31 (9.68%)  | 2 / 34 (5.88%)  |
| occurrences (all)                    | 3               | 5               | 2               |
| Blood and lymphatic system disorders |                 |                 |                 |
| Lymphadenopathy                      |                 |                 |                 |
| subjects affected / exposed          | 0 / 22 (0.00%)  | 0 / 31 (0.00%)  | 2 / 34 (5.88%)  |
| occurrences (all)                    | 0               | 0               | 2               |
| Anaemia                              |                 |                 |                 |
| subjects affected / exposed          | 3 / 22 (13.64%) | 4 / 31 (12.90%) | 5 / 34 (14.71%) |
| occurrences (all)                    | 3               | 4               | 6               |
| Lymphopenia                          |                 |                 |                 |
| subjects affected / exposed          | 0 / 22 (0.00%)  | 2 / 31 (6.45%)  | 0 / 34 (0.00%)  |
| occurrences (all)                    | 0               | 2               | 0               |
| Ear and labyrinth disorders          |                 |                 |                 |
| Ear Pain                             |                 |                 |                 |
| subjects affected / exposed          | 0 / 22 (0.00%)  | 0 / 31 (0.00%)  | 2 / 34 (5.88%)  |
| occurrences (all)                    | 0               | 0               | 3               |
| Vertigo                              |                 |                 |                 |
| subjects affected / exposed          | 2 / 22 (9.09%)  | 1 / 31 (3.23%)  | 2 / 34 (5.88%)  |
| occurrences (all)                    | 2               | 1               | 2               |
| Eye disorders                        |                 |                 |                 |

|                                     |                 |                  |                 |
|-------------------------------------|-----------------|------------------|-----------------|
| Accommodation Disorder              |                 |                  |                 |
| subjects affected / exposed         | 2 / 22 (9.09%)  | 5 / 31 (16.13%)  | 2 / 34 (5.88%)  |
| occurrences (all)                   | 2               | 5                | 2               |
| Blepharitis                         |                 |                  |                 |
| subjects affected / exposed         | 0 / 22 (0.00%)  | 2 / 31 (6.45%)   | 0 / 34 (0.00%)  |
| occurrences (all)                   | 0               | 2                | 0               |
| Cataract Subcapsular                |                 |                  |                 |
| subjects affected / exposed         | 0 / 22 (0.00%)  | 0 / 31 (0.00%)   | 2 / 34 (5.88%)  |
| occurrences (all)                   | 0               | 0                | 2               |
| Lacrimation Increased               |                 |                  |                 |
| subjects affected / exposed         | 0 / 22 (0.00%)  | 1 / 31 (3.23%)   | 0 / 34 (0.00%)  |
| occurrences (all)                   | 0               | 1                | 0               |
| Eye Pain                            |                 |                  |                 |
| subjects affected / exposed         | 0 / 22 (0.00%)  | 2 / 31 (6.45%)   | 1 / 34 (2.94%)  |
| occurrences (all)                   | 0               | 2                | 1               |
| Dry Eye                             |                 |                  |                 |
| subjects affected / exposed         | 2 / 22 (9.09%)  | 0 / 31 (0.00%)   | 1 / 34 (2.94%)  |
| occurrences (all)                   | 2               | 0                | 2               |
| Colour Blindness Acquired           |                 |                  |                 |
| subjects affected / exposed         | 5 / 22 (22.73%) | 4 / 31 (12.90%)  | 2 / 34 (5.88%)  |
| occurrences (all)                   | 6               | 4                | 2               |
| Night Blindness                     |                 |                  |                 |
| subjects affected / exposed         | 5 / 22 (22.73%) | 10 / 31 (32.26%) | 6 / 34 (17.65%) |
| occurrences (all)                   | 9               | 13               | 7               |
| Loss Of Visual Contrast Sensitivity |                 |                  |                 |
| subjects affected / exposed         | 0 / 22 (0.00%)  | 0 / 31 (0.00%)   | 2 / 34 (5.88%)  |
| occurrences (all)                   | 0               | 0                | 2               |
| Ocular Toxicity                     |                 |                  |                 |
| subjects affected / exposed         | 3 / 22 (13.64%) | 3 / 31 (9.68%)   | 1 / 34 (2.94%)  |
| occurrences (all)                   | 3               | 5                | 1               |
| Photophobia                         |                 |                  |                 |
| subjects affected / exposed         | 0 / 22 (0.00%)  | 2 / 31 (6.45%)   | 5 / 34 (14.71%) |
| occurrences (all)                   | 0               | 2                | 5               |
| Retinal Disorder                    |                 |                  |                 |
| subjects affected / exposed         | 5 / 22 (22.73%) | 7 / 31 (22.58%)  | 1 / 34 (2.94%)  |
| occurrences (all)                   | 5               | 7                | 1               |

|                             |                  |                  |                  |
|-----------------------------|------------------|------------------|------------------|
| Photopsia                   |                  |                  |                  |
| subjects affected / exposed | 10 / 22 (45.45%) | 6 / 31 (19.35%)  | 10 / 34 (29.41%) |
| occurrences (all)           | 11               | 6                | 11               |
| Vision Blurred              |                  |                  |                  |
| subjects affected / exposed | 6 / 22 (27.27%)  | 6 / 31 (19.35%)  | 7 / 34 (20.59%)  |
| occurrences (all)           | 6                | 6                | 9                |
| Visual Acuity Reduced       |                  |                  |                  |
| subjects affected / exposed | 7 / 22 (31.82%)  | 5 / 31 (16.13%)  | 7 / 34 (20.59%)  |
| occurrences (all)           | 7                | 6                | 10               |
| Vitreous Floaters           |                  |                  |                  |
| subjects affected / exposed | 1 / 22 (4.55%)   | 2 / 31 (6.45%)   | 1 / 34 (2.94%)   |
| occurrences (all)           | 1                | 2                | 1                |
| Visual Impairment           |                  |                  |                  |
| subjects affected / exposed | 6 / 22 (27.27%)  | 7 / 31 (22.58%)  | 3 / 34 (8.82%)   |
| occurrences (all)           | 6                | 8                | 4                |
| Gastrointestinal disorders  |                  |                  |                  |
| Abdominal Distension        |                  |                  |                  |
| subjects affected / exposed | 2 / 22 (9.09%)   | 0 / 31 (0.00%)   | 2 / 34 (5.88%)   |
| occurrences (all)           | 2                | 0                | 2                |
| Abdominal Pain              |                  |                  |                  |
| subjects affected / exposed | 6 / 22 (27.27%)  | 2 / 31 (6.45%)   | 4 / 34 (11.76%)  |
| occurrences (all)           | 10               | 2                | 4                |
| Abdominal Pain Upper        |                  |                  |                  |
| subjects affected / exposed | 0 / 22 (0.00%)   | 2 / 31 (6.45%)   | 2 / 34 (5.88%)   |
| occurrences (all)           | 0                | 3                | 2                |
| Dry Mouth                   |                  |                  |                  |
| subjects affected / exposed | 0 / 22 (0.00%)   | 1 / 31 (3.23%)   | 6 / 34 (17.65%)  |
| occurrences (all)           | 0                | 1                | 6                |
| Diarrhoea                   |                  |                  |                  |
| subjects affected / exposed | 17 / 22 (77.27%) | 24 / 31 (77.42%) | 25 / 34 (73.53%) |
| occurrences (all)           | 79               | 105              | 72               |
| Constipation                |                  |                  |                  |
| subjects affected / exposed | 5 / 22 (22.73%)  | 5 / 31 (16.13%)  | 5 / 34 (14.71%)  |
| occurrences (all)           | 6                | 5                | 6                |
| Dyspepsia                   |                  |                  |                  |

|                                        |                  |                  |                  |
|----------------------------------------|------------------|------------------|------------------|
| subjects affected / exposed            | 4 / 22 (18.18%)  | 3 / 31 (9.68%)   | 1 / 34 (2.94%)   |
| occurrences (all)                      | 11               | 5                | 1                |
| Flatulence                             |                  |                  |                  |
| subjects affected / exposed            | 0 / 22 (0.00%)   | 0 / 31 (0.00%)   | 1 / 34 (2.94%)   |
| occurrences (all)                      | 0                | 0                | 1                |
| Nausea                                 |                  |                  |                  |
| subjects affected / exposed            | 11 / 22 (50.00%) | 12 / 31 (38.71%) | 13 / 34 (38.24%) |
| occurrences (all)                      | 21               | 22               | 18               |
| Oral Pain                              |                  |                  |                  |
| subjects affected / exposed            | 0 / 22 (0.00%)   | 0 / 31 (0.00%)   | 0 / 34 (0.00%)   |
| occurrences (all)                      | 0                | 0                | 0                |
| Rectal Haemorrhage                     |                  |                  |                  |
| subjects affected / exposed            | 0 / 22 (0.00%)   | 0 / 31 (0.00%)   | 1 / 34 (2.94%)   |
| occurrences (all)                      | 0                | 0                | 1                |
| Stomatitis                             |                  |                  |                  |
| subjects affected / exposed            | 0 / 22 (0.00%)   | 1 / 31 (3.23%)   | 2 / 34 (5.88%)   |
| occurrences (all)                      | 0                | 1                | 2                |
| Vomiting                               |                  |                  |                  |
| subjects affected / exposed            | 9 / 22 (40.91%)  | 4 / 31 (12.90%)  | 4 / 34 (11.76%)  |
| occurrences (all)                      | 18               | 26               | 11               |
| Skin and subcutaneous tissue disorders |                  |                  |                  |
| Pruritus                               |                  |                  |                  |
| subjects affected / exposed            | 1 / 22 (4.55%)   | 4 / 31 (12.90%)  | 1 / 34 (2.94%)   |
| occurrences (all)                      | 1                | 5                | 1                |
| Pain Of Skin                           |                  |                  |                  |
| subjects affected / exposed            | 0 / 22 (0.00%)   | 0 / 31 (0.00%)   | 2 / 34 (5.88%)   |
| occurrences (all)                      | 0                | 0                | 10               |
| Dry Skin                               |                  |                  |                  |
| subjects affected / exposed            | 0 / 22 (0.00%)   | 4 / 31 (12.90%)  | 1 / 34 (2.94%)   |
| occurrences (all)                      | 0                | 5                | 1                |
| Dermatitis Acneiform                   |                  |                  |                  |
| subjects affected / exposed            | 1 / 22 (4.55%)   | 2 / 31 (6.45%)   | 0 / 34 (0.00%)   |
| occurrences (all)                      | 1                | 7                | 0                |
| Rash                                   |                  |                  |                  |
| subjects affected / exposed            | 1 / 22 (4.55%)   | 1 / 31 (3.23%)   | 0 / 34 (0.00%)   |
| occurrences (all)                      | 1                | 1                | 0                |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Back Pain                                       |                 |                 |                 |
| subjects affected / exposed                     | 3 / 22 (13.64%) | 7 / 31 (22.58%) | 8 / 34 (23.53%) |
| occurrences (all)                               | 4               | 7               | 8               |
| Arthralgia                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 22 (0.00%)  | 1 / 31 (3.23%)  | 2 / 34 (5.88%)  |
| occurrences (all)                               | 0               | 1               | 2               |
| Musculoskeletal Chest Pain                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 22 (4.55%)  | 2 / 31 (6.45%)  | 2 / 34 (5.88%)  |
| occurrences (all)                               | 1               | 3               | 2               |
| Muscle Spasms                                   |                 |                 |                 |
| subjects affected / exposed                     | 3 / 22 (13.64%) | 0 / 31 (0.00%)  | 1 / 34 (2.94%)  |
| occurrences (all)                               | 4               | 0               | 3               |
| Flank Pain                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 22 (0.00%)  | 4 / 31 (12.90%) | 0 / 34 (0.00%)  |
| occurrences (all)                               | 0               | 6               | 0               |
| Musculoskeletal Pain                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 22 (4.55%)  | 2 / 31 (6.45%)  | 5 / 34 (14.71%) |
| occurrences (all)                               | 1               | 2               | 7               |
| Bone Pain                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 22 (4.55%)  | 3 / 31 (9.68%)  | 1 / 34 (2.94%)  |
| occurrences (all)                               | 1               | 7               | 1               |
| Myalgia                                         |                 |                 |                 |
| subjects affected / exposed                     | 5 / 22 (22.73%) | 6 / 31 (19.35%) | 4 / 34 (11.76%) |
| occurrences (all)                               | 13              | 13              | 7               |
| Neck Pain                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 22 (4.55%)  | 2 / 31 (6.45%)  | 4 / 34 (11.76%) |
| occurrences (all)                               | 1               | 2               | 4               |
| Pain In Extremity                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 22 (4.55%)  | 1 / 31 (3.23%)  | 4 / 34 (11.76%) |
| occurrences (all)                               | 2               | 1               | 4               |
| Infections and infestations                     |                 |                 |                 |
| Conjunctivitis                                  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 22 (9.09%)  | 1 / 31 (3.23%)  | 0 / 34 (0.00%)  |
| occurrences (all)                               | 2               | 1               | 0               |
| Influenza                                       |                 |                 |                 |

|                                    |                 |                  |                  |
|------------------------------------|-----------------|------------------|------------------|
| subjects affected / exposed        | 0 / 22 (0.00%)  | 3 / 31 (9.68%)   | 1 / 34 (2.94%)   |
| occurrences (all)                  | 0               | 3                | 1                |
| Nasopharyngitis                    |                 |                  |                  |
| subjects affected / exposed        | 1 / 22 (4.55%)  | 4 / 31 (12.90%)  | 1 / 34 (2.94%)   |
| occurrences (all)                  | 1               | 6                | 3                |
| Respiratory Tract Infection        |                 |                  |                  |
| subjects affected / exposed        | 0 / 22 (0.00%)  | 0 / 31 (0.00%)   | 2 / 34 (5.88%)   |
| occurrences (all)                  | 0               | 0                | 2                |
| Upper Respiratory Tract Infection  |                 |                  |                  |
| subjects affected / exposed        | 2 / 22 (9.09%)  | 4 / 31 (12.90%)  | 1 / 34 (2.94%)   |
| occurrences (all)                  | 4               | 6                | 2                |
| Urinary Tract Infection            |                 |                  |                  |
| subjects affected / exposed        | 0 / 22 (0.00%)  | 1 / 31 (3.23%)   | 0 / 34 (0.00%)   |
| occurrences (all)                  | 0               | 1                | 0                |
| Metabolism and nutrition disorders |                 |                  |                  |
| Decreased Appetite                 |                 |                  |                  |
| subjects affected / exposed        | 8 / 22 (36.36%) | 10 / 31 (32.26%) | 12 / 34 (35.29%) |
| occurrences (all)                  | 9               | 15               | 15               |
| Dehydration                        |                 |                  |                  |
| subjects affected / exposed        | 1 / 22 (4.55%)  | 1 / 31 (3.23%)   | 3 / 34 (8.82%)   |
| occurrences (all)                  | 1               | 1                | 3                |
| Hyperglycaemia                     |                 |                  |                  |
| subjects affected / exposed        | 0 / 22 (0.00%)  | 1 / 31 (3.23%)   | 1 / 34 (2.94%)   |
| occurrences (all)                  | 0               | 1                | 1                |
| Hypokalaemia                       |                 |                  |                  |
| subjects affected / exposed        | 2 / 22 (9.09%)  | 1 / 31 (3.23%)   | 0 / 34 (0.00%)   |
| occurrences (all)                  | 2               | 2                | 0                |
| Hypomagnesaemia                    |                 |                  |                  |
| subjects affected / exposed        | 0 / 22 (0.00%)  | 0 / 31 (0.00%)   | 1 / 34 (2.94%)   |
| occurrences (all)                  | 0               | 0                | 1                |
| Hyponatraemia                      |                 |                  |                  |
| subjects affected / exposed        | 0 / 22 (0.00%)  | 1 / 31 (3.23%)   | 0 / 34 (0.00%)   |
| occurrences (all)                  | 0               | 1                | 0                |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 11 February 2011 | <p>This amendment was issued 14 months after study start (09 Nov 2010) and after the inclusion of 116 patients, introduced the following changes: The main purpose of this amendment was to add an additional fifth stratum that would enroll 30 patients with EGFR activating mutations (i.e. exon 18 21), who were less heavily pretreated than patients in the current EGFR stratum (up to two prior lines in comparison to four prior therapies). Preliminary data from the ongoing trial had shown evidence of activity in patients with EGFR activating mutations that had been previously treated with EGFR TKIs. As of 15-Nov-2011, 5/22 evaluable patients had a partial response (four confirmed, one unconfirmed). Because of the efficacy trend observed in the EGFR mutant cohort, 30 additional patients with EGFR mutation were to be enrolled to further assess AUY922 activity in this patient population. In contrast to the previous EGFR mutant stratum, patients enrolled to this new stratum were less heavily pretreated (up to two prior lines), would have no history of CNS metastasis, and would have a performance status of 0 to 1. The reason to enroll less heavily pretreated patients with EGFR mutations was due to the observation that a high number of EGFR mutant patients, nine patients in total, discontinued study participation due to early disease progression prior to completing first radiological assessment (6 ±1weeks), reflecting the fact that most patients had advanced disease, brain metastasis, and had received multiple previous lines of therapies; In addition, all patients to be enrolled to the fifth EGFR mutation stratum were required to undergo baseline biopsy prior to study enrollment in order to understand resistance mechanism to EGFR TKI, as pre-clinical data suggested that HSP90 inhibition may have different sensitivity based on the mutated EGFR, such as T790M (Shimamura et al 2005);</p> |
| 12 January 2012  | <p>This amendment was issued 14 months after study start (09 Nov 2010) and after the inclusion of 116 patients, introduced the following changes: The main purpose of this amendment was to add an additional fifth stratum that would enroll 30 patients with EGFR activating mutations (i.e. exon 18 21), who were less heavily pretreated than patients in the current EGFR stratum (up to two prior lines in comparison to four prior therapies). Preliminary data from the ongoing trial had shown evidence of activity in patients with EGFR activating mutations that had been previously treated with EGFR TKIs. As of 15-Nov-2011, 5/22 evaluable patients had a partial response (four confirmed, one unconfirmed). Because of the efficacy trend observed in the EGFR mutant cohort, 30 additional patients with EGFR mutation were to be enrolled to further assess AUY922 activity in this patient population. In contrast to the previous EGFR mutant stratum, patients enrolled to this new stratum were less heavily pretreated (up to two prior lines), would have no history of CNS metastasis, and would have a performance status of 0 to 1. The reason to enroll less heavily pretreated patients with EGFR mutations was due to the observation that a high number of EGFR mutant patients, nine patients in total, discontinued study participation due to early disease progression prior to completing first radiological assessment (6 ±1weeks), reflecting the fact that most patients had advanced disease, brain metastasis, and had received multiple previous lines of therapies; In addition, all patients to be enrolled to the fifth EGFR mutation stratum were required to undergo baseline biopsy prior to study enrollment in order to understand resistance mechanism to EGFR TKI, as pre-clinical data suggested that HSP90 inhibition may have different sensitivity based on the mutated EGFR, such as T790M (Shimamura et al 2005);</p> |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported