



## Clinical trial results:

### Protocol I4T-MC-JVCZ Randomized Phase 2 Trial Evaluating Alternative Ramucirumab Doses in Combination with Paclitaxel in Second-Line Metastatic or Locally Advanced, Unresectable Gastric or Gastroesophageal Junction Adenocarcinoma

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2014-005067-32    |
| Trial protocol           | DE CZ SE GR BE ES |
| Global end of trial date | 28 December 2018  |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 05 January 2020 |
| First version publication date | 05 January 2020 |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | I4T-MC-JVCZ |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |                     |
|------------------------------------|---------------------|
| ISRCTN number                      | -                   |
| ClinicalTrials.gov id (NCT number) | NCT02514551         |
| WHO universal trial number (UTN)   | -                   |
| Other trial identifiers            | Trial Number: 15541 |

Notes:

##### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Eli Lilly and Company   |
| Sponsor organisation address | Lilly Corporate Center, Indianapolis, IN, United States, 46285            |
| Public contact               | Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877CTLilly, |
| Scientific contact           | Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 8772854559, |

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                       | 28 December 2018 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 28 December 2018 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The main purpose of this study is to evaluate the efficacy of an alternative dose of ramucirumab in combination with paclitaxel in participants with second-line metastatic or locally advanced, unresectable gastric or gastroesophageal junction adenocarcinoma (GEJ).

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 12 October 2015  |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety, Efficacy |
| Long term follow-up duration                              | 21 Months        |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Greece: 21         |
| Country: Number of subjects enrolled | Canada: 4          |
| Country: Number of subjects enrolled | Sweden: 2          |
| Country: Number of subjects enrolled | Turkey: 40         |
| Country: Number of subjects enrolled | Belgium: 11        |
| Country: Number of subjects enrolled | United States: 24  |
| Country: Number of subjects enrolled | Ukraine: 44        |
| Country: Number of subjects enrolled | Italy: 23          |
| Country: Number of subjects enrolled | Germany: 4         |
| Country: Number of subjects enrolled | Spain: 56          |
| Country: Number of subjects enrolled | Czech Republic: 16 |
| Worldwide total number of subjects   | 245                |
| EEA total number of subjects         | 133                |

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)                      | 165 |
| From 65 to 84 years                       | 80  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

No Text Available

### Pre-assignment

Screening details:

Completers are defined as participants who died or had progressive disease (PD) or completed treatment or did not complete treatment and were followed for survival data. Final study data will be provided after study completion.

### Period 1

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

### Arms

|                              |   |
|------------------------------|---|
| Are arms mutually exclusive? | Yes   |
| <b>Arm title</b>             | 12mg/kg Ramucirumab + 80 mg/m <sup>2</sup> Paclitaxel |

Arm description:

12 milligram per kilogram (mg/kg) ramucirumab administered intravenously (IV) on day 1 and day 15 (28 day cycles) in combination with 80 milligram per square meter (mg/m<sup>2</sup>) paclitaxel administered IV on day 1, day 8 and day 15.

|  |                             |
|--|-----------------------------|
| Arm type                               | Experimental                |
| Investigational medicinal product name | Ramucirumab                 |
| Investigational medicinal product code |                             |
| Other name                             | LY3009806,IMC-1121B,Cyramza |
| Pharmaceutical forms                   | Infusion                    |
| Routes of administration               | Intravenous use             |

Dosage and administration details:

12 milligram per kilogram (mg/kg) ramucirumab administered intravenously (IV) on day 1 and day 15 (28 day cycles)

|  |                 |
|--|-----------------|
| Investigational medicinal product name | Paclitaxel      |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

Dosage and administration details:

80 milligram per square meter (mg/m<sup>2</sup>) paclitaxel administered IV on day 1, day 8 and day 15.

|                  |   |
|------------------|---|
| <b>Arm title</b> | 8 mg/kg Ramucirumab + 80 mg/m <sup>2</sup> Paclitaxel |
|------------------|---|

Arm description:

8 mg/kg ramucirumab administered IV on day 1 and day 15 (28 day cycles) in combination with 80 mg/m<sup>2</sup> paclitaxel administered IV on day 1, day 8 and day 15.

|  |                      |
|--|----------------------|
| Arm type                               | Active comparator    |
| Investigational medicinal product name | Ramucirumab          |
| Investigational medicinal product code |                      |
| Other name                             | LY3009806, IMC-1121B |
| Pharmaceutical forms                   | Infusion             |
| Routes of administration               | Intravenous use      |

Dosage and administration details:

8 mg/kg ramucirumab administered IV on day 1 and day 15 (28 day cycles).

|  |                 |
|--|-----------------|
| Investigational medicinal product name | Paclitaxel      |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

Dosage and administration details:

80 mg/m<sup>2</sup> paclitaxel administered IV on day 1, day 8 and day 15.

| <b>Number of subjects in period 1</b>    | 12mg/kg<br>Ramucirumab + 80<br>mg/m <sup>2</sup> Paclitaxel | 8 mg/kg<br>Ramucirumab + 80<br>mg/m <sup>2</sup> Paclitaxel |
|--|---|---|
| Started                                  | 123   | 122   |
| Received at least one dose of study drug | 123   | 120   |
| Completed                                | 123   | 119   |
| Not completed                            | 0   | 3   |
| Participant Never Treated                | -   | 2   |
| Lost to follow-up                        | -   | 1   |

## Baseline characteristics

### Reporting groups

|   |   |
|---|---|
| Reporting group title   | 12mg/kg Ramucirumab + 80 mg/m <sup>2</sup> Paclitaxel |
| Reporting group description:<br>12 milligram per kilogram (mg/kg) ramucirumab administered intravenously (IV) on day 1 and day 15 (28 day cycles) in combination with 80 milligram per square meter (mg/m <sup>2</sup> ) paclitaxel administered IV on day 1, day 8 and day 15. |   |
| Reporting group title   | 8 mg/kg Ramucirumab + 80 mg/m <sup>2</sup> Paclitaxel |
| Reporting group description:<br>8 mg/kg ramucirumab administered IV on day 1 and day 15 (28 day cycles) in combination with 80 mg/m <sup>2</sup> paclitaxel administered IV on day 1, day 8 and day 15.   |   |

| Reporting group values  | 12mg/kg<br>Ramucirumab + 80<br>mg/m <sup>2</sup> Paclitaxel | 8 mg/kg<br>Ramucirumab + 80<br>mg/m <sup>2</sup> Paclitaxel | Total |
|---|---|---|-------|
| Number of subjects  | 123   | 122   | 245   |
| Age categorical<br>Units: Subjects                                      |   |   |       |
| Adults (18-64 years)  | 83  | 82  | 165   |
| Adults (65-84 years)  | 40  | 40  | 80    |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 58.6<br>± 11.4  | 57.9<br>± 12.3  | -     |
| Gender categorical<br>Units: Subjects                                   |   |   |       |
| Female  | 40  | 44  | 84    |
| Male  | 83  | 78  | 161   |
| Ethnicity (NIH/OMB)<br>Units: Subjects                                  |   |   |       |
| Hispanic or Latino  | 8   | 7   | 15    |
| Not Hispanic or Latino  | 110   | 108   | 218   |
| Unknown or Not Reported   | 5   | 7   | 12    |
| Race (NIH/OMB)<br>Units: Subjects                                       |   |   |       |
| American Indian or Alaska Native  | 1   | 0   | 1     |
| Asian   | 0   | 3   | 3     |
| Native Hawaiian or Other Pacific Islander                               | 0   | 0   | 0     |
| Black or African American   | 2   | 2   | 4     |
| White   | 119   | 117   | 236   |
| More than one race  | 0   | 0   | 0     |
| Unknown or Not Reported   | 1   | 0   | 1     |
| Region of Enrollment<br>Units: Subjects                                 |   |   |       |
| Greece  | 10  | 11  | 21    |
| Canada  | 0   | 4   | 4     |
| Sweden  | 1   | 1   | 2     |
| Turkey  | 24  | 16  | 40    |
| Belgium   | 6   | 5   | 11    |

|               |    |    |    |
|---------------|----|----|----|
| United States | 16 | 8  | 24 |
| Czechia       | 7  | 9  | 16 |
| Ukraine       | 18 | 26 | 44 |
| Italy         | 16 | 7  | 23 |
| Germany       | 2  | 2  | 4  |
| Spain         | 23 | 33 | 56 |

## End points

### End points reporting groups

|   |  |
|---|--|
| Reporting group title   | 12mg/kg Ramucirumab + 80 mg/m <sup>2</sup> Paclitaxel              |
| Reporting group description:<br>12 milligram per kilogram (mg/kg) ramucirumab administered intravenously (IV) on day 1 and day 15 (28 day cycles) in combination with 80 milligram per square meter (mg/m <sup>2</sup> ) paclitaxel administered IV on day 1, day 8 and day 15. |  |
| Reporting group title   | 8 mg/kg Ramucirumab + 80 mg/m <sup>2</sup> Paclitaxel              |
| Reporting group description:<br>8 mg/kg ramucirumab administered IV on day 1 and day 15 (28 day cycles) in combination with 80 mg/m <sup>2</sup> paclitaxel administered IV on day 1, day 8 and day 15.   |  |
| Subject analysis set title  | I4T-MC-JVCZ: 12mg/kg Ramucirumab + 80 mg/m <sup>2</sup> Paclitaxel |
| Subject analysis set type   | Per protocol   |
| Subject analysis set description:<br>12mg/kg ramucirumab administered intravenously (IV) on day 1 and day 15 (28 day cycles) in combination with 80 mg/m <sup>2</sup> paclitaxel administered IV on day 1, day 8 and day 15.  |  |

### Primary: Progression Free Survival (PFS) in Ramucirumab 12mg/kg arm I4T-MC-JVCZ

|   |   |
|---|---|
| End point title   | Progression Free Survival (PFS) in Ramucirumab 12mg/kg arm I4T-MC-JVCZ <sup>[1]</sup> |
| End point description:<br>PFS was defined as time from the date of randomization(RD) to date of radiographic documentation of progression(RDP) or the date of death due to any cause, whichever is earlier as defined by RECIST v.1.1. Participants with no tumor progression and no death were censored at date of last adequate radiological assessment (AST) or date of RD(whichever is later). This analysis were comparison of PFS for participants treated with ramucirumab 12 mg/kg plus paclitaxel in Study I4T-MC-JVCZ versus placebo plus paclitaxel in I4T-IE-JVBE (NCT01170663) using meta-analysis. Placebo + 80 mg/m <sup>2</sup> Paclitaxel in I4T-IE-JVBE Number of participants: 335, Median (95% CI), months: 2.86 (2.79 to 3.02). Hazard Ratio (HR) = 0.617, 2 sided Confidence Interval (0.447 to 0.853 ). HR was estimated by Unstratified cox proportional hazards model comparing Ramucirumab I4T-MC-JVCZ and I4T-IE-JVBE (NCT01170663). |   |
| End point type  | Primary   |
| End point timeframe:<br>Randomization to Objective Progressive Disease or Death (Up To 21 Months)<br>Analysis Population Description (APD). All randomized participants in arm 12mg/kg Ramucirumab + 80 mg/m <sup>2</sup> Paclitaxel. Censored: Ramucirumab 12 mg/kg + 80 mg/m <sup>2</sup> Paclitaxel= 25.   |   |

#### 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: Statistical analysis are reported in the outcome measure description. This was a meta-analysis of two studies JVCZ and JVBE. There is no JVBE arm in the participant flow hence comparison data cannot be reported in the statistical analysis section.

|                                  |  |  |  |  |
|----------------------------------|--|--|--|--|
| <b>End point values</b>          | I4T-MC-JVCZ:<br>12mg/kg<br>Ramucirumab<br>+ 80 mg/m <sup>2</sup><br>Paclitaxel |  |  |  |
| Subject group type               | Subject analysis set   |  |  |  |
| Number of subjects analysed      | 123  |  |  |  |
| Units: months                    |  |  |  |  |
| median (confidence interval 95%) | 5.42 (4.40 to 6.01)  |  |  |  |



## Statistical analyses

No statistical analyses for this end point

### Secondary: Progression Free Survival (PFS) Ramucirumab 12mg/kg Arm and 8mg/kg Arm in I4T-MC-JVCZ

|                 |   |
|-----------------|---|
| End point title | Progression Free Survival (PFS) Ramucirumab 12mg/kg Arm and 8mg/kg Arm in I4T-MC-JVCZ |
|-----------------|---|

End point description:

PFS was defined as time from the date of randomization(RD) to date of radiographic documentation of progression(RDP) or the date of death due to any cause, whichever is earlier as defined by RECIST v.1.1. Participants with no tumor progression and no death were censored at date of last adequate radiological assessment(AST) or date of RD(whichever is later).PD is at least a 20% increase in sum of diameters of target lesions,taking as reference the smallest sum on study.In addition to the relative increase of 20%,the sum must also demonstrate an absolute increase of at least 5 mm.The appearance of 1 or more new lesions is also considered progression.Non-Target PD is unequivocal progression of existing nontarget lesions.A participant with incomplete baseline disease had PFS time censored at the enrollment date.A participant not known to have died or have RDP as of the data inclusion cutoff date for the analysis had PFS time censored at date of the last complete RDP-free disease AST.

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

End point timeframe:

Randomization to Objective Progressive Disease or Death (Up To 21 Months)

APD: All randomized participants. Censored: Ramucirumab 12 mg/kg + Paclitaxel 80 mg/m<sup>2</sup> = 25 and 8 mg/kg Ramucirumab + 80 mg/m<sup>2</sup> Paclitaxel =23.

| End point values                 | 12mg/kg<br>Ramucirumab<br>+ 80 mg/m <sup>2</sup><br>Paclitaxel | 8 mg/kg<br>Ramucirumab<br>+ 80 mg/m <sup>2</sup><br>Paclitaxel |  |  |
|----------------------------------|--|--|--|--|
| Subject group type               | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed      | 123  | 122  |  |  |
| Units: months                    |  |  |  |  |
| median (confidence interval 95%) | 5.42 (4.40 to 6.01)  | 5.16 (3.81 to 5.65)  |  |  |

## Statistical analyses

|                            |   |
|----------------------------|---|
| Statistical analysis title | Progression Free Survival (PFS) Ramucirumab 12mg/   |
| Comparison groups          | 12mg/kg Ramucirumab + 80 mg/m <sup>2</sup> Paclitaxel v 8 mg/kg Ramucirumab + 80 mg/m <sup>2</sup> Paclitaxel |

|   |                   |
|---|-------------------|
| Number of subjects included in analysis | 245               |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | superiority       |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 0.963             |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.727             |
| upper limit                             | 1.274             |

### Secondary: Pharmacokinetics (PK): Minimum Concentration (Cmin) of Ramucirumab in Combination with Paclitaxel

|                 |   |
|-----------------|---|
| End point title | Pharmacokinetics (PK): Minimum Concentration (Cmin) of Ramucirumab in Combination with Paclitaxel |
|-----------------|---|

End point description:

Pharmacokinetics (PK): Minimum Concentration (Cmin) of Ramucirumab in Combination with Paclitaxel.

Analysis Population Description: All randomized participants who received at least one dose of study drug and had evaluable PK data.

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

End point timeframe:

Cycle(C) 1 Day(D) 1: Prior to Infusion(PTI), 1 to 1.5 hours(hrs) after end of Infusion(EOI); C1 D15: 3 days PTI; C2 D1: 3 days PTI; C2 D15: 3 days PTI, 1 to 1.5 hrs after EOI; C3 D1 and 15: 3 days PTI; C4 D1: 3 days PTI and 1 to 1.5 hrs after EOI

| End point values                                    | 12mg/kg<br>Ramucirumab<br>+ 80 mg/m <sup>2</sup><br>Paclitaxel | 8 mg/kg<br>Ramucirumab<br>+ 80 mg/m <sup>2</sup><br>Paclitaxel |  |  |
|---|--|--|--|--|
| Subject group type                                  | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed                         | 103  | 95   |  |  |
| Units: Microgram per milliliter (µg/mL)             |  |  |  |  |
| geometric mean (geometric coefficient of variation) |  |  |  |  |
| Cycle 1 Day 15 (Week 2)                             | 39.2 (± 43)  | 21.4 (± 58)  |  |  |
| Cycle 2 Day 1 (Week 4)                              | 63.6 (± 40)  | 37.1 (± 50)  |  |  |
| Cycle 2 Day 15 (Week 6)                             | 76.7 (± 42)  | 43.5 (± 53)  |  |  |
| Cycle 3 Day 1 (Week 8)                              | 91.2 (± 40)  | 51.5 (± 55)  |  |  |
| Cycle 3 Day 15 (Week 10)                            | 99.0 (± 44)  | 52.9 (± 56)  |  |  |
| Cycle 4 Day 1 (Week 12)                             | 101 (± 55)   | 56.1 (± 56)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants Who Achieve Best Overall Tumor Response of

## Complete Response (CR) or Partial Response (PR) (Objective Response Rates [ORR])

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants Who Achieve Best Overall Tumor Response of Complete Response (CR) or Partial Response (PR) (Objective Response Rates [ORR]) |
|-----------------|--|

End point description:

ORR was defined as the percentage of participants who achieved a PR or CR per RECIST v.1.1. CR is the disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10mm. Tumor marker results must have normalized. PR is at least a 30% decrease in the sum of diameter of target lesions, taking as reference the baseline sum diameters. ORR is calculated as a total number of participants with CR or PR divided by the total number of participants treated multiplied by 100.

Analysis Population Description: All randomized participants.

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

End point timeframe:

Baseline to Objective Progressive Disease (Up To 21 Months)

| End point values                  | 12mg/kg<br>Ramucirumab<br>+ 80 mg/m <sup>2</sup><br>Paclitaxel | 8 mg/kg<br>Ramucirumab<br>+ 80 mg/m <sup>2</sup><br>Paclitaxel |  |  |
|-----------------------------------|--|--|--|--|
| Subject group type                | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed       | 123  | 122  |  |  |
| Units: percentage of participants |  |  |  |  |
| number (not applicable)           | 27.6   | 25.4   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants who Exhibit Stable Disease (SD) or Confirmed Response (CR) or Partial Response (PR) [Disease Control Rate (DCR)]

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants who Exhibit Stable Disease (SD) or Confirmed Response (CR) or Partial Response (PR) [Disease Control Rate (DCR)] |
|-----------------|---|

End point description:

DCR is defined as the percentage of participants who achieved CR, PR, or SD per RECIST v.1.1. CR is the disappearance of all target lesions. Any pathological lymph nodes (target or non-target) must have reduction in short axis to <10 mm. Tumor marker results must have normalized. PR is at least a 30% decrease in the sum of diameter of target lesions, taking as reference the baseline sum diameters. SD is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. PD is at least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression. Non-Target PD is unequivocal progression of existing nontarget lesions.  $DCR = CR + PR + SD / \text{total number of participants} * 100$ .

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

End point timeframe:

Baseline to Objective Progressive Disease (Up To 21 Months)

Analysis Population Description: All randomized participants.

| <b>End point values</b>           | 12mg/kg<br>Ramucirumab<br>+ 80 mg/m <sup>2</sup><br>Paclitaxel | 8 mg/kg<br>Ramucirumab<br>+ 80 mg/m <sup>2</sup><br>Paclitaxel |  |  |
|-----------------------------------|--|--|--|--|
| Subject group type                | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed       | 123  | 122  |  |  |
| Units: percentage of participants |  |  |  |  |
| number (not applicable)           | 78.9   | 75.4   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants with Anti-Ramucirumab Antibodies

|                 |   |
|-----------------|---|
| End point title | Number of Participants with Anti-Ramucirumab Antibodies |
|-----------------|---|

End point description:

Participants who had anti-ramucirumab antibodies at postbaseline.

Analysis Population Description: All randomized participants who received at least one dose of study drug and were evaluable for ramucirumab anti-drug antibody.

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

End point timeframe:

Cycle 1 Predose through Follow-up (Up To 24 Months)

| <b>End point values</b>     | 12mg/kg<br>Ramucirumab<br>+ 80 mg/m <sup>2</sup><br>Paclitaxel | 8 mg/kg<br>Ramucirumab<br>+ 80 mg/m <sup>2</sup><br>Paclitaxel |  |  |
|-----------------------------|--|--|--|--|
| Subject group type          | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed | 105  | 89   |  |  |
| Units: participants         | 2  | 1  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up To 40 Months

Adverse event reporting additional description:

All randomized participants who received at least one dose of study drug.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 21.1 |
|--------------------|------|

### Reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | 12mg/kg Ramucirumab + 80 mg/m <sup>2</sup> Paclitaxel |
|-----------------------|---|

Reporting group description:

12mg/kg ramucirumab administered intravenously (IV) on day 1 and day 15 (28 day cycles) in combination with 80 mg/m<sup>2</sup> paclitaxel administered IV on day 1, day 8 and day 15.

|                       |   |
|-----------------------|---|
| Reporting group title | 8 mg/kg Ramucirumab + 80 mg/m <sup>2</sup> Paclitaxel |
|-----------------------|---|

Reporting group description:

8 mg/kg ramucirumab administered IV on day 1 and day 15 (28 day cycles) in combination with 80 mg/m<sup>2</sup> paclitaxel administered IV on day 1, day 8 and day 15.

| Serious adverse events  | 12mg/kg<br>Ramucirumab + 80<br>mg/m <sup>2</sup> Paclitaxel | 8 mg/kg<br>Ramucirumab + 80<br>mg/m <sup>2</sup> Paclitaxel |  |
|---|---|---|--|
| Total subjects affected by serious adverse events                   |   |   |  |
| subjects affected / exposed   | 47 / 123 (38.21%)   | 32 / 120 (26.67%)   |  |
| number of deaths (all causes)                                       | 10  | 8   |  |
| number of deaths resulting from adverse events                      | 5   | 4   |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |   |   |  |
| lymphangiosis carcinomatosa   |   |   |  |
| alternative dictionary used: MedDRA 21.1                            |   |   |  |
| subjects affected / exposed   | 0 / 123 (0.00%)   | 1 / 120 (0.83%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0   | 0 / 1   |  |
| deaths causally related to treatment / all                          | 0 / 0   | 0 / 0   |  |
| tumour haemorrhage  |   |   |  |
| alternative dictionary used: MedDRA 21.1                            |   |   |  |
| subjects affected / exposed   | 0 / 123 (0.00%)   | 1 / 120 (0.83%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0   | 1 / 1   |  |
| deaths causally related to treatment / all                          | 0 / 0   | 0 / 0   |  |
| tumour perforation  |   |   |  |
| alternative dictionary used:  |   |   |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| MedDRA 21.1  |                 |                 |  |
| subjects affected / exposed                          | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 1 / 1           | 0 / 0           |  |
| Vascular disorders                                   |                 |                 |  |
| hypotension  |                 |                 |  |
| alternative dictionary used: MedDRA 21.1             |                 |                 |  |
| subjects affected / exposed                          | 0 / 123 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| shock haemorrhagic                                   |                 |                 |  |
| alternative dictionary used: MedDRA 21.1             |                 |                 |  |
| subjects affected / exposed                          | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 1 / 1           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| asthenia   |                 |                 |  |
| alternative dictionary used: MedDRA 21.1             |                 |                 |  |
| subjects affected / exposed                          | 2 / 123 (1.63%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| death  |                 |                 |  |
| alternative dictionary used: MedDRA 21.1             |                 |                 |  |
| subjects affected / exposed                          | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0           |  |
| fatigue  |                 |                 |  |
| alternative dictionary used: MedDRA 21.1             |                 |                 |  |
| subjects affected / exposed                          | 1 / 123 (0.81%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| general physical health deterioration                |                 |                 |  |
| alternative dictionary used: MedDRA 21.1             |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 123 (1.63%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 2 / 2           | 0 / 0           |  |
| localised oedema                                |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| malaise   |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| oedema  |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| organ failure                                   |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| pyrexia   |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Reproductive system and breast disorders        |                 |                 |  |
| oedema genital                                  |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| aspiration                                      |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| dyspnoea  |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| hiccups   |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| hypoxia   |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| pneumonitis                                     |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| pneumothorax                                    |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| pulmonary embolism                              |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| pulmonary hypertension                          |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| respiratory distress                            |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| Investigations                                  |                 |                 |  |
| aspartate aminotransferase increased            |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| blood bilirubin increased                       |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 2 / 123 (1.63%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| neutrophil count decreased                      |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 6 / 123 (4.88%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 6 / 6           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| femoral neck fracture                           |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| infusion related reaction                       |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| tibia fracture                                  |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| cardiac failure                                 |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| cardiopulmonary failure                         |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| cardiovascular insufficiency                    |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Nervous system disorders                        |                 |                 |  |
| syncope   |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| anaemia   |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 3 / 123 (2.44%) | 3 / 120 (2.50%) |  |
| occurrences causally related to treatment / all | 2 / 3           | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| bone marrow failure                             |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| febrile neutropenia                             |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 4 / 123 (3.25%) | 3 / 120 (2.50%) |  |
| occurrences causally related to treatment / all | 4 / 4           | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| leukocytosis                                    |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| neutropenia                                     |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| abdominal pain                                  |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 4 / 123 (3.25%) | 2 / 120 (1.67%) |  |
| occurrences causally related to treatment / all | 2 / 5           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| ascites   |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| diarrhoea                                       |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| dysphagia                                       |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| gastric haemorrhage                             |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 3 / 123 (2.44%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 5 / 6           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| gastric perforation                             |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| gastric stenosis                                |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| gastrointestinal haemorrhage                    |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 2 / 123 (1.63%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| haematemesis                                    |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| ileus   |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 2 / 120 (1.67%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| large intestinal haemorrhage                    |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| nausea  |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| oesophageal fistula                                |                 |                 |  |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                        | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all      | 1 / 1           | 0 / 0           |  |
| oesophageal haemorrhage                            |                 |                 |  |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                        | 0 / 123 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| oesophageal obstruction                            |                 |                 |  |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                        | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| oesophageal perforation                            |                 |                 |  |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                        | 0 / 123 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| pneumoperitoneum                                   |                 |                 |  |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                        | 0 / 123 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| small intestinal obstruction                       |                 |                 |  |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                        | 1 / 123 (0.81%) | 1 / 120 (0.83%) |  |
| occurrences causally related to<br>treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| tongue oedema                                      |                 |                 |  |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed   | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all                                   | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all  | 0 / 0           | 0 / 0           |  |
| upper gastrointestinal haemorrhage<br>alternative dictionary used:<br>MedDRA 21.1 |                 |                 |  |
| subjects affected / exposed   | 1 / 123 (0.81%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all                                   | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all  | 0 / 0           | 1 / 1           |  |
| vomiting<br>alternative dictionary used:<br>MedDRA 21.1                           |                 |                 |  |
| subjects affected / exposed   | 3 / 123 (2.44%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all                                   | 2 / 3           | 1 / 1           |  |
| deaths causally related to treatment / all  | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders   |                 |                 |  |
| cholangitis<br>alternative dictionary used:<br>MedDRA 21.1                        |                 |                 |  |
| subjects affected / exposed   | 0 / 123 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all                                   | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all  | 0 / 0           | 0 / 0           |  |
| cholecystitis<br>alternative dictionary used:<br>MedDRA 21.1                      |                 |                 |  |
| subjects affected / exposed   | 0 / 123 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all                                   | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all  | 0 / 0           | 0 / 0           |  |
| cholecystitis acute<br>alternative dictionary used:<br>MedDRA 21.1                |                 |                 |  |
| subjects affected / exposed   | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all                                   | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all  | 0 / 0           | 0 / 0           |  |
| cholelithiasis<br>alternative dictionary used:<br>MedDRA 21.1                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| gallbladder rupture                             |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| hepatitis toxic                                 |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| jaundice  |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 2 / 123 (1.63%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| acute kidney injury                             |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| proteinuria                                     |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| renal failure                                   |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| back pain                                       |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| bacteraemia                                     |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| bronchitis                                      |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| clostridium difficile colitis                   |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| device related infection                        |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| enteritis infectious                            |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| escherichia infection                           |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| infection                                       |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 2 / 123 (1.63%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| lung infection                                  |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| peritonitis                                     |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| pneumonia                                       |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| pneumonia necrotising                           |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| respiratory tract infection<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed                    | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to<br>treatment / all   | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all  | 0 / 0           | 0 / 0           |  |
| sepsis<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed   | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to<br>treatment / all   | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all  | 0 / 1           | 0 / 0           |  |
| septic shock<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed                                   | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to<br>treatment / all   | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all  | 0 / 1           | 0 / 0           |  |
| Metabolism and nutrition disorders<br>cachexia<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to<br>treatment / all   | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all  | 0 / 1           | 0 / 0           |  |
| decreased appetite<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed                             | 0 / 123 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to<br>treatment / all   | 0 / 0           | 1 / 1           |  |
| deaths causally related to<br>treatment / all  | 0 / 0           | 0 / 0           |  |
| dehydration<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed                                    | 0 / 123 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to<br>treatment / all   | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all  | 0 / 0           | 0 / 0           |  |
| hyperkalaemia<br>alternative dictionary used:<br>MedDRA 21.1   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| hypokalaemia                                    |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| hyponatraemia                                   |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| malnutrition                                    |                 |                 |  |
| alternative dictionary used: MedDRA 21.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | 12mg/kg<br>Ramucirumab + 80<br>mg/m <sup>2</sup> Paclitaxel | 8 mg/kg<br>Ramucirumab + 80<br>mg/m <sup>2</sup> Paclitaxel |  |
|---|---|---|--|
| Total subjects affected by non-serious adverse events |   |   |  |
| subjects affected / exposed                           | 117 / 123 (95.12%)  | 115 / 120 (95.83%)  |  |
| Investigations  |   |   |  |
| alanine aminotransferase increased                    |   |   |  |
| alternative dictionary used: MedDRA 21.1              |   |   |  |
| subjects affected / exposed                           | 14 / 123 (11.38%)   | 7 / 120 (5.83%)   |  |
| occurrences (all)                                     | 27  | 8   |  |
| aspartate aminotransferase increased                  |   |   |  |
| alternative dictionary used: MedDRA 21.1              |   |   |  |
| subjects affected / exposed                           | 20 / 123 (16.26%)   | 8 / 120 (6.67%)   |  |
| occurrences (all)                                     | 43  | 15  |  |

|  |                         |                         |  |
|--|-------------------------|-------------------------|--|
| blood alkaline phosphatase increased<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)                  | 9 / 123 (7.32%)<br>25   | 10 / 120 (8.33%)<br>14  |  |
| blood bilirubin increased<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)                             | 8 / 123 (6.50%)<br>12   | 2 / 120 (1.67%)<br>3    |  |
| neutrophil count decreased<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)                            | 30 / 123 (24.39%)<br>91 | 24 / 120 (20.00%)<br>60 |  |
| platelet count decreased<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)                              | 9 / 123 (7.32%)<br>15   | 7 / 120 (5.83%)<br>13   |  |
| weight decreased<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)                                      | 14 / 123 (11.38%)<br>16 | 13 / 120 (10.83%)<br>17 |  |
| white blood cell count decreased<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)                      | 13 / 123 (10.57%)<br>33 | 14 / 120 (11.67%)<br>35 |  |
| Vascular disorders<br>hypertension<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)                    | 24 / 123 (19.51%)<br>44 | 21 / 120 (17.50%)<br>46 |  |
| Nervous system disorders<br>dysgeusia<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)<br><br>headache | 5 / 123 (4.07%)<br>5    | 9 / 120 (7.50%)<br>13   |  |

|  |                                    |                                    |  |
|--|------------------------------------|------------------------------------|--|
| <p>alternative dictionary used:<br/>MedDRA 21.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>10 / 123 (8.13%)</p> <p>12</p>  | <p>9 / 120 (7.50%)</p> <p>12</p>   |  |
| <p>neuropathy peripheral</p> <p>alternative dictionary used:<br/>MedDRA 21.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                               | <p>15 / 123 (12.20%)</p> <p>38</p> | <p>15 / 120 (12.50%)</p> <p>22</p> |  |
| <p>paraesthesia</p> <p>alternative dictionary used:<br/>MedDRA 21.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>13 / 123 (10.57%)</p> <p>30</p> | <p>13 / 120 (10.83%)</p> <p>29</p> |  |
| <p>peripheral sensory neuropathy</p> <p>alternative dictionary used:<br/>MedDRA 21.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                       | <p>8 / 123 (6.50%)</p> <p>15</p>   | <p>20 / 120 (16.67%)</p> <p>46</p> |  |
| <p>Blood and lymphatic system disorders</p> <p>anaemia</p> <p>alternative dictionary used:<br/>MedDRA 21.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>34 / 123 (27.64%)</p> <p>72</p> | <p>39 / 120 (32.50%)</p> <p>77</p> |  |
| <p>leukopenia</p> <p>alternative dictionary used:<br/>MedDRA 21.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>9 / 123 (7.32%)</p> <p>44</p>   | <p>9 / 120 (7.50%)</p> <p>18</p>   |  |
| <p>neutropenia</p> <p>alternative dictionary used:<br/>MedDRA 21.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>22 / 123 (17.89%)</p> <p>78</p> | <p>24 / 120 (20.00%)</p> <p>62</p> |  |
| <p>thrombocytopenia</p> <p>alternative dictionary used:<br/>MedDRA 21.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                    | <p>7 / 123 (5.69%)</p> <p>10</p>   | <p>4 / 120 (3.33%)</p> <p>5</p>    |  |
| <p>General disorders and administration<br/>site conditions</p>  |                                    |                                    |  |

|   |                         |                         |  |
|---|-------------------------|-------------------------|--|
| asthenia<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)             | 15 / 123 (12.20%)<br>35 | 19 / 120 (15.83%)<br>49 |  |
| fatigue<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)              | 43 / 123 (34.96%)<br>85 | 46 / 120 (38.33%)<br>82 |  |
| oedema peripheral<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)    | 10 / 123 (8.13%)<br>11  | 16 / 120 (13.33%)<br>22 |  |
| pyrexia<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)              | 9 / 123 (7.32%)<br>10   | 8 / 120 (6.67%)<br>8    |  |
| Gastrointestinal disorders  |                         |                         |  |
| abdominal distension<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all) | 7 / 123 (5.69%)<br>9    | 6 / 120 (5.00%)<br>8    |  |
| abdominal pain<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)       | 20 / 123 (16.26%)<br>31 | 19 / 120 (15.83%)<br>22 |  |
| abdominal pain upper<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all) | 8 / 123 (6.50%)<br>13   | 12 / 120 (10.00%)<br>16 |  |
| ascites<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)              | 9 / 123 (7.32%)<br>11   | 5 / 120 (4.17%)<br>8    |  |
| constipation<br>alternative dictionary used:<br>MedDRA 21.1   |                         |                         |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 23 / 123 (18.70%) | 21 / 120 (17.50%) |  |
| occurrences (all)                               | 33                | 27                |  |
| diarrhoea                                       |                   |                   |  |
| alternative dictionary used:<br>MedDRA 21.1     |                   |                   |  |
| subjects affected / exposed                     | 31 / 123 (25.20%) | 35 / 120 (29.17%) |  |
| occurrences (all)                               | 78                | 65                |  |
| dysphagia                                       |                   |                   |  |
| alternative dictionary used:<br>MedDRA 21.1     |                   |                   |  |
| subjects affected / exposed                     | 11 / 123 (8.94%)  | 4 / 120 (3.33%)   |  |
| occurrences (all)                               | 12                | 4                 |  |
| nausea  |                   |                   |  |
| alternative dictionary used:<br>MedDRA 21.1     |                   |                   |  |
| subjects affected / exposed                     | 27 / 123 (21.95%) | 38 / 120 (31.67%) |  |
| occurrences (all)                               | 52                | 95                |  |
| stomatitis                                      |                   |                   |  |
| alternative dictionary used:<br>MedDRA 21.1     |                   |                   |  |
| subjects affected / exposed                     | 15 / 123 (12.20%) | 18 / 120 (15.00%) |  |
| occurrences (all)                               | 19                | 41                |  |
| vomiting  |                   |                   |  |
| alternative dictionary used:<br>MedDRA 21.1     |                   |                   |  |
| subjects affected / exposed                     | 29 / 123 (23.58%) | 27 / 120 (22.50%) |  |
| occurrences (all)                               | 51                | 44                |  |
| Respiratory, thoracic and mediastinal disorders |                   |                   |  |
| cough   |                   |                   |  |
| alternative dictionary used:<br>MedDRA 21.1     |                   |                   |  |
| subjects affected / exposed                     | 14 / 123 (11.38%) | 8 / 120 (6.67%)   |  |
| occurrences (all)                               | 17                | 11                |  |
| dysphonia                                       |                   |                   |  |
| alternative dictionary used:<br>MedDRA 21.1     |                   |                   |  |
| subjects affected / exposed                     | 11 / 123 (8.94%)  | 6 / 120 (5.00%)   |  |
| occurrences (all)                               | 15                | 7                 |  |
| dyspnoea  |                   |                   |  |
| alternative dictionary used:<br>MedDRA 21.1     |                   |                   |  |



|  |  |   |  |
|--|--|---|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>epistaxis</p> <p>alternative dictionary used:<br/>MedDRA 21.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>4 / 123 (3.25%)</p> <p>5</p> <p>26 / 123 (21.14%)</p> <p>43</p>                                   | <p>12 / 120 (10.00%)</p> <p>13</p> <p>28 / 120 (23.33%)</p> <p>36</p>                             |  |
| <p>Skin and subcutaneous tissue disorders</p> <p>alopecia</p> <p>alternative dictionary used:<br/>MedDRA 21.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>19 / 123 (15.45%)</p> <p>19</p>   | <p>24 / 120 (20.00%)</p> <p>28</p>  |  |
| <p>Renal and urinary disorders</p> <p>proteinuria</p> <p>alternative dictionary used:<br/>MedDRA 21.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>9 / 123 (7.32%)</p> <p>19</p>   | <p>8 / 120 (6.67%)</p> <p>11</p>  |  |
| <p>Musculoskeletal and connective tissue disorders</p> <p>arthralgia</p> <p>alternative dictionary used:<br/>MedDRA 21.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>back pain</p> <p>alternative dictionary used:<br/>MedDRA 21.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>myalgia</p> <p>alternative dictionary used:<br/>MedDRA 21.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>8 / 123 (6.50%)</p> <p>13</p> <p>10 / 123 (8.13%)</p> <p>13</p> <p>11 / 123 (8.94%)</p> <p>18</p> | <p>5 / 120 (4.17%)</p> <p>5</p> <p>9 / 120 (7.50%)</p> <p>14</p> <p>9 / 120 (7.50%)</p> <p>16</p> |  |
| <p>Metabolism and nutrition disorders</p> <p>decreased appetite</p> <p>alternative dictionary used:<br/>MedDRA 21.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>hyperglycaemia</p>  | <p>25 / 123 (20.33%)</p> <p>41</p>   | <p>32 / 120 (26.67%)</p> <p>58</p>  |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| alternative dictionary used:<br>MedDRA 21.1 |                  |                   |  |
| subjects affected / exposed                 | 8 / 123 (6.50%)  | 11 / 120 (9.17%)  |  |
| occurrences (all)                           | 18               | 20                |  |
| hypoalbuminaemia                            |                  |                   |  |
| alternative dictionary used:<br>MedDRA 21.1 |                  |                   |  |
| subjects affected / exposed                 | 10 / 123 (8.13%) | 14 / 120 (11.67%) |  |
| occurrences (all)                           | 13               | 34                |  |
| hyponatraemia                               |                  |                   |  |
| alternative dictionary used:<br>MedDRA 21.1 |                  |                   |  |
| subjects affected / exposed                 | 7 / 123 (5.69%)  | 7 / 120 (5.83%)   |  |
| occurrences (all)                           | 13               | 8                 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported