



## Clinical trial results:

Open-label, randomized, controlled, multicenter Phase II study investigating 2 cilengitide regimens in combination with cetuximab and platinum-based chemotherapy (cisplatin/vinorelbine or cisplatin/gemcitabine) compared to cetuximab and platinum-based chemotherapy alone as first-line treatment for patients with advanced Non Small Cell Lung Cancer (NSCLC).

### Summary

|                          |                      |
|--------------------------|----------------------|
| EudraCT number           | 2008-004148-35       |
| Trial protocol           | IE BE DE ES FR IT CZ |
| Global end of trial date | 29 July 2013         |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 23 May 2016  |
| First version publication date | 29 July 2015 |

### Trial information

#### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | EMR200037-014 |
|-----------------------|---------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00842712 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |                                                                           |
|------------------------------|---------------------------------------------------------------------------|
| Sponsor organisation name    | Merck KGaA                                                                |
| Sponsor organisation address | Frankfurter Str. 250, Darmstadt, Germany, 64293                           |
| Public contact               | Communication Centre, Merck KGaA, 49 6151-72-5200, service@merckgroup.com |
| Scientific contact           | Communication Centre, Merck KGaA, 49 6151-72-5200, service@merckgroup.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:

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**Results analysis stage**

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|                                                      |              |
|------------------------------------------------------|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 29 July 2013 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 29 July 2013 |
| Was the trial ended prematurely?                     | No           |

Notes:

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**General information about the trial**

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Main objective of the trial:

To assess the efficacy of cilengitide in combination with cetuximab and platinum-based chemotherapy (cisplatin/vinorelbine or cisplatin/gemcitabine) compared to cetuximab and platinum-based chemotherapy alone in terms of progression free survival (PFS) time (based on independent assessment, IRC) in the total population (regardless of endothelial growth factor receptor [EGFR] expression) and in the subgroup of subjects with high EGFR expression.

Protection of trial subjects:

In this trial highest medical and ethical standards were followed, in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 23 February 2009 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Belgium: 35 |
| Country: Number of subjects enrolled | France: 61  |
| Country: Number of subjects enrolled | Germany: 60 |
| Country: Number of subjects enrolled | Ireland: 4  |
| Country: Number of subjects enrolled | Italy: 23   |
| Country: Number of subjects enrolled | Spain: 12   |
| Country: Number of subjects enrolled | Poland: 37  |
| Worldwide total number of subjects   | 232         |
| EEA total number of subjects         | 232         |

Notes:

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**Subjects enrolled per age group**

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|                                           |   |
|-------------------------------------------|---|
| 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)                     | 182 |
| From 65 to 84 years                      | 50  |
| 85 years and over                        | 0   |

## Subject disposition

### Recruitment

Recruitment details:

First/last subject (informed consent): Feb 2009/Jun 2012. Clinical data cut-off: 26 Jun 2013, Study completion date: July 2013.

### Pre-assignment

Screening details:

In safety run-in part of study, a total of 12 subjects were enrolled and treated. In randomized part of study, 220 subjects were enrolled and out of these 220 subjects, 215 were treated.

### 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>             | Randomized Part: Cil (Once Weekly) + Cetuximab + Chemotherapy |

Arm description:

Cilengitide (Cil) was administered at a dose of 2000 mg as intravenous infusion once weekly over 1 hour on Days 1, 8 and 15 of each 3-week cycle + Cetuximab was administered at a dose of 400 mg/m<sup>2</sup> as intravenous infusion over 2 hours on Day 1 of Cycle 1 followed by cetuximab 250 mg/m<sup>2</sup> intravenous infusion over 1 hour once weekly on Days 8 and 15 of Cycle 1 and Days 1, 8, and 15 of all subsequent cycles until progressive disease, death, unacceptable toxicity, or consent withdrawal. Chemotherapy (Cisplatin [cis] at a dose of 80 mg/m<sup>2</sup> was administered as intravenous infusion on Day 1 + Vinorelbine [Vin] 25 mg/m<sup>2</sup> or Cisplatin at a dose of 75 mg/m<sup>2</sup> was administered as intravenous infusion on Day 1 + Gemcitabine (Gem) was administered at a dose of 1250 mg/m<sup>2</sup> as intravenous infusion on Days 1 and 8 of each 3-week cycle) along with Cilengitide and cetuximab as per Investigator's discretion up to a maximum of 6 cycles.

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | Cilengitide            |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

Dosage and administration details:

Cilengitide was administered at a dose of 2000 mg as intravenous infusion twice weekly over 1 hour on Days 1 and 4.

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Cetuximab              |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

Dosage and administration details:

Cetuximab was administered at a dose of 400 milligram per square meter (mg/m<sup>2</sup>) as intravenous infusion over 2 hours on Day 1.

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Cisplatin              |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

**Dosage and administration details:**

Cisplatin was administered at a dose of 80 mg/m<sup>2</sup> as intravenous infusion on Day 1.

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Vinorelbine            |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

**Dosage and administration details:**

Vinorelbine was administered at a dose of 25 mg/m<sup>2</sup> as intravenous infusion on Days 1 and 8.

|                  |                                                                |
|------------------|----------------------------------------------------------------|
| <b>Arm title</b> | Randomized Part: Cil (Twice Weekly) + Cetuximab + Chemotherapy |
|------------------|----------------------------------------------------------------|

**Arm description:**

Cilengitide (cil) was administered at a dose of 2000 mg as intravenous infusion twice weekly over 1 hour on Days 1, 4, 8, 11, 15, and 18 of each 3-week cycle followed by once weekly administration after end of chemotherapy + Cetuximab was administered at a dose of 400 mg/m<sup>2</sup> as intravenous infusion over 2 hours on Day 1 of Cycle 1 followed by cetuximab at a dose of 250 mg/m<sup>2</sup> as intravenous infusion over 1 hour once weekly on Days 8 and 15 of Cycle 1 and Days 1, 8, and 15 of all subsequent cycles until progressive disease, death, unacceptable toxicity, or consent withdrawal. Chemotherapy (Cisplatin [cis] at a dose of 80 mg/m<sup>2</sup> was administered as intravenous infusion on Day 1 + Vinorelbine [Vin] at a dose of 25 mg/m<sup>2</sup> or Cisplatin [Cis] at a dose of 75 mg/m<sup>2</sup> as intravenous infusion on Day 1 + Gemcitabine at a dose of 1250 mg/m<sup>2</sup> intravenous infusion on Days 1 and 8 of each 3-week cycle) along with Cilengitide and cetuximab as per Investigator's discretion up to a maximum of 6 cycles.

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | Cilengitide            |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

**Dosage and administration details:**

Cilengitide was administered at a dose of 2000 mg as intravenous infusion once weekly over 1 hour on Days 1, 8 and 15 of each 3-week cycle until progressive disease, death, unacceptable toxicity, or consent withdrawal.

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Cetuximab              |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

**Dosage and administration details:**

Cetuximab was administered at a dose of 400 mg/m<sup>2</sup> as intravenous infusion over 2 hours on Day 1 of Cycle 1 followed by 250 mg/m<sup>2</sup> intravenous infusion over 1 hour once weekly on Days 8 and 15 of Cycle 1 and Days 1, 8, and 15 of all subsequent cycles until progressive disease, death, unacceptable toxicity, or consent withdrawal.

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Chemotherapy           |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

**Dosage and administration details:**

Cisplatin was administered at a dose of 80 mg/m<sup>2</sup> intravenous infusion on Day 1 + Vinorelbine was administered at a dose of 25 mg/m<sup>2</sup> or Cisplatin at a dose of 75 mg/m<sup>2</sup> was administered as intravenous infusion on Day 1 + Gemcitabine was administered at a dose of 1250 mg/m<sup>2</sup> as intravenous infusion on Days 1 and 8 of each 3-week cycle along with Cilengitide and cetuximab as per Investigator's discretion up to a maximum of 6 cycles.

|                  |                                           |
|------------------|-------------------------------------------|
| <b>Arm title</b> | Randomized Part: Cetuximab + Chemotherapy |
|------------------|-------------------------------------------|

**Arm description:**

Cetuximab was administered at a dose of 400 mg/m<sup>2</sup> as intravenous infusion over 2 hours on Day 1 of Cycle 1 followed by cetuximab at a dose of 250 mg/m<sup>2</sup> was administered as intravenous infusion over

1 hour once weekly on Days 8 and 15 of Cycle 1 and Days 1, 8, and 15 of all subsequent cycles until progressive disease, death, unacceptable toxicity, or consent withdrawal. Chemotherapy (Cisplatin [Cis] at a dose of 80 mg/m<sup>2</sup> was administered as intravenous infusion on Day 1 + Vinorelbine [Vin] was administered at a dose of 25 mg/m<sup>2</sup> or Cisplatin at a dose of 75 mg/m<sup>2</sup> was administered as intravenous infusion on Day 1 + Gemcitabine [Gem] at a dose of 1250 mg/m<sup>2</sup> was administered as intravenous infusion on Days 1 and 8 of each 3-week cycle) along with Cilengitide and cetuximab as per Investigator's discretion up to a maximum of 6 cycles.

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Active comparator      |
| Investigational medicinal product name | Cetuximab              |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

**Dosage and administration details:**

Cetuximab was administered at a dose of 400 mg/m<sup>2</sup> as intravenous infusion over 2 hours on Day 1 of Cycle 1 followed by 250 mg/m<sup>2</sup> intravenous infusion over 1 hour once weekly on Days 8 and 15 of Cycle 1 and Days 1, 8, and 15 of all subsequent cycles until progressive disease, death, unacceptable toxicity, or consent withdrawal.

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Chemotherapy           |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

**Dosage and administration details:**

Cisplatin was administered at a dose of 80 mg/m<sup>2</sup> as intravenous infusion on Day 1 + Vinorelbine was administered at a dose of 25 mg/m<sup>2</sup> or Cisplatin was administered at a dose of 75 mg/m<sup>2</sup> as intravenous infusion on Day 1 + Gemcitabine was administered at a dose of 1250 mg/m<sup>2</sup> as intravenous infusion on Days 1 and 8 of each 3-week cycle along with Cil and cetuximab as per Investigator's discretion up to a maximum of 6 cycles.

|                  |                                                           |
|------------------|-----------------------------------------------------------|
| <b>Arm title</b> | Safety run-in Part: Cil (1000 mg) + Cetuximab + Cis + Gem |
|------------------|-----------------------------------------------------------|

**Arm description:**

Cilengitide (Cil) was administered at a dose of 1000 milligram (mg) as intravenous infusion twice weekly over 1 hour on Days 1 and 4 along with Cetuximab at a dose of 400 milligram per square meter (mg/m<sup>2</sup>) as intravenous infusion over 2 hours on Day 1 plus Cisplatin (Cis) 75 mg/m<sup>2</sup> intravenous infusion on Day 1 and Gemcitabine (Gem) at a dose of 1250 mg/m<sup>2</sup> was administered as intravenous infusion on Days 1 and 8 for a period of 3 weeks.

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | Cilengitide            |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

**Dosage and administration details:**

Cilengitide was administered at a dose of 2000 mg as intravenous infusion twice weekly over 1 hour on Days 1 and 4.

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Cetuximab              |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

**Dosage and administration details:**

Cetuximab was administered at a dose of 400 milligram per square meter (mg/m<sup>2</sup>) as intravenous infusion over 2 hours on Day 1.

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Cisplatin              |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                           |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|
| Routes of administration                                                                                                                                                                                                                                                                                                                                                                                                                                           | Intravenous use                                           |
| Dosage and administration details:                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                           |
| Cisplatin (Cis) was administered at a dose of 75 mg/m <sup>2</sup> as intravenous infusion on Day 1.                                                                                                                                                                                                                                                                                                                                                               |                                                           |
| Investigational medicinal product name                                                                                                                                                                                                                                                                                                                                                                                                                             | Gemcitabine                                               |
| Investigational medicinal product code                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                           |
| Other name                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                           |
| Pharmaceutical forms                                                                                                                                                                                                                                                                                                                                                                                                                                               | Solution for injection                                    |
| Routes of administration                                                                                                                                                                                                                                                                                                                                                                                                                                           | Intravenous use                                           |
| Dosage and administration details:                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                           |
| Gemcitabine (Gem) was administered at a dose of 1250 mg/m <sup>2</sup> as intravenous infusion on Days 1 and 8 for 3 weeks.                                                                                                                                                                                                                                                                                                                                        |                                                           |
| <b>Arm title</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Safety run-in Part: Cil (1000 mg) + Cetuximab + Cis + Vin |
| Arm description:                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                           |
| Cilengitide was administered at a dose of 1000 mg as intravenous infusion twice weekly over 1 hour on Days 1 and 4 + Cetuximab was administered at a dose of 400 mg/m <sup>2</sup> as intravenous infusion over 2 hours on Day 1 + Cisplatin [Cis] was administered at a dose of 80 mg/m <sup>2</sup> as intravenous infusion on Day 1 + Vinorelbine (Vin) was administered at a dose of 25 mg/m <sup>2</sup> as intravenous infusion on Days 1 and 8 for 3 weeks. |                                                           |
| Arm type                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Experimental                                              |
| Investigational medicinal product name                                                                                                                                                                                                                                                                                                                                                                                                                             | Cilengitide                                               |
| Investigational medicinal product code                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                           |
| Other name                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                           |
| Pharmaceutical forms                                                                                                                                                                                                                                                                                                                                                                                                                                               | Solution for injection                                    |
| Routes of administration                                                                                                                                                                                                                                                                                                                                                                                                                                           | Intravenous use                                           |
| Dosage and administration details:                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                           |
| Cilengitide was administered at a dose of 2000 mg as intravenous infusion twice weekly over 1 hour on Days 1 and 4.                                                                                                                                                                                                                                                                                                                                                |                                                           |
| Investigational medicinal product name                                                                                                                                                                                                                                                                                                                                                                                                                             | Cetuximab                                                 |
| Investigational medicinal product code                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                           |
| Other name                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                           |
| Pharmaceutical forms                                                                                                                                                                                                                                                                                                                                                                                                                                               | Solution for injection                                    |
| Routes of administration                                                                                                                                                                                                                                                                                                                                                                                                                                           | Intravenous use                                           |
| Dosage and administration details:                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                           |
| Cetuximab was administered at a dose of 400 mg/m <sup>2</sup> as intravenous infusion over 2 hours on Day 1                                                                                                                                                                                                                                                                                                                                                        |                                                           |
| Investigational medicinal product name                                                                                                                                                                                                                                                                                                                                                                                                                             | Cisplatin                                                 |
| Investigational medicinal product code                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                           |
| Other name                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                           |
| Pharmaceutical forms                                                                                                                                                                                                                                                                                                                                                                                                                                               | Solution for injection                                    |
| Routes of administration                                                                                                                                                                                                                                                                                                                                                                                                                                           | Intravenous use                                           |
| Dosage and administration details:                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                           |
| Cisplatin was administered at a dose of 75 mg/m <sup>2</sup> as intravenous infusion on Day 1.                                                                                                                                                                                                                                                                                                                                                                     |                                                           |
| Investigational medicinal product name                                                                                                                                                                                                                                                                                                                                                                                                                             | Vinorelbine                                               |
| Investigational medicinal product code                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                           |
| Other name                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                           |
| Pharmaceutical forms                                                                                                                                                                                                                                                                                                                                                                                                                                               | Solution for injection                                    |
| Routes of administration                                                                                                                                                                                                                                                                                                                                                                                                                                           | Intravenous use                                           |
| Dosage and administration details:                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                           |
| Vinorelbine was administered at a dose of 25 mg/m <sup>2</sup> intravenous infusion on Days 1 and 8 for 3 weeks.                                                                                                                                                                                                                                                                                                                                                   |                                                           |
| <b>Arm title</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Safety run-in Part: Cil (2000 mg) + Cetuximab + Cis + Gem |
| Arm description:                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                           |
| Cilengitide was administered at a dose of 2000 mg as intravenous infusion twice weekly over 1 hour on Days 1 and 4 + Cetuximab was administered at a dose of 400 mg/m <sup>2</sup> as intravenous infusion over 2 hours on Day 1 + Cisplatin (Cis) was administered at a dose of 75 mg/m <sup>2</sup> as intravenous infusion on                                                                                                                                   |                                                           |

Day 1 + Gemcitabine (Gem) was administered at a dose of 1250 mg/m<sup>2</sup> as intravenous infusion on Days 1 and 8 for 3 weeks.

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | Cilengitide            |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

Dosage and administration details:

Cilengitide was administered at a dose of 2000 mg as intravenous infusion twice weekly over 1 hour on Days 1 and 4.

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Cetuximab              |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

Dosage and administration details:

Cetuximab was administered at a dose of 400 mg/m<sup>2</sup> as intravenous infusion over 2 hours on Day 1

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Cisplatin              |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

Dosage and administration details:

Cisplatin was administered at dose of 75 mg/m<sup>2</sup> as intravenous infusion on Day 1.

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Gemcitabine            |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

Dosage and administration details:

Gem was administered at a dose of 1250 mg/m<sup>2</sup> intravenous infusion on Days 1 and 8 for 3 weeks.

|                  |                                                           |
|------------------|-----------------------------------------------------------|
| <b>Arm title</b> | Safety run-in Part: Cil (2000 mg) + Cetuximab + Cis + Vin |
|------------------|-----------------------------------------------------------|

Arm description:

Cilengitide was administered at a dose of 2000 mg as intravenous infusion twice weekly over 1 hour on Days 1 and 4 + Cetuximab was administered at a dose of 400 mg/m<sup>2</sup> as intravenous infusion over 2 hours on Day 1 + Cisplatin (Cis) was administered at a dose of 80 mg/m<sup>2</sup> as intravenous infusion on Day 1 + Vinorelbine (Vin) was administered at a dose of 25 mg/m<sup>2</sup> as intravenous infusion on Days 1 and 8 for 3 weeks.

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | Cilengitide            |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

Dosage and administration details:

Cilengitide was administered at a dose of 2000 mg as intravenous infusion twice weekly over 1 hour on Days 1 and 4.

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Cetuximab              |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

Dosage and administration details:

Cetuximab was administered at a dose of 400 mg/m<sup>2</sup> intravenous infusion over 2 hours on Day 1.

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Cisplatin              |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

Dosage and administration details:

Cisplatin was administered at a dose of 80 mg/m<sup>2</sup> as intravenous infusion on Day 1.

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Vinorelbine            |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

Dosage and administration details:

Vinorelbine was administered at a dose of 25 mg/m<sup>2</sup> as intravenous infusion on Days 1 and 8 for 3 weeks.

| <b>Number of subjects in period 1</b> | Randomized Part:<br>Cil (Once Weekly) +<br>Cetuximab +<br>Chemotherapy | Randomized Part: Cil<br>(Twice Weekly) +<br>Cetuximab +<br>Chemotherapy | Randomized Part:<br>Cetuximab +<br>Chemotherapy |
|---------------------------------------|------------------------------------------------------------------------|-------------------------------------------------------------------------|-------------------------------------------------|
| Started                               | 85                                                                     | 51                                                                      | 84                                              |
| Completed                             | 85                                                                     | 50                                                                      | 78                                              |
| Not completed                         | 0                                                                      | 1                                                                       | 6                                               |
| Randomized but not treated            | -                                                                      | 1                                                                       | 4                                               |
| Adverse event, non-fatal              | -                                                                      | -                                                                       | -                                               |
| Progressive disease                   | -                                                                      | -                                                                       | -                                               |
| Ongoing at cut-off date               | -                                                                      | -                                                                       | 2                                               |

| <b>Number of subjects in period 1</b> | Safety run-in Part:<br>Cil (1000 mg) +<br>Cetuximab + Cis +<br>Gem | Safety run-in Part:<br>Cil (1000 mg) +<br>Cetuximab + Cis +<br>Vin | Safety run-in Part:<br>Cil (2000 mg) +<br>Cetuximab + Cis +<br>Gem |
|---------------------------------------|--------------------------------------------------------------------|--------------------------------------------------------------------|--------------------------------------------------------------------|
| Started                               | 3                                                                  | 3                                                                  | 3                                                                  |
| Completed                             | 3                                                                  | 1                                                                  | 3                                                                  |
| Not completed                         | 0                                                                  | 2                                                                  | 0                                                                  |
| Randomized but not treated            | -                                                                  | -                                                                  | -                                                                  |
| Adverse event, non-fatal              | -                                                                  | 1                                                                  | -                                                                  |
| Progressive disease                   | -                                                                  | 1                                                                  | -                                                                  |
| Ongoing at cut-off date               | -                                                                  | -                                                                  | -                                                                  |

| <b>Number of subjects in period 1</b> | Safety run-in Part:<br>Cil (2000 mg) +<br>Cetuximab + Cis +<br>Vin |
|---------------------------------------|--------------------------------------------------------------------|
| Started                               | 3                                                                  |
| Completed                             | 2                                                                  |
| Not completed                         | 1                                                                  |

|                            |   |
|----------------------------|---|
| Randomized but not treated | - |
| Adverse event, non-fatal   | - |
| Progressive disease        | 1 |
| Ongoing at cut-off date    | - |

## Baseline characteristics

### Reporting groups

|                       |                                                               |
|-----------------------|---------------------------------------------------------------|
| Reporting group title | Randomized Part: Cil (Once Weekly) + Cetuximab + Chemotherapy |
|-----------------------|---------------------------------------------------------------|

#### Reporting group description:

Cilengitide (Cil) was administered at a dose of 2000 mg as intravenous infusion once weekly over 1 hour on Days 1, 8 and 15 of each 3-week cycle + Cetuximab was administered at a dose of 400 mg/m<sup>2</sup> as intravenous infusion over 2 hours on Day 1 of Cycle 1 followed by cetuximab 250 mg/m<sup>2</sup> intravenous infusion over 1 hour once weekly on Days 8 and 15 of Cycle 1 and Days 1, 8, and 15 of all subsequent cycles until progressive disease, death, unacceptable toxicity, or consent withdrawal. Chemotherapy (Cisplatin [Cis] at a dose of 80 mg/m<sup>2</sup> was administered as intravenous infusion on Day 1 + Vinorelbine [Vin] 25 mg/m<sup>2</sup> or Cisplatin at a dose of 75 mg/m<sup>2</sup> was administered as intravenous infusion on Day 1 + Gemcitabine (Gem) was administered at a dose of 1250 mg/m<sup>2</sup> as intravenous infusion on Days 1 and 8 of each 3-week cycle) along with Cilengitide and cetuximab as per Investigator's discretion up to a maximum of 6 cycles.

|                       |                                                                |
|-----------------------|----------------------------------------------------------------|
| Reporting group title | Randomized Part: Cil (Twice Weekly) + Cetuximab + Chemotherapy |
|-----------------------|----------------------------------------------------------------|

#### Reporting group description:

Cilengitide (cil) was administered at a dose of 2000 mg as intravenous infusion twice weekly over 1 hour on Days 1, 4, 8, 11, 15, and 18 of each 3-week cycle followed by once weekly administration after end of chemotherapy + Cetuximab was administered at a dose of 400 mg/m<sup>2</sup> as intravenous infusion over 2 hours on Day 1 of Cycle 1 followed by cetuximab at a dose of 250 mg/m<sup>2</sup> as intravenous infusion over 1 hour once weekly on Days 8 and 15 of Cycle 1 and Days 1, 8, and 15 of all subsequent cycles until progressive disease, death, unacceptable toxicity, or consent withdrawal. Chemotherapy (Cisplatin [Cis] at a dose of 80 mg/m<sup>2</sup> was administered as intravenous infusion on Day 1 + Vinorelbine [Vin] at a dose of 25 mg/m<sup>2</sup> or Cisplatin [Cis] at a dose of 75 mg/m<sup>2</sup> as intravenous infusion on Day 1 + Gemcitabine at a dose of 1250 mg/m<sup>2</sup> intravenous infusion on Days 1 and 8 of each 3-week cycle) along with Cilengitide and cetuximab as per Investigator's discretion up to a maximum of 6 cycles.

|                       |                                           |
|-----------------------|-------------------------------------------|
| Reporting group title | Randomized Part: Cetuximab + Chemotherapy |
|-----------------------|-------------------------------------------|

#### Reporting group description:

Cetuximab was administered at a dose of 400 mg/m<sup>2</sup> as intravenous infusion over 2 hours on Day 1 of Cycle 1 followed by cetuximab at a dose of 250 mg/m<sup>2</sup> was administered as intravenous infusion over 1 hour once weekly on Days 8 and 15 of Cycle 1 and Days 1, 8, and 15 of all subsequent cycles until progressive disease, death, unacceptable toxicity, or consent withdrawal. Chemotherapy (Cisplatin [Cis] at a dose of 80 mg/m<sup>2</sup> was administered as intravenous infusion on Day 1 + Vinorelbine [Vin] was administered at a dose of 25 mg/m<sup>2</sup> or Cisplatin at a dose of 75 mg/m<sup>2</sup> was administered as intravenous infusion on Day 1 + Gemcitabine [Gem] at a dose of 1250 mg/m<sup>2</sup> was administered as intravenous infusion on Days 1 and 8 of each 3-week cycle) along with Cilengitide and cetuximab as per Investigator's discretion up to a maximum of 6 cycles.

|                       |                                                           |
|-----------------------|-----------------------------------------------------------|
| Reporting group title | Safety run-in Part: Cil (1000 mg) + Cetuximab + Cis + Gem |
|-----------------------|-----------------------------------------------------------|

#### Reporting group description:

Cilengitide (Cil) was administered at a dose of 1000 milligram (mg) as intravenous infusion twice weekly over 1 hour on Days 1 and 4 along with Cetuximab at a dose of 400 milligram per square meter (mg/m<sup>2</sup>) as intravenous infusion over 2 hours on Day 1 plus Cisplatin (Cis) 75 mg/m<sup>2</sup> intravenous infusion on Day 1 and Gemcitabine (Gem) at a dose of 1250 mg/m<sup>2</sup> was administered as intravenous infusion on Days 1 and 8 for a period of 3 weeks.

|                       |                                                           |
|-----------------------|-----------------------------------------------------------|
| Reporting group title | Safety run-in Part: Cil (1000 mg) + Cetuximab + Cis + Vin |
|-----------------------|-----------------------------------------------------------|

#### Reporting group description:

Cilengitide was administered at a dose of 1000 mg as intravenous infusion twice weekly over 1 hour on Days 1 and 4 + Cetuximab was administered at a dose of 400 mg/m<sup>2</sup> as intravenous infusion over 2 hours on Day 1 + Cisplatin [Cis] was administered at a dose of 80 mg/m<sup>2</sup> as intravenous infusion on Day 1 + Vinorelbine (Vin) was administered at a dose of 25 mg/m<sup>2</sup> as intravenous infusion on Days 1 and 8 for 3 weeks.

|                       |                                                           |
|-----------------------|-----------------------------------------------------------|
| Reporting group title | Safety run-in Part: Cil (2000 mg) + Cetuximab + Cis + Gem |
|-----------------------|-----------------------------------------------------------|

#### Reporting group description:

Cilengitide was administered at a dose of 2000 mg as intravenous infusion twice weekly over 1 hour on Days 1 and 4 + Cetuximab was administered at a dose of 400 mg/m<sup>2</sup> as intravenous infusion over 2 hours on Day 1 + Cisplatin (Cis) was administered at a dose of 75 mg/m<sup>2</sup> as intravenous infusion on Day 1 + Gemcitabine (Gem) was administered at a dose of 1250 mg/m<sup>2</sup> as intravenous infusion on Days 1 and 8 for 3 weeks.

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                           |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                              | Safety run-in Part: Cil (2000 mg) + Cetuximab + Cis + Vin |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                           |
| Cilengitide was administered at a dose of 2000 mg as intravenous infusion twice weekly over 1 hour on Days 1 and 4 + Cetuximab was administered at a dose of 400 mg/m <sup>2</sup> as intravenous infusion over 2 hours on Day 1 + Cisplatin (Cis) was administered at a dose of 80 mg/m <sup>2</sup> as intravenous infusion on Day 1 + Vinorelbine (Vin) was administered at a dose of 25 mg/m <sup>2</sup> as intravenous infusion on Days 1 and 8 for 3 weeks. |                                                           |

| Reporting group values                | Randomized Part:<br>Cil (Once Weekly) +<br>Cetuximab +<br>Chemotherapy | Randomized Part: Cil<br>(Twice Weekly) +<br>Cetuximab +<br>Chemotherapy | Randomized Part:<br>Cetuximab +<br>Chemotherapy |
|---------------------------------------|------------------------------------------------------------------------|-------------------------------------------------------------------------|-------------------------------------------------|
| Number of subjects                    | 85                                                                     | 51                                                                      | 84                                              |
| Age categorical<br>Units: Subjects    |                                                                        |                                                                         |                                                 |
| Less than 65 years                    | 68                                                                     | 37                                                                      | 66                                              |
| Greater than or equal to 65 years     | 17                                                                     | 14                                                                      | 18                                              |
| Gender categorical<br>Units: Subjects |                                                                        |                                                                         |                                                 |
| Female                                | 34                                                                     | 19                                                                      | 27                                              |
| Male                                  | 51                                                                     | 32                                                                      | 57                                              |

| Reporting group values                | Safety run-in Part:<br>Cil (1000 mg) +<br>Cetuximab + Cis +<br>Gem | Safety run-in Part:<br>Cil (1000 mg) +<br>Cetuximab + Cis +<br>Vin | Safety run-in Part:<br>Cil (2000 mg) +<br>Cetuximab + Cis +<br>Gem |
|---------------------------------------|--------------------------------------------------------------------|--------------------------------------------------------------------|--------------------------------------------------------------------|
| Number of subjects                    | 3                                                                  | 3                                                                  | 3                                                                  |
| Age categorical<br>Units: Subjects    |                                                                    |                                                                    |                                                                    |
| Less than 65 years                    | 3                                                                  | 2                                                                  | 3                                                                  |
| Greater than or equal to 65 years     | 0                                                                  | 1                                                                  | 0                                                                  |
| Gender categorical<br>Units: Subjects |                                                                    |                                                                    |                                                                    |
| Female                                | 1                                                                  | 0                                                                  | 2                                                                  |
| Male                                  | 2                                                                  | 3                                                                  | 1                                                                  |

| Reporting group values                | Safety run-in Part:<br>Cil (2000 mg) +<br>Cetuximab + Cis +<br>Vin | Total |  |
|---------------------------------------|--------------------------------------------------------------------|-------|--|
| Number of subjects                    | 3                                                                  | 232   |  |
| Age categorical<br>Units: Subjects    |                                                                    |       |  |
| Less than 65 years                    | 3                                                                  | 182   |  |
| Greater than or equal to 65 years     | 0                                                                  | 50    |  |
| Gender categorical<br>Units: Subjects |                                                                    |       |  |
| Female                                | 2                                                                  | 85    |  |
| Male                                  | 1                                                                  | 147   |  |

## End points

### End points reporting groups

|                       |                                                               |
|-----------------------|---------------------------------------------------------------|
| Reporting group title | Randomized Part: Cil (Once Weekly) + Cetuximab + Chemotherapy |
|-----------------------|---------------------------------------------------------------|

#### Reporting group description:

Cilengitide (Cil) was administered at a dose of 2000 mg as intravenous infusion once weekly over 1 hour on Days 1, 8 and 15 of each 3-week cycle + Cetuximab was administered at a dose of 400 mg/m<sup>2</sup> as intravenous infusion over 2 hours on Day 1 of Cycle 1 followed by cetuximab 250 mg/m<sup>2</sup> intravenous infusion over 1 hour once weekly on Days 8 and 15 of Cycle 1 and Days 1, 8, and 15 of all subsequent cycles until progressive disease, death, unacceptable toxicity, or consent withdrawal. Chemotherapy (Cisplatin [Cis] at a dose of 80 mg/m<sup>2</sup> was administered as intravenous infusion on Day 1 + Vinorelbine [Vin] 25 mg/m<sup>2</sup> or Cisplatin at a dose of 75 mg/m<sup>2</sup> was administered as intravenous infusion on Day 1 + Gemcitabine (Gem) was administered at a dose of 1250 mg/m<sup>2</sup> as intravenous infusion on Days 1 and 8 of each 3-week cycle) along with Cilengitide and cetuximab as per Investigator's discretion up to a maximum of 6 cycles.

|                       |                                                                |
|-----------------------|----------------------------------------------------------------|
| Reporting group title | Randomized Part: Cil (Twice Weekly) + Cetuximab + Chemotherapy |
|-----------------------|----------------------------------------------------------------|

#### Reporting group description:

Cilengitide (cil) was administered at a dose of 2000 mg as intravenous infusion twice weekly over 1 hour on Days 1, 4, 8, 11, 15, and 18 of each 3-week cycle followed by once weekly administration after end of chemotherapy + Cetuximab was administered at a dose of 400 mg/m<sup>2</sup> as intravenous infusion over 2 hours on Day 1 of Cycle 1 followed by cetuximab at a dose of 250 mg/m<sup>2</sup> as intravenous infusion over 1 hour once weekly on Days 8 and 15 of Cycle 1 and Days 1, 8, and 15 of all subsequent cycles until progressive disease, death, unacceptable toxicity, or consent withdrawal. Chemotherapy (Cisplatin [Cis] at a dose of 80 mg/m<sup>2</sup> was administered as intravenous infusion on Day 1 + Vinorelbine [Vin] at a dose of 25 mg/m<sup>2</sup> or Cisplatin [Cis] at a dose of 75 mg/m<sup>2</sup> as intravenous infusion on Day 1 + Gemcitabine at a dose of 1250 mg/m<sup>2</sup> intravenous infusion on Days 1 and 8 of each 3-week cycle) along with Cilengitide and cetuximab as per Investigator's discretion up to a maximum of 6 cycles.

|                       |                                           |
|-----------------------|-------------------------------------------|
| Reporting group title | Randomized Part: Cetuximab + Chemotherapy |
|-----------------------|-------------------------------------------|

#### Reporting group description:

Cetuximab was administered at a dose of 400 mg/m<sup>2</sup> as intravenous infusion over 2 hours on Day 1 of Cycle 1 followed by cetuximab at a dose of 250 mg/m<sup>2</sup> was administered as intravenous infusion over 1 hour once weekly on Days 8 and 15 of Cycle 1 and Days 1, 8, and 15 of all subsequent cycles until progressive disease, death, unacceptable toxicity, or consent withdrawal. Chemotherapy (Cisplatin [Cis] at a dose of 80 mg/m<sup>2</sup> was administered as intravenous infusion on Day 1 + Vinorelbine [Vin] was administered at a dose of 25 mg/m<sup>2</sup> or Cisplatin at a dose of 75 mg/m<sup>2</sup> was administered as intravenous infusion on Day 1 + Gemcitabine [Gem] at a dose of 1250 mg/m<sup>2</sup> was administered as intravenous infusion on Days 1 and 8 of each 3-week cycle) along with Cilengitide and cetuximab as per Investigator's discretion up to a maximum of 6 cycles.

|                       |                                                           |
|-----------------------|-----------------------------------------------------------|
| Reporting group title | Safety run-in Part: Cil (1000 mg) + Cetuximab + Cis + Gem |
|-----------------------|-----------------------------------------------------------|

#### Reporting group description:

Cilengitide (Cil) was administered at a dose of 1000 milligram (mg) as intravenous infusion twice weekly over 1 hour on Days 1 and 4 along with Cetuximab at a dose of 400 milligram per square meter (mg/m<sup>2</sup>) as intravenous infusion over 2 hours on Day 1 plus Cisplatin (Cis) 75 mg/m<sup>2</sup> intravenous infusion on Day 1 and Gemcitabine (Gem) at a dose of 1250 mg/m<sup>2</sup> was administered as intravenous infusion on Days 1 and 8 for a period of 3 weeks.

|                       |                                                           |
|-----------------------|-----------------------------------------------------------|
| Reporting group title | Safety run-in Part: Cil (1000 mg) + Cetuximab + Cis + Vin |
|-----------------------|-----------------------------------------------------------|

#### Reporting group description:

Cilengitide was administered at a dose of 1000 mg as intravenous infusion twice weekly over 1 hour on Days 1 and 4 + Cetuximab was administered at a dose of 400 mg/m<sup>2</sup> as intravenous infusion over 2 hours on Day 1 + Cisplatin [Cis] was administered at a dose of 80 mg/m<sup>2</sup> as intravenous infusion on Day 1 + Vinorelbine (Vin) was administered at a dose of 25 mg/m<sup>2</sup> as intravenous infusion on Days 1 and 8 for 3 weeks.

|                       |                                                           |
|-----------------------|-----------------------------------------------------------|
| Reporting group title | Safety run-in Part: Cil (2000 mg) + Cetuximab + Cis + Gem |
|-----------------------|-----------------------------------------------------------|

#### Reporting group description:

Cilengitide was administered at a dose of 2000 mg as intravenous infusion twice weekly over 1 hour on Days 1 and 4 + Cetuximab was administered at a dose of 400 mg/m<sup>2</sup> as intravenous infusion over 2 hours on Day 1 + Cisplatin (Cis) was administered at a dose of 75 mg/m<sup>2</sup> as intravenous infusion on Day 1 + Gemcitabine (Gem) was administered at a dose of 1250 mg/m<sup>2</sup> as intravenous infusion on Days 1 and 8 for 3 weeks.

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                           |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                              | Safety run-in Part: Cil (2000 mg) + Cetuximab + Cis + Vin |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                           |
| Cilengitide was administered at a dose of 2000 mg as intravenous infusion twice weekly over 1 hour on Days 1 and 4 + Cetuximab was administered at a dose of 400 mg/m <sup>2</sup> as intravenous infusion over 2 hours on Day 1 + Cisplatin (Cis) was administered at a dose of 80 mg/m <sup>2</sup> as intravenous infusion on Day 1 + Vinorelbine (Vin) was administered at a dose of 25 mg/m <sup>2</sup> as intravenous infusion on Days 1 and 8 for 3 weeks. |                                                           |

### Primary: Safety run-in Part: Number of subjects with dose limiting toxicities (DLTs)

|                                                                                                                                                                                                                           |                                                                                               |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                           | Safety run-in Part: Number of subjects with dose limiting toxicities (DLTs) <sup>[1][2]</sup> |
| End point description:                                                                                                                                                                                                    |                                                                                               |
| The DLT population included all subjects who completed first 3 weeks of treatment (first chemotherapy cycle) or who discontinued treatment due to any DLT during the first 3 weeks of treatment in the safetyrun-in part. |                                                                                               |
| End point type                                                                                                                                                                                                            | Primary                                                                                       |
| End point timeframe:                                                                                                                                                                                                      |                                                                                               |
| Up to Week 3                                                                                                                                                                                                              |                                                                                               |

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: The statistical analyses was not planned for this outcome measure.

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

Justification: The statistics was reported only for the groups in the safety run-in part of the study as per planned analysis

| End point values            | Safety run-in Part: Cil (1000 mg) + Cetuximab + Cis + Gem | Safety run-in Part: Cil (1000 mg) + Cetuximab + Cis + Vin | Safety run-in Part: Cil (2000 mg) + Cetuximab + Cis + Gem | Safety run-in Part: Cil (2000 mg) + Cetuximab + Cis + Vin |
|-----------------------------|-----------------------------------------------------------|-----------------------------------------------------------|-----------------------------------------------------------|-----------------------------------------------------------|
| Subject group type          | Reporting group                                           | Reporting group                                           | Reporting group                                           | Reporting group                                           |
| Number of subjects analysed | 3                                                         | 3                                                         | 3                                                         | 3                                                         |
| Units: Subjects             |                                                           |                                                           |                                                           |                                                           |
| Independent Read            | 0                                                         | 0                                                         | 0                                                         | 0                                                         |

### Statistical analyses

No statistical analyses for this end point

### Primary: Randomized part: Progression free survival (PFS) time - Independent read

|                                                                                                                                                                                                                                                                                                                                                                      |                                                                                         |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                      | Randomized part: Progression free survival (PFS) time - Independent read <sup>[3]</sup> |
| End point description:                                                                                                                                                                                                                                                                                                                                               |                                                                                         |
| The PFS time is defined as the duration from randomization to either first observation of progressive disease (PD) or occurrence of death due to any cause. Independent Read is the assessment of all imaging centrally by an Independent Review Committee (IRC). Intent-to-treat (ITT) population included all participants who were randomized to trial treatment. |                                                                                         |
| End point type                                                                                                                                                                                                                                                                                                                                                       | Primary                                                                                 |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                 |                                                                                         |
| Time from randomization until disease progression, death or last tumor assessment, reported between                                                                                                                                                                                                                                                                  |                                                                                         |

day of first subject randomized, that is, Feb 2009 until cut-off date, (26 Jun 2013).

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: The statistics was reported only for the groups in the randomized part of the study as per planned analysis

| <b>End point values</b>          | Randomized Part: Cil (Once Weekly) + Cetuximab + Chemotherapy | Randomized Part: Cil (Twice Weekly) + Cetuximab + Chemotherapy | Randomized Part: Cetuximab + Chemotherapy |  |
|----------------------------------|---------------------------------------------------------------|----------------------------------------------------------------|-------------------------------------------|--|
| Subject group type               | Reporting group                                               | Reporting group                                                | Reporting group                           |  |
| Number of subjects analysed      | 85                                                            | 51                                                             | 84                                        |  |
| Units: Months                    |                                                               |                                                                |                                           |  |
| median (confidence interval 95%) | 6.2 (5.6 to 7.4)                                              | 5.6 (4 to 7.5)                                                 | 5 (4.2 to 5.6)                            |  |

## Statistical analyses

|                                         |                                                                                                           |
|-----------------------------------------|-----------------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 1                                                                                    |
| Comparison groups                       | Randomized Part: Cil (Once Weekly) + Cetuximab + Chemotherapy v Randomized Part: Cetuximab + Chemotherapy |
| Number of subjects included in analysis | 169                                                                                                       |
| Analysis specification                  | Pre-specified                                                                                             |
| Analysis type                           | other                                                                                                     |
| P-value                                 | = 0.0845                                                                                                  |
| Method                                  | Logrank                                                                                                   |
| Parameter estimate                      | Hazard ratio (HR)                                                                                         |
| Point estimate                          | 0.718                                                                                                     |
| Confidence interval                     |                                                                                                           |
| level                                   | 95 %                                                                                                      |
| sides                                   | 2-sided                                                                                                   |
| lower limit                             | 0.492                                                                                                     |
| upper limit                             | 1.048                                                                                                     |

## Secondary: Randomized Part: Progression Free Survival (PFS) Time - Investigator Read

|                 |                                                                                          |
|-----------------|------------------------------------------------------------------------------------------|
| End point title | Randomized Part: Progression Free Survival (PFS) Time - Investigator Read <sup>[4]</sup> |
|-----------------|------------------------------------------------------------------------------------------|

End point description:

The PFS time is defined as the duration from randomization to either first observation of progressive disease (PD) or occurrence of death due to any cause. Investigator read is the assessment of all imaging by the treating physician at the local trial site. ITT population included all participants who were randomized to trial treatment.

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

End point timeframe:

Time from randomization until disease progression, death or last tumor assessment, reported between day of first subject randomized, that is, Feb 2009 until cut-off date, (26 Jun 2013).

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The statistics was reported only for the groups in the randomized part of the study as per planned analysis

| End point values                 | Randomized Part: Cil (Once Weekly) + Cetuximab + Chemotherapy | Randomized Part: Cil (Twice Weekly) + Cetuximab + Chemotherapy | Randomized Part: Cetuximab + Chemotherapy |  |
|----------------------------------|---------------------------------------------------------------|----------------------------------------------------------------|-------------------------------------------|--|
| Subject group type               | Reporting group                                               | Reporting group                                                | Reporting group                           |  |
| Number of subjects analysed      | 85                                                            | 51                                                             | 84                                        |  |
| Units: Months                    |                                                               |                                                                |                                           |  |
| median (confidence interval 95%) | 5.6 (5.4 to 6.7)                                              | 5.6 (4.2 to 7)                                                 | 5.3 (4.2 to 5.7)                          |  |

## Statistical analyses

|                                         |                                                                                                           |
|-----------------------------------------|-----------------------------------------------------------------------------------------------------------|
| Statistical analysis title              | Statistical Analysis 1                                                                                    |
| Comparison groups                       | Randomized Part: Cil (Once Weekly) + Cetuximab + Chemotherapy v Randomized Part: Cetuximab + Chemotherapy |
| Number of subjects included in analysis | 169                                                                                                       |
| Analysis specification                  | Pre-specified                                                                                             |
| Analysis type                           | other                                                                                                     |
| P-value                                 | = 0.5912                                                                                                  |
| Method                                  | Logrank                                                                                                   |
| Parameter estimate                      | Hazard ratio (HR)                                                                                         |
| Point estimate                          | 0.909                                                                                                     |
| Confidence interval                     |                                                                                                           |
| level                                   | 95 %                                                                                                      |
| sides                                   | 2-sided                                                                                                   |
| lower limit                             | 0.642                                                                                                     |
| upper limit                             | 1.286                                                                                                     |

## Secondary: Randomized Part: Overall Survival (OS) Time

|                        |                                                                                                                                                                                                                                                                                                                         |
|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title        | Randomized Part: Overall Survival (OS) Time <sup>[5]</sup>                                                                                                                                                                                                                                                              |
| End point description: | The OS time is defined as the time (in months) from randomization to death or last day known to be alive. Subjects without event are censored at the last date known to be alive or at the clinical cut-off date, whatever is earlier. ITT population included all participants who were randomized to trial treatment. |
| End point type         | Secondary                                                                                                                                                                                                                                                                                                               |
| End point timeframe:   | Time from randomization until death or last day known to be alive, reported between day of first subject randomized, that is, Feb 2009 until cut-off date,(26 Jun 2013).                                                                                                                                                |

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The statistics was reported only for the groups in the randomized part of the study as per planned analysis

| <b>End point values</b>          | Randomized Part: Cil (Once Weekly) + Cetuximab + Chemotherapy | Randomized Part: Cil (Twice Weekly) + Cetuximab + Chemotherapy | Randomized Part: Cetuximab + Chemotherapy |  |
|----------------------------------|---------------------------------------------------------------|----------------------------------------------------------------|-------------------------------------------|--|
| Subject group type               | Reporting group                                               | Reporting group                                                | Reporting group                           |  |
| Number of subjects analysed      | 85                                                            | 51                                                             | 84                                        |  |
| Units: months                    |                                                               |                                                                |                                           |  |
| median (confidence interval 95%) | 13.6 (9.5 to 18.6)                                            | 13.6 (8.7 to 16.7)                                             | 9.7 (7.9 to 13.4)                         |  |

## Statistical analyses

| <b>Statistical analysis title</b>       | Statistical Analysis 1                                                                                    |
|-----------------------------------------|-----------------------------------------------------------------------------------------------------------|
| Comparison groups                       | Randomized Part: Cil (Once Weekly) + Cetuximab + Chemotherapy v Randomized Part: Cetuximab + Chemotherapy |
| Number of subjects included in analysis | 169                                                                                                       |
| Analysis specification                  | Pre-specified                                                                                             |
| Analysis type                           | other                                                                                                     |
| P-value                                 | = 0.2648                                                                                                  |
| Method                                  | Logrank                                                                                                   |
| Parameter estimate                      | Hazard ratio (HR)                                                                                         |
| Point estimate                          | 0.813                                                                                                     |
| Confidence interval                     |                                                                                                           |
| level                                   | 95 %                                                                                                      |
| sides                                   | 2-sided                                                                                                   |
| lower limit                             | 0.564                                                                                                     |
| upper limit                             | 1.171                                                                                                     |

## Secondary: Randomized Part: Best Overall Response (BOR) Rate

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Randomized Part: Best Overall Response (BOR) Rate <sup>[6]</sup> |
| <p>End point description:</p> <p>The BOR rate is defined as the percentage of subjects having achieved confirmed complete response (CR) or partial response (PR) as the best overall response, based on radiological assessments (based on response evaluation criteria in solid tumors [RECIST]) as assessed by Independent Review Committee (IRC): CR = disappearance of all target lesions; PR = at least 30% decrease in the sum of the longest diameter of target lesions. ITT population included all participants who were randomized to trial treatment.</p> |                                                                  |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Secondary                                                        |
| <p>End point timeframe:</p> <p>Time from randomization until treatment failure or last tumor assessment, reported between day of first subject randomized, that was, Feb 2009 until cut-off date,(26 Jun 2013)</p>                                                                                                                                                                                                                                                                                                                                                   |                                                                  |
| <p>Notes:</p> <p>[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The statistics was reported only for the groups in the randomized part of the study as per planned analysis</p>                                                                                                                                                                                              |                                                                  |

| End point values                 | Randomized Part: Cil (Once Weekly) + Cetuximab + Chemotherapy | Randomized Part: Cil (Twice Weekly) + Cetuximab + Chemotherapy | Randomized Part: Cetuximab + Chemotherapy |  |
|----------------------------------|---------------------------------------------------------------|----------------------------------------------------------------|-------------------------------------------|--|
| Subject group type               | Reporting group                                               | Reporting group                                                | Reporting group                           |  |
| Number of subjects analysed      | 85                                                            | 51                                                             | 84                                        |  |
| Units: percentage                |                                                               |                                                                |                                           |  |
| number (confidence interval 95%) | 37.6 (27.4 to 48.8)                                           | 27.5 (15.9 to 41.7)                                            | 29.8 (20.3 to 40.7)                       |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Randomized Part: Time to Treatment Failure

|                 |                                                           |
|-----------------|-----------------------------------------------------------|
| End point title | Randomized Part: Time to Treatment Failure <sup>[7]</sup> |
|-----------------|-----------------------------------------------------------|

End point description:

Time to treatment failure was defined as the time from first administration of trial treatment until the date of the first occurrence of one of the events defining treatment failure: Progressive Disease (PD) assessed by the investigator, discontinuation of treatment due to PD, discontinuation of treatment due to an adverse event (AE), start of any new anticancer therapy, or withdrawal of consent or death within 60 days of the last tumor assessment or first administration of trial treatment. Time to treatment failure was assessed according to modified World Health Organization (WHO) criteria by Independent Review Committee (IRC). ITT population included all participants who were randomized to trial treatment.

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

End point timeframe:

Time from randomization until treatment failure or last tumor assessment, reported between day of first subject randomized, that is, Feb 2009 until cut-off date,(26 Jun 2013).

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The statistics was reported only for the groups in the randomized part of the study as per planned analysis

| End point values                 | Randomized Part: Cil (Once Weekly) + Cetuximab + Chemotherapy | Randomized Part: Cil (Twice Weekly) + Cetuximab + Chemotherapy | Randomized Part: Cetuximab + Chemotherapy |  |
|----------------------------------|---------------------------------------------------------------|----------------------------------------------------------------|-------------------------------------------|--|
| Subject group type               | Reporting group                                               | Reporting group                                                | Reporting group                           |  |
| Number of subjects analysed      | 85                                                            | 51                                                             | 84                                        |  |
| Units: months                    |                                                               |                                                                |                                           |  |
| median (confidence interval 95%) | 4.4 (3.5 to 5.6)                                              | 2.8 (1.4 to 4.2)                                               | 4.2 (2.8 to 5.3)                          |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Time from first dose up to 28 days after last dose of study treatment, reported between day of first subject randomized, that was, Feb 2009 until cut-off date (26 Jun 2013)

Adverse event reporting additional description:

The analysis was performed on safety population, defined as all subjects who received any dose of the trial treatment (cilengitide, cetuximab, or chemotherapy), whereby subjects were analyzed according to the actual treatment they received.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 15.0 |
|--------------------|------|

### Reporting groups

|                       |                                              |
|-----------------------|----------------------------------------------|
| Reporting group title | Cil (Once Weekly) + Cetuximab + Chemotherapy |
|-----------------------|----------------------------------------------|

Reporting group description:

Cil 2000 mg intravenous infusion once weekly over 1 hour on Days 1, 8 and 15 of each 3-week cycle + Cetuximab 400 mg/m<sup>2</sup> intravenous infusion over 2 hours on Day 1 of Cycle 1 followed by cetuximab 250 mg/m<sup>2</sup> intravenous infusion over 1 hour once weekly on Days 8 and 15 of Cycle 1 and Days 1, 8, and 15 of all subsequent cycles until progressive disease, death, unacceptable toxicity, or consent withdrawal. Chemotherapy (Cis 80 mg/m<sup>2</sup> intravenous infusion on Day 1 + Vin 25 mg/m<sup>2</sup> or Cis 75 mg/m<sup>2</sup> intravenous infusion on Day 1 + Gem 1250 mg/m<sup>2</sup> intravenous infusion on Days 1 and 8 of each 3-week cycle) was administered along with Cil and cetuximab as per Investigator's discretion up to a maximum of 6 cycles.

|                       |                                                                |
|-----------------------|----------------------------------------------------------------|
| Reporting group title | Randomized Part: Cil (Twice Weekly) + Cetuximab + Chemotherapy |
|-----------------------|----------------------------------------------------------------|

Reporting group description:

Cil 2000 mg intravenous infusion twice weekly over 1 hour on Days 1, 4, 8, 11, 15, and 18 of each 3-week cycle followed by once weekly administration after end of chemotherapy + Cetuximab 400 mg/m<sup>2</sup> intravenous infusion over 2 hours on Day 1 of Cycle 1 followed by cetuximab 250 mg/m<sup>2</sup> intravenous infusion over 1 hour once weekly on Days 8 and 15 of Cycle 1 and Days 1, 8, and 15 of all subsequent cycles until progressive disease, death, unacceptable toxicity, or consent withdrawal. Chemotherapy (Cis 80 mg/m<sup>2</sup> intravenous infusion on Day 1 + Vin 25 mg/m<sup>2</sup> or Cis 75 mg/m<sup>2</sup> intravenous infusion on Day 1 + Gem 1250 mg/m<sup>2</sup> intravenous infusion on Days 1 and 8 of each 3-week cycle) was administered along with Cil and cetuximab as per Investigator's discretion up to a maximum of 6 cycles.

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Cetuximab + Chemotherapy |
|-----------------------|--------------------------|

Reporting group description:

Cetuximab 400 mg/m<sup>2</sup> intravenous infusion over 2 hours on Day 1 of Cycle 1 followed by cetuximab 250 mg/m<sup>2</sup> intravenous infusion over 1 hour once weekly on Days 8 and 15 of Cycle 1 and Days 1, 8, and 15 of all subsequent cycles until progressive disease, death, unacceptable toxicity, or consent withdrawal. Chemotherapy (Cis 80 mg/m<sup>2</sup> intravenous infusion on Day 1 + Vin 25 mg/m<sup>2</sup> or Cis 75 mg/m<sup>2</sup> intravenous infusion on Day 1 + Gem 1250 mg/m<sup>2</sup> intravenous infusion on Days 1 and 8 of each 3-week cycle) was administered along with Cil and cetuximab as per Investigator's discretion up to a maximum of 6 cycles.

| Serious adverse events                            | Cil (Once Weekly) + Cetuximab + Chemotherapy | Randomized Part: Cil (Twice Weekly) + Cetuximab + Chemotherapy | Cetuximab + Chemotherapy |
|---------------------------------------------------|----------------------------------------------|----------------------------------------------------------------|--------------------------|
| Total subjects affected by serious adverse events |                                              |                                                                |                          |
| subjects affected / exposed                       | 42 / 85 (49.41%)                             | 29 / 50 (58.00%)                                               | 45 / 80 (56.25%)         |
| number of deaths (all causes)                     | 56                                           | 39                                                             | 58                       |
| number of deaths resulting from                   |                                              |                                                                |                          |

|                                                                     |                |                |                |
|---------------------------------------------------------------------|----------------|----------------|----------------|
| adverse events                                                      |                |                |                |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                |                |                |
| MALIGNANT PLEURAL EFFUSION                                          |                |                |                |
| subjects affected / exposed                                         | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 0 / 80 (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          |
| METASTASES TO MENINGES                                              |                |                |                |
| subjects affected / exposed                                         | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 1          |
| TUMOUR EMBOLISM                                                     |                |                |                |
| subjects affected / exposed                                         | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 0 / 80 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 1          | 0 / 0          | 0 / 0          |
| Vascular disorders                                                  |                |                |                |
| AORTIC THROMBOSIS                                                   |                |                |                |
| subjects affected / exposed                                         | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all                     | 1 / 1          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| ARTERIAL DISORDER                                                   |                |                |                |
| subjects affected / exposed                                         | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| ARTERIAL THROMBOSIS LIMB                                            |                |                |                |
| subjects affected / exposed                                         | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 0 / 80 (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          |
| AXILLARY VEIN THROMBOSIS                                            |                |                |                |
| subjects affected / exposed                                         | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| DEEP VEIN THROMBOSIS                                                |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 2 / 80 (2.50%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| HYPOTENSION                                     |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| HYPOVOLAEMIC SHOCK                              |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 1 / 50 (2.00%) | 0 / 80 (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          |
| JUGULAR VEIN THROMBOSIS                         |                |                |                |
| subjects affected / exposed                     | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 0 / 80 (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          |
| PERIPHERAL ARTERIAL OCCLUSIVE DISEASE           |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 2 / 80 (2.50%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| PERIPHERAL EMBOLISM                             |                |                |                |
| subjects affected / exposed                     | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 0 / 80 (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          |
| SHOCK                                           |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| SUBCLAVIAN VEIN THROMBOSIS                      |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| SUPERIOR VENA CAVA SYNDROME                     |                |                |                |

|                                                      |                |                |                |
|------------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                          | 0 / 85 (0.00%) | 1 / 50 (2.00%) | 0 / 80 (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          |
| THROMBOSIS                                           |                |                |                |
| subjects affected / exposed                          | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| VENA CAVA THROMBOSIS                                 |                |                |                |
| subjects affected / exposed                          | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 0 / 80 (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          |
| General disorders and administration site conditions |                |                |                |
| ASTHENIA                                             |                |                |                |
| subjects affected / exposed                          | 0 / 85 (0.00%) | 1 / 50 (2.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| CHEST PAIN                                           |                |                |                |
| subjects affected / exposed                          | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| DISEASE PROGRESSION                                  |                |                |                |
| subjects affected / exposed                          | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 1          | 0 / 0          | 0 / 1          |
| FATIGUE                                              |                |                |                |
| subjects affected / exposed                          | 0 / 85 (0.00%) | 1 / 50 (2.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 1          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| GENERAL PHYSICAL HEALTH DETERIORATION                |                |                |                |
| subjects affected / exposed                          | 4 / 85 (4.71%) | 1 / 50 (2.00%) | 3 / 80 (3.75%) |
| occurrences causally related to treatment / all      | 1 / 4          | 0 / 1          | 1 / 3          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 1          | 0 / 1          |
| IMPAIRED HEALING                                     |                |                |                |

|                                                        |                |                |                |
|--------------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                            | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>MALAISE</b>                                         |                |                |                |
| subjects affected / exposed                            | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all        | 1 / 1          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>MEDICAL DEVICE COMPLICATION</b>                     |                |                |                |
| subjects affected / exposed                            | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 0 / 80 (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          |
| <b>PYREXIA</b>                                         |                |                |                |
| subjects affected / exposed                            | 1 / 85 (1.18%) | 1 / 50 (2.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all        | 0 / 1          | 1 / 1          | 1 / 1          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Immune system disorders</b>                         |                |                |                |
| <b>ANAPHYLACTIC REACTION</b>                           |                |                |                |
| subjects affected / exposed                            | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>DRUG HYPERSENSITIVITY</b>                           |                |                |                |
| subjects affected / exposed                            | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 0 / 80 (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          |
| <b>Respiratory, thoracic and mediastinal disorders</b> |                |                |                |
| <b>ACUTE RESPIRATORY DISTRESS SYNDROME</b>             |                |                |                |
| subjects affected / exposed                            | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 0 / 80 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all             | 0 / 1          | 0 / 0          | 0 / 0          |
| <b>DYSPNOEA</b>                                        |                |                |                |
| subjects affected / exposed                            | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |

|                                                 |                |                 |                 |
|-------------------------------------------------|----------------|-----------------|-----------------|
| DYSпноEA EXERTIONAL                             |                |                 |                 |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%)  | 1 / 80 (1.25%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| EPISTAXIS                                       |                |                 |                 |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 1 / 50 (2.00%)  | 1 / 80 (1.25%)  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| HAEMOPTYSIS                                     |                |                 |                 |
| subjects affected / exposed                     | 1 / 85 (1.18%) | 1 / 50 (2.00%)  | 0 / 80 (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           |
| PLEURAL EFFUSION                                |                |                 |                 |
| subjects affected / exposed                     | 1 / 85 (1.18%) | 1 / 50 (2.00%)  | 0 / 80 (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           |
| PNEUMOTHORAX                                    |                |                 |                 |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%)  | 1 / 80 (1.25%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| PULMONARY EMBOLISM                              |                |                 |                 |
| subjects affected / exposed                     | 4 / 85 (4.71%) | 5 / 50 (10.00%) | 8 / 80 (10.00%) |
| occurrences causally related to treatment / all | 3 / 4          | 1 / 5           | 1 / 8           |
| deaths causally related to treatment / all      | 1 / 1          | 0 / 0           | 0 / 1           |
| PULMONARY THROMBOSIS                            |                |                 |                 |
| subjects affected / exposed                     | 1 / 85 (1.18%) | 1 / 50 (2.00%)  | 0 / 80 (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           |
| RESPIRATORY DISTRESS                            |                |                 |                 |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%)  | 1 / 80 (1.25%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| RESPIRATORY FAILURE                             |                |                 |                 |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 85 (0.00%) | 2 / 50 (4.00%) | 0 / 80 (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                           |                |                |                |
| ANXIETY                                         |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| CONFUSIONAL STATE                               |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Investigations                                  |                |                |                |
| HAEMOGLOBIN DECREASED                           |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| PLATELET COUNT DECREASED                        |                |                |                |
| subjects affected / exposed                     | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 0 / 80 (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          |
| Injury, poisoning and procedural complications  |                |                |                |
| FAILURE TO ANASTOMOSE                           |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| HIP FRACTURE                                    |                |                |                |
| subjects affected / exposed                     | 2 / 85 (2.35%) | 0 / 50 (0.00%) | 0 / 80 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| INCISIONAL HERNIA                               |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 1 / 50 (2.00%) | 0 / 80 (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          |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| LIMB INJURY                                     |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| SPINAL COMPRESSION FRACTURE                     |                |                |                |
| subjects affected / exposed                     | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 0 / 80 (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          |
| SPLENIC RUPTURE                                 |                |                |                |
| subjects affected / exposed                     | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 0 / 80 (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          |
| Cardiac disorders                               |                |                |                |
| ACUTE MYOCARDIAL INFARCTION                     |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| ARRHYTHMIA SUPRAVENTRICULAR                     |                |                |                |
| subjects affected / exposed                     | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 0 / 80 (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          |
| ATRIAL FIBRILLATION                             |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| PERICARDIAL EFFUSION                            |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 1 / 50 (2.00%) | 0 / 80 (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          |
| STRESS CARDIOMYOPATHY                           |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| VENTRICULAR TACHYCARDIA                         |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 85 (0.00%) | 1 / 50 (2.00%) | 0 / 80 (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          |
| <b>Nervous system disorders</b>                 |                |                |                |
| <b>CENTRAL NERVOUS SYSTEM LESION</b>            |                |                |                |
| subjects affected / exposed                     | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 0 / 80 (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          |
| <b>CEREBROVASCULAR ACCIDENT</b>                 |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 2 / 50 (4.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 2          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>COMA</b>                                     |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| <b>CONVULSION</b>                               |                |                |                |
| subjects affected / exposed                     | 2 / 85 (2.35%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>SOMNOLENCE</b>                               |                |                |                |
| subjects affected / exposed                     | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 0 / 80 (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          |
| <b>STATUS EPILEPTICUS</b>                       |                |                |                |
| subjects affected / exposed                     | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 0 / 80 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| <b>SYNCOPE</b>                                  |                |                |                |
| subjects affected / exposed                     | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Blood and lymphatic system disorders</b>     |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| ANAEMIA                                         |                |                |                |
| subjects affected / exposed                     | 1 / 85 (1.18%) | 1 / 50 (2.00%) | 2 / 80 (2.50%) |
| occurrences causally related to treatment / all | 1 / 1          | 1 / 1          | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| FEBRILE BONE MARROW APLASIA                     |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| FEBRILE NEUTROPENIA                             |                |                |                |
| subjects affected / exposed                     | 3 / 85 (3.53%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 3 / 3          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 1 / 1          | 0 / 0          | 0 / 0          |
| LEUKOPENIA                                      |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| NEUTROPENIA                                     |                |                |                |
| subjects affected / exposed                     | 4 / 85 (4.71%) | 1 / 50 (2.00%) | 3 / 80 (3.75%) |
| occurrences causally related to treatment / all | 3 / 4          | 1 / 1          | 3 / 3          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| PANCYTOPENIA                                    |                |                |                |
| subjects affected / exposed                     | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 0 / 80 (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          |
| THROMBOCYTOPENIA                                |                |                |                |
| subjects affected / exposed                     | 1 / 85 (1.18%) | 1 / 50 (2.00%) | 4 / 80 (5.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 1 / 1          | 4 / 4          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Ear and labyrinth disorders                     |                |                |                |
| HYPOACUSIS                                      |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Eye disorders                                   |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| PERIORBITAL OEDEMA                              |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |                |                |                |
| ABDOMINAL PAIN                                  |                |                |                |
| subjects affected / exposed                     | 1 / 85 (1.18%) | 1 / 50 (2.00%) | 2 / 80 (2.50%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| ABDOMINAL PAIN UPPER                            |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| CONSTIPATION                                    |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| 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 / 85 (1.18%) | 1 / 50 (2.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 1 / 1          | 1 / 1          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| DIVERTICULAR PERFORATION                        |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| DUODENAL ULCER HAEMORRHAGE                      |                |                |                |
| subjects affected / exposed                     | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 0 / 80 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| LARGE INTESTINE PERFORATION                     |                |                |                |
| subjects affected / exposed                     | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 0 / 80 (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          |
| NAUSEA                                          |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 85 (1.18%) | 2 / 50 (4.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 1 / 1          | 2 / 2          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| PROCTITIS                                       |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| VOMITING                                        |                |                |                |
| subjects affected / exposed                     | 2 / 85 (2.35%) | 1 / 50 (2.00%) | 4 / 80 (5.00%) |
| occurrences causally related to treatment / all | 2 / 2          | 1 / 1          | 3 / 4          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hepatobiliary disorders                         |                |                |                |
| CHOLECYSTITIS                                   |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                |                |                |
| RENAL FAILURE                                   |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 1 / 50 (2.00%) | 0 / 80 (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          |
| RENAL FAILURE ACUTE                             |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Musculoskeletal and connective tissue disorders |                |                |                |
| BACK PAIN                                       |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| 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                     |                |                |                |
| BRONCHITIS                                      |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 85 (0.00%) | 1 / 50 (2.00%) | 0 / 80 (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          |
| BRONCHOPNEUMONIA                                |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 1 / 50 (2.00%) | 0 / 80 (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          |
| BRONCHOPULMONARY ASPERGILLOSIS                  |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| CYSTITIS                                        |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 1 / 50 (2.00%) | 0 / 80 (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          |
| DEVICE RELATED INFECTION                        |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| DIVERTICULITIS                                  |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| GASTROINTESTINAL INFECTION                      |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 1 / 50 (2.00%) | 0 / 80 (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          |
| LUNG INFECTION                                  |                |                |                |
| subjects affected / exposed                     | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 0 / 80 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| NAIL BED INFECTION                              |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>PNEUMONIA</b>                                |                |                |                |
| subjects affected / exposed                     | 1 / 85 (1.18%) | 1 / 50 (2.00%) | 4 / 80 (5.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 1          | 3 / 4          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 2 / 2          |
| <b>PNEUMONIA BACTERIAL</b>                      |                |                |                |
| subjects affected / exposed                     | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 0 / 80 (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          |
| <b>PROTEUS INFECTION</b>                        |                |                |                |
| subjects affected / exposed                     | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 0 / 80 (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          |
| <b>SEPSIS</b>                                   |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 2 / 50 (4.00%) | 0 / 80 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| <b>STAPHYLOCOCCAL INFECTION</b>                 |                |                |                |
| subjects affected / exposed                     | 1 / 85 (1.18%) | 1 / 50 (2.00%) | 0 / 80 (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          |
| <b>STAPHYLOCOCCAL SKIN INFECTION</b>            |                |                |                |
| subjects affected / exposed                     | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 0 / 80 (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          |
| <b>URINARY TRACT INFECTION</b>                  |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Metabolism and nutrition disorders</b>       |                |                |                |
| <b>DECREASED APPETITE</b>                       |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 85 (0.00%) | 1 / 50 (2.00%) | 0 / 80 (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          |
| DEHYDRATION                                     |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| HYPERCALCAEMIA                                  |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 1 / 50 (2.00%) | 0 / 80 (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          |
| HYPOKALAEMIA                                    |                |                |                |
| subjects affected / exposed                     | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 0 / 80 (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          |
| HYPOMAGNESAEMIA                                 |                |                |                |
| subjects affected / exposed                     | 0 / 85 (0.00%) | 1 / 50 (2.00%) | 0 / 80 (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          |

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

| <b>Non-serious adverse events</b>                     | Cil (Once Weekly) +<br>Cetuximab +<br>Chemotherapy | Randomized Part: Cil<br>(Twice Weekly) +<br>Cetuximab +<br>Chemotherapy | Cetuximab +<br>Chemotherapy |
|-------------------------------------------------------|----------------------------------------------------|-------------------------------------------------------------------------|-----------------------------|
| Total subjects affected by non-serious adverse events |                                                    |                                                                         |                             |
| subjects affected / exposed                           | 84 / 85 (98.82%)                                   | 48 / 50 (96.00%)                                                        | 78 / 80 (97.50%)            |
| Vascular disorders                                    |                                                    |                                                                         |                             |
| DEEP VEIN THROMBOSIS                                  |                                                    |                                                                         |                             |
| subjects affected / exposed                           | 5 / 85 (5.88%)                                     | 1 / 50 (2.00%)                                                          | 0 / 80 (0.00%)              |
| occurrences (all)                                     | 5                                                  | 1                                                                       | 0                           |
| HYPERTENSION                                          |                                                    |                                                                         |                             |
| subjects affected / exposed                           | 9 / 85 (10.59%)                                    | 6 / 50 (12.00%)                                                         | 5 / 80 (6.25%)              |
| occurrences (all)                                     | 9                                                  | 6                                                                       | 5                           |
| HYPOTENSION                                           |                                                    |                                                                         |                             |

|                                                         |                     |                     |                     |
|---------------------------------------------------------|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)        | 1 / 85 (1.18%)<br>1 | 4 / 50 (8.00%)<br>4 | 4 / 80 (5.00%)<br>4 |
| General disorders and administration<br>site conditions |                     |                     |                     |
| ASTHENIA                                                |                     |                     |                     |
| subjects affected / exposed                             | 20 / 85 (23.53%)    | 15 / 50 (30.00%)    | 23 / 80 (28.75%)    |
| occurrences (all)                                       | 20                  | 15                  | 23                  |
| CHEST PAIN                                              |                     |                     |                     |
| subjects affected / exposed                             | 5 / 85 (5.88%)      | 5 / 50 (10.00%)     | 2 / 80 (2.50%)      |
| occurrences (all)                                       | 5                   | 5                   | 2                   |
| CHILLS                                                  |                     |                     |                     |
| subjects affected / exposed                             | 2 / 85 (2.35%)      | 3 / 50 (6.00%)      | 2 / 80 (2.50%)      |
| occurrences (all)                                       | 2                   | 3                   | 2                   |
| FATIGUE                                                 |                     |                     |                     |
| subjects affected / exposed                             | 29 / 85 (34.12%)    | 13 / 50 (26.00%)    | 19 / 80 (23.75%)    |
| occurrences (all)                                       | 29                  | 13                  | 19                  |
| GENERAL PHYSICAL HEALTH<br>DETERIORATION                |                     |                     |                     |
| subjects affected / exposed                             | 2 / 85 (2.35%)      | 0 / 50 (0.00%)      | 4 / 80 (5.00%)      |
| occurrences (all)                                       | 2                   | 0                   | 4                   |
| NON-CARDIAC CHEST PAIN                                  |                     |                     |                     |
| subjects affected / exposed                             | 5 / 85 (5.88%)      | 2 / 50 (4.00%)      | 2 / 80 (2.50%)      |
| occurrences (all)                                       | 5                   | 2                   | 2                   |
| OEDEMA PERIPHERAL                                       |                     |                     |                     |
| subjects affected / exposed                             | 5 / 85 (5.88%)      | 5 / 50 (10.00%)     | 5 / 80 (6.25%)      |
| occurrences (all)                                       | 5                   | 5                   | 5                   |
| PYREXIA                                                 |                     |                     |                     |
| subjects affected / exposed                             | 8 / 85 (9.41%)      | 14 / 50 (28.00%)    | 15 / 80 (18.75%)    |
| occurrences (all)                                       | 8                   | 14                  | 15                  |
| XEROSIS                                                 |                     |                     |                     |
| subjects affected / exposed                             | 0 / 85 (0.00%)      | 1 / 50 (2.00%)      | 4 / 80 (5.00%)      |
| occurrences (all)                                       | 0                   | 1                   | 4                   |
| Respiratory, thoracic and mediastinal<br>disorders      |                     |                     |                     |
| COUGH                                                   |                     |                     |                     |
| subjects affected / exposed                             | 13 / 85 (15.29%)    | 11 / 50 (22.00%)    | 12 / 80 (15.00%)    |
| occurrences (all)                                       | 13                  | 11                  | 12                  |
| DYSPHONIA                                               |                     |                     |                     |

|                                                                                                             |                        |                        |                        |
|-------------------------------------------------------------------------------------------------------------|------------------------|------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)                                                            | 2 / 85 (2.35%)<br>2    | 2 / 50 (4.00%)<br>2    | 5 / 80 (6.25%)<br>5    |
| DYSпноEA<br>subjects affected / exposed<br>occurrences (all)                                                | 11 / 85 (12.94%)<br>11 | 6 / 50 (12.00%)<br>6   | 5 / 80 (6.25%)<br>5    |
| DYSпноEA EXERTIONAL<br>subjects affected / exposed<br>occurrences (all)                                     | 9 / 85 (10.59%)<br>9   | 10 / 50 (20.00%)<br>10 | 7 / 80 (8.75%)<br>7    |
| EPISTAXIS<br>subjects affected / exposed<br>occurrences (all)                                               | 10 / 85 (11.76%)<br>10 | 10 / 50 (20.00%)<br>10 | 13 / 80 (16.25%)<br>13 |
| HAEMOPTYSIS<br>subjects affected / exposed<br>occurrences (all)                                             | 3 / 85 (3.53%)<br>3    | 4 / 50 (8.00%)<br>4    | 7 / 80 (8.75%)<br>7    |
| PRODUCTIVE COUGH<br>subjects affected / exposed<br>occurrences (all)                                        | 0 / 85 (0.00%)<br>0    | 1 / 50 (2.00%)<br>1    | 5 / 80 (6.25%)<br>5    |
| Psychiatric disorders<br>ANXIETY<br>subjects affected / exposed<br>occurrences (all)                        | 4 / 85 (4.71%)<br>4    | 4 / 50 (8.00%)<br>4    | 9 / 80 (11.25%)<br>9   |
| DEPRESSION<br>subjects affected / exposed<br>occurrences (all)                                              | 3 / 85 (3.53%)<br>3    | 2 / 50 (4.00%)<br>2    | 4 / 80 (5.00%)<br>4    |
| INSOMNIA<br>subjects affected / exposed<br>occurrences (all)                                                | 4 / 85 (4.71%)<br>4    | 3 / 50 (6.00%)<br>3    | 9 / 80 (11.25%)<br>9   |
| HAEMATURIA<br>subjects affected / exposed<br>occurrences (all)                                              | 0 / 85 (0.00%)<br>0    | 3 / 50 (6.00%)<br>3    | 1 / 80 (1.25%)<br>1    |
| Investigations<br>ALANINE AMINOTRANSFERASE<br>INCREASED<br>subjects affected / exposed<br>occurrences (all) | 6 / 85 (7.06%)<br>6    | 1 / 50 (2.00%)<br>1    | 1 / 80 (1.25%)<br>1    |
| BLOOD CREATININE INCREASED                                                                                  |                        |                        |                        |

|                                                  |                      |                      |                        |
|--------------------------------------------------|----------------------|----------------------|------------------------|
| subjects affected / exposed<br>occurrences (all) | 3 / 85 (3.53%)<br>3  | 5 / 50 (10.00%)<br>5 | 5 / 80 (6.25%)<br>5    |
| GAMMA-GLUTAMYLTRANSFERASE<br>INCREASED           |                      |                      |                        |
| subjects affected / exposed<br>occurrences (all) | 5 / 85 (5.88%)<br>5  | 0 / 50 (0.00%)<br>0  | 4 / 80 (5.00%)<br>4    |
| HAEMOGLOBIN DECREASED                            |                      |                      |                        |
| subjects affected / exposed<br>occurrences (all) | 8 / 85 (9.41%)<br>8  | 7 / 50 (14.00%)<br>7 | 8 / 80 (10.00%)<br>8   |
| PLATELET COUNT DECREASED                         |                      |                      |                        |
| subjects affected / exposed<br>occurrences (all) | 5 / 85 (5.88%)<br>5  | 1 / 50 (2.00%)<br>1  | 3 / 80 (3.75%)<br>3    |
| WEIGHT DECREASED                                 |                      |                      |                        |
| subjects affected / exposed<br>occurrences (all) | 9 / 85 (10.59%)<br>9 | 3 / 50 (6.00%)<br>3  | 15 / 80 (18.75%)<br>15 |
| WHITE BLOOD CELL COUNT<br>DECREASED              |                      |                      |                        |
| subjects affected / exposed<br>occurrences (all) | 6 / 85 (7.06%)<br>6  | 1 / 50 (2.00%)<br>1  | 3 / 80 (3.75%)<br>3    |
| Cardiac disorders                                |                      |                      |                        |
| TACHYCARDIA                                      |                      |                      |                        |
| subjects affected / exposed<br>occurrences (all) | 1 / 85 (1.18%)<br>1  | 3 / 50 (6.00%)<br>3  | 1 / 80 (1.25%)<br>1    |
| Nervous system disorders                         |                      |                      |                        |
| DIZZINESS                                        |                      |                      |                        |
| subjects affected / exposed<br>occurrences (all) | 8 / 85 (9.41%)<br>8  | 4 / 50 (8.00%)<br>4  | 2 / 80 (2.50%)<br>2    |
| DYSGEUSIA                                        |                      |                      |                        |
| subjects affected / exposed<br>occurrences (all) | 7 / 85 (8.24%)<br>7  | 4 / 50 (8.00%)<br>4  | 5 / 80 (6.25%)<br>5    |
| HEADACHE                                         |                      |                      |                        |
| subjects affected / exposed<br>occurrences (all) | 9 / 85 (10.59%)<br>9 | 6 / 50 (12.00%)<br>6 | 6 / 80 (7.50%)<br>6    |
| NEUROPATHY PERIPHERAL                            |                      |                      |                        |
| subjects affected / exposed<br>occurrences (all) | 1 / 85 (1.18%)<br>1  | 3 / 50 (6.00%)<br>3  | 1 / 80 (1.25%)<br>1    |
| PARAESTHESIA                                     |                      |                      |                        |

|                                                  |                     |                     |                      |
|--------------------------------------------------|---------------------|---------------------|----------------------|
| subjects affected / exposed<br>occurrences (all) | 3 / 85 (3.53%)<br>3 | 1 / 50 (2.00%)<br>1 | 8 / 80 (10.00%)<br>8 |
| Blood and lymphatic system disorders             |                     |                     |                      |
| ANAEMIA                                          |                     |                     |                      |
| subjects affected / exposed                      | 33 / 85 (38.82%)    | 22 / 50 (44.00%)    | 24 / 80 (30.00%)     |
| occurrences (all)                                | 33                  | 22                  | 24                   |
| LEUKOPENIA                                       |                     |                     |                      |
| subjects affected / exposed                      | 20 / 85 (23.53%)    | 7 / 50 (14.00%)     | 10 / 80 (12.50%)     |
| occurrences (all)                                | 20                  | 7                   | 10                   |
| LYMPHOPENIA                                      |                     |                     |                      |
| subjects affected / exposed                      | 4 / 85 (4.71%)      | 3 / 50 (6.00%)      | 4 / 80 (5.00%)       |
| occurrences (all)                                | 4                   | 3                   | 4                    |
| NEUTROPENIA                                      |                     |                     |                      |
| subjects affected / exposed                      | 43 / 85 (50.59%)    | 22 / 50 (44.00%)    | 35 / 80 (43.75%)     |
| occurrences (all)                                | 46                  | 22                  | 35                   |
| THROMBOCYTOPENIA                                 |                     |                     |                      |
| subjects affected / exposed                      | 29 / 85 (34.12%)    | 17 / 50 (34.00%)    | 24 / 80 (30.00%)     |
| occurrences (all)                                | 29                  | 17                  | 24                   |
| THROMBOCYTOSIS                                   |                     |                     |                      |
| subjects affected / exposed                      | 3 / 85 (3.53%)      | 4 / 50 (8.00%)      | 1 / 80 (1.25%)       |
| occurrences (all)                                | 3                   | 4                   | 1                    |
| Ear and labyrinth disorders                      |                     |                     |                      |
| TINNITUS                                         |                     |                     |                      |
| subjects affected / exposed                      | 1 / 85 (1.18%)      | 3 / 50 (6.00%)      | 6 / 80 (7.50%)       |
| occurrences (all)                                | 1                   | 3                   | 6                    |
| Eye disorders                                    |                     |                     |                      |
| CONJUNCTIVITIS                                   |                     |                     |                      |
| subjects affected / exposed                      | 10 / 85 (11.76%)    | 7 / 50 (14.00%)     | 5 / 80 (6.25%)       |
| occurrences (all)                                | 10                  | 7                   | 5                    |
| Gastrointestinal disorders                       |                     |                     |                      |
| ABDOMINAL PAIN                                   |                     |                     |                      |
| subjects affected / exposed                      | 7 / 85 (8.24%)      | 2 / 50 (4.00%)      | 6 / 80 (7.50%)       |
| occurrences (all)                                | 7                   | 2                   | 6                    |
| ABDOMINAL PAIN UPPER                             |                     |                     |                      |
| subjects affected / exposed                      | 7 / 85 (8.24%)      | 5 / 50 (10.00%)     | 6 / 80 (7.50%)       |
| occurrences (all)                                | 7                   | 5                   | 6                    |
| CONSTIPATION                                     |                     |                     |                      |

|                                        |                  |                  |                  |
|----------------------------------------|------------------|------------------|------------------|
| subjects affected / exposed            | 17 / 85 (20.00%) | 14 / 50 (28.00%) | 19 / 80 (23.75%) |
| occurrences (all)                      | 17               | 14               | 19               |
| DIARRHOEA                              |                  |                  |                  |
| subjects affected / exposed            | 22 / 85 (25.88%) | 14 / 50 (28.00%) | 22 / 80 (27.50%) |
| occurrences (all)                      | 22               | 14               | 19               |
| DYSPEPSIA                              |                  |                  |                  |
| subjects affected / exposed            | 4 / 85 (4.71%)   | 5 / 50 (10.00%)  | 2 / 80 (2.50%)   |
| occurrences (all)                      | 4                | 5                | 2                |
| GASTROOESOPHAGEAL REFLUX DISEASE       |                  |                  |                  |
| subjects affected / exposed            | 0 / 85 (0.00%)   | 3 / 50 (6.00%)   | 1 / 80 (1.25%)   |
| occurrences (all)                      | 0                | 3                | 1                |
| HAEMORRHOIDS                           |                  |                  |                  |
| subjects affected / exposed            | 2 / 85 (2.35%)   | 4 / 50 (8.00%)   | 1 / 80 (1.25%)   |
| occurrences (all)                      | 2                | 4                | 1                |
| NAUSEA                                 |                  |                  |                  |
| subjects affected / exposed            | 50 / 85 (58.82%) | 27 / 50 (54.00%) | 42 / 80 (52.50%) |
| occurrences (all)                      | 50               | 27               | 42               |
| STOMATITIS                             |                  |                  |                  |
| subjects affected / exposed            | 15 / 85 (17.65%) | 10 / 50 (20.00%) | 11 / 80 (13.75%) |
| occurrences (all)                      | 15               | 10               | 11               |
| VOMITING                               |                  |                  |                  |
| subjects affected / exposed            | 18 / 85 (21.18%) | 14 / 50 (28.00%) | 23 / 80 (28.75%) |
| occurrences (all)                      | 18               | 14               | 23               |
| Skin and subcutaneous tissue disorders |                  |                  |                  |
| ACNE                                   |                  |                  |                  |
| subjects affected / exposed            | 19 / 85 (22.35%) | 11 / 50 (22.00%) | 17 / 80 (21.25%) |
| occurrences (all)                      | 19               | 11               | 17               |
| ALOPECIA                               |                  |                  |                  |
| subjects affected / exposed            | 13 / 85 (15.29%) | 7 / 50 (14.00%)  | 9 / 80 (11.25%)  |
| occurrences (all)                      | 13               | 7                | 9                |
| DERMATITIS ACNEIFORM                   |                  |                  |                  |
| subjects affected / exposed            | 17 / 85 (20.00%) | 7 / 50 (14.00%)  | 16 / 80 (20.00%) |
| occurrences (all)                      | 17               | 7                | 16               |
| DRY SKIN                               |                  |                  |                  |

|                                                  |                        |                        |                        |
|--------------------------------------------------|------------------------|------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all) | 13 / 85 (15.29%)<br>13 | 5 / 50 (10.00%)<br>5   | 9 / 80 (11.25%)<br>9   |
| ERYTHEMA                                         |                        |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 1 / 85 (1.18%)<br>1    | 5 / 50 (10.00%)<br>5   | 4 / 80 (5.00%)<br>4    |
| NAIL TOXICITY                                    |                        |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 4 / 85 (4.71%)<br>4    | 3 / 50 (6.00%)<br>3    | 1 / 80 (1.25%)<br>1    |
| PRURITUS                                         |                        |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 7 / 85 (8.24%)<br>7    | 6 / 50 (12.00%)<br>6   | 3 / 80 (3.75%)<br>3    |
| RASH                                             |                        |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 35 / 85 (41.18%)<br>35 | 17 / 50 (34.00%)<br>17 | 29 / 80 (36.25%)<br>29 |
| SKIN FISSURES                                    |                        |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 6 / 85 (7.06%)<br>6    | 2 / 50 (4.00%)<br>2    | 6 / 80 (7.50%)<br>6    |
| SKIN TOXICITY                                    |                        |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 10 / 85 (11.76%)<br>10 | 8 / 50 (16.00%)<br>8   | 7 / 80 (8.75%)<br>7    |
| Renal and urinary disorders                      |                        |                        |                        |
| DYSURIA                                          |                        |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 4 / 85 (4.71%)<br>4    | 4 / 50 (8.00%)<br>4    | 1 / 80 (1.25%)<br>1    |
| Musculoskeletal and connective tissue disorders  |                        |                        |                        |
| ARTHRALGIA                                       |                        |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 2 / 85 (2.35%)<br>2    | 1 / 50 (2.00%)<br>1    | 5 / 80 (6.25%)<br>5    |
| BACK PAIN                                        |                        |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 13 / 85 (15.29%)<br>13 | 8 / 50 (16.00%)<br>8   | 8 / 80 (10.00%)<br>8   |
| MUSCLE SPASMS                                    |                        |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 2 / 85 (2.35%)<br>2    | 4 / 50 (8.00%)<br>4    | 2 / 80 (2.50%)<br>2    |
| MUSCULOSKELETAL CHEST PAIN                       |                        |                        |                        |

|                                                                             |                        |                        |                        |
|-----------------------------------------------------------------------------|------------------------|------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)                            | 2 / 85 (2.35%)<br>2    | 1 / 50 (2.00%)<br>1    | 4 / 80 (5.00%)<br>4    |
| MUSCULOSKELETAL PAIN<br>subjects affected / exposed<br>occurrences (all)    | 4 / 85 (4.71%)<br>4    | 3 / 50 (6.00%)<br>3    | 4 / 80 (5.00%)<br>4    |
| PAIN IN EXTREMITY<br>subjects affected / exposed<br>occurrences (all)       | 10 / 85 (11.76%)<br>10 | 3 / 50 (6.00%)<br>3    | 6 / 80 (7.50%)<br>6    |
| Infections and infestations                                                 |                        |                        |                        |
| BRONCHITIS<br>subjects affected / exposed<br>occurrences (all)              | 3 / 85 (3.53%)<br>3    | 3 / 50 (6.00%)<br>3    | 5 / 80 (6.25%)<br>5    |
| FOLLICULITIS<br>subjects affected / exposed<br>occurrences (all)            | 2 / 85 (2.35%)<br>2    | 5 / 50 (10.00%)<br>5   | 5 / 80 (6.25%)<br>5    |
| NASOPHARYNGITIS<br>subjects affected / exposed<br>occurrences (all)         | 5 / 85 (5.88%)<br>5    | 5 / 50 (10.00%)<br>5   | 7 / 80 (8.75%)<br>7    |
| PARONYCHIA<br>subjects affected / exposed<br>occurrences (all)              | 14 / 85 (16.47%)<br>14 | 1 / 50 (2.00%)<br>1    | 8 / 80 (10.00%)<br>8   |
| URINARY TRACT INFECTION<br>subjects affected / exposed<br>occurrences (all) | 0 / 85 (0.00%)<br>0    | 0 / 50 (0.00%)<br>0    | 4 / 80 (5.00%)<br>14   |
| Metabolism and nutrition disorders                                          |                        |                        |                        |
| DECREASED APPETITE<br>subjects affected / exposed<br>occurrences (all)      | 30 / 85 (35.29%)<br>30 | 13 / 50 (26.00%)<br>13 | 21 / 80 (26.25%)<br>21 |
| HYPERKALAEMIA<br>subjects affected / exposed<br>occurrences (all)           | 2 / 85 (2.35%)<br>2    | 3 / 50 (6.00%)<br>3    | 3 / 80 (3.75%)<br>3    |
| HYPOCALCAEMIA<br>subjects affected / exposed<br>occurrences (all)           | 6 / 85 (7.06%)<br>6    | 3 / 50 (6.00%)<br>3    | 6 / 80 (7.50%)<br>6    |
| HYPOKALAEMIA                                                                |                        |                        |                        |

|                             |                  |                  |                |
|-----------------------------|------------------|------------------|----------------|
| subjects affected / exposed | 11 / 85 (12.94%) | 5 / 50 (10.00%)  | 7 / 80 (8.75%) |
| occurrences (all)           | 11               | 5                | 7              |
| HYPOMAGNESAEMIA             |                  |                  |                |
| subjects affected / exposed | 18 / 85 (21.18%) | 10 / 50 (20.00%) | 7 / 80 (8.75%) |
| occurrences (all)           | 18               | 10               | 7              |
| HYPONATRAEMIA               |                  |                  |                |
| subjects affected / exposed | 6 / 85 (7.06%)   | 1 / 50 (2.00%)   | 2 / 80 (2.50%) |
| occurrences (all)           | 6                | 1                | 2              |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 30 December 2008 | To be compliant with the suggestions of health authorities: Additional exclusion criteria due to contra-indications and precautions included in the approved summary of product characteristics of vinorelbine, gemcitabine, and cisplatin were included, the safety monitoring of hematological and biochemistry parameters during the safety run-in part of the protocol were intensified to rule out the synergistic toxicities. The sequence of administration of the platinum-based chemotherapy (cisplatin, vinorelbine, and gemcitabine) was corrected to comply with the summary of product characteristics information.                                                                                                                                                          |
| 25 November 2009 | As per this amendment, the final dose of cilengitide for the randomized part of the study will be increased to 2000 mg/m <sup>2</sup> after the safety run-in part has been completed. The dose of gemcitabine will be increased from 1000 mg/m <sup>2</sup> on day 1 and 8 to the standard label dose of 1250 mg/m <sup>2</sup> gemcitabine on day 1 and 8, additional cardiac safety monitoring would be implemented, changes in the exclusion criteria with respect to partial thromboplastin time, addition of exclusion criteria pertaining to concurrent chronic immunosuppressive or hormone anti-cancer therapy, decreasing timepoints for the collection of circulating endothelial cells or circulating tumor cells, to update safety information of cetuximab and cilengitide. |
| 20 December 2010 | The purpose of this amendment was to adjust the sample size and number of study centers, to stop randomizing subjects to Group B on cilengitide 2000 mg twice weekly in combination with cetuximab and platinum-based chemotherapy, a pre-screening visit was added for the assessment of EGFR expression by immunohistochemistry and selective recruitment of subjects with high epidermal growth factor receptor.                                                                                                                                                                                                                                                                                                                                                                       |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported