



## Clinical trial results:

### A Randomized, 4-Arm, Placebo-Controlled Phase 2 Trial of AMG 386 in Combination with Bevacizumab and Paclitaxel or AMG386 plus Paclitaxel as First-Line Therapy in Subjects with Her2-Negative, Metastatic or Locally Recurrent Breast Cancer

#### Summary

|                          |                            |
|--------------------------|----------------------------|
| EudraCT number           | 2007-003384-51             |
| Trial protocol           | FR GB AT BE DK FI NL ES HU |
| Global end of trial date | 19 May 2014                |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 20 June 2016   |
| First version publication date | 05 August 2015 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 20060341 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00511459 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Amgen, Inc.   |
| Sponsor organisation address | One Amgen Center Drive, Thousand Oaks, CA, United States, 91320                       |
| Public contact               | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com |
| Scientific contact           | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com |

Notes:

#### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |             |
|--|-------------|
| Analysis stage                                       | Final       |
| Date of interim/final analysis                       | 19 May 2014 |
| Is this the analysis of the primary completion data? | No          |
| Global end of trial reached?                         | Yes         |
| Global end of trial date                             | 19 May 2014 |
| Was the trial ended prematurely?                     | No          |

Notes:

## General information about the trial

Main objective of the trial:

To estimate the treatment effect as measured by progression free survival (PFS) of subjects receiving trebananib (at two doses) in combination with paclitaxel and bevacizumab relative to paclitaxel plus bevacizumab and placebo.

Protection of trial subjects:

This study was conducted in accordance with United States Food and Drug Administration (FDA) regulations/guidelines set forth in 21 Code of Federal Regulations Parts 11, 50, 54, 56, and 312 and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.

The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 27 June 2007 |
| Long term follow-up planned                               | Yes          |
| Long term follow-up rationale                             | Efficacy     |
| Long term follow-up duration                              | 48 Months    |
| Independent data monitoring committee (IDMC) involvement? | No           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Netherlands: 2     |
| Country: Number of subjects enrolled | Poland: 24         |
| Country: Number of subjects enrolled | Spain: 13          |
| Country: Number of subjects enrolled | United Kingdom: 15 |
| Country: Number of subjects enrolled | Austria: 11        |
| Country: Number of subjects enrolled | Belgium: 32        |
| Country: Number of subjects enrolled | Denmark: 1         |
| Country: Number of subjects enrolled | Finland: 10        |
| Country: Number of subjects enrolled | France: 53         |
| Country: Number of subjects enrolled | Hungary: 1         |
| Country: Number of subjects enrolled | Australia: 7       |
| Country: Number of subjects enrolled | India: 14          |
| Country: Number of subjects enrolled | United States: 45  |

|                                    |     |
|------------------------------------|-----|
| Worldwide total number of subjects | 228 |
| EEA total number of subjects       | 162 |

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)                      | 185 |
| From 65 to 84 years                       | 43  |
| 85 years and over                         | 0   |

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## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 263 subjects were screened; 7 of these were rescreened, for a total of 270 screening assessments. Of these, 42 subjects failed screening and a total of 228 subjects were randomized to 1 of 4 treatment arms.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Double blind                   |
| Roles blinded                | Subject, Investigator          |

Blinding implementation details:

Treatment arms A, B, and C were double-blinded. Treatment arm D (Open-label [OL] Trebananib 10 mg/kg + Paclitaxel) was not blinded.

### Arms

|                              |                                    |
|------------------------------|------------------------------------|
| Are arms mutually exclusive? | Yes                                |
| Arm title                    | Placebo + Paclitaxel + Bevacizumab |

Arm description:

Subjects received blinded placebo administered as an IV infusion weekly, paclitaxel 90 mg/m<sup>2</sup> IV infusion on Weeks 1, 2, and 3 of every 4-week cycle and bevacizumab 10 mg/kg IV on Weeks 1 and 3 of each 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death.

|  |                                       |
|--|---------------------------------------|
| Arm type                               | Active comparator                     |
| Investigational medicinal product name | Placebo                               |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Administered as an intravenous infusion (IV) infusion weekly

|  |                                       |
|--|---------------------------------------|
| Investigational medicinal product name | Paclitaxel                            |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Paclitaxel 90 mg/m<sup>2</sup> administered as a  $\geq$  1-hour IV infusion on Weeks 1, 2, and 3 of every 4-week cycle.

|  |                                       |
|--|---------------------------------------|
| Investigational medicinal product name | Bevacizumab                           |
| Investigational medicinal product code |                                       |
| Other name                             | Avastin                               |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Bevacizumab 10 mg/kg administered as a 90-minute IV infusion on Weeks 1 and 3 of each 4-week cycle.

|   |  |
|---|--|
| <b>Arm title</b>  | Trebananib 3 mg/kg + Paclitaxel + Bevacizumab  |
| Arm description:  |  |
| Subjects received blinded trebananib 3 mg/kg administered as an IV infusion weekly, paclitaxel 90 mg/m <sup>2</sup> IV infusion on Weeks 1, 2, and 3 of every 4-week cycle and bevacizumab 10 mg/kg IV on Weeks 1 and 3 of each 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death.  |  |
| Arm type  | Experimental                                   |
| Investigational medicinal product name  | Trebananib                                     |
| Investigational medicinal product code  | AMG 386  |
| Other name  |  |
| Pharmaceutical forms  | Concentrate for solution for infusion          |
| Routes of administration  | Intravenous use                                |
| Dosage and administration details:  |  |
| Trebananib administered by IV infusion weekly   |  |
| Investigational medicinal product name  | Paclitaxel                                     |
| Investigational medicinal product code  |  |
| Other name  |  |
| Pharmaceutical forms  | Concentrate for solution for infusion          |
| Routes of administration  | Intravenous use                                |
| Dosage and administration details:  |  |
| Paclitaxel 90 mg/m <sup>2</sup> administered as a $\geq$ 1-hour IV infusion on Weeks 1, 2, and 3 of every 4-week cycle.   |  |
| Investigational medicinal product name  | Bevacizumab                                    |
| Investigational medicinal product code  |  |
| Other name  | Avastin  |
| Pharmaceutical forms  | Concentrate for solution for infusion          |
| Routes of administration  | Intravenous use                                |
| Dosage and administration details:  |  |
| Bevacizumab 10 mg/kg administered as a 90-minute IV infusion on Weeks 1 and 3 of each 4-week cycle.   |  |
| <b>Arm title</b>  | Trebananib 10 mg/kg + Paclitaxel + Bevacizumab |
| Arm description:  |  |
| Subjects received blinded trebananib 10 mg/kg administered as an IV infusion weekly, paclitaxel 90 mg/m <sup>2</sup> IV infusion on Weeks 1, 2, and 3 of every 4-week cycle and bevacizumab 10 mg/kg IV on Weeks 1 and 3 of each 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death. |  |
| Arm type  | Experimental                                   |
| Investigational medicinal product name  | Trebananib                                     |
| Investigational medicinal product code  | AMG 386  |
| Other name  |  |
| Pharmaceutical forms  | Concentrate for solution for infusion          |
| Routes of administration  | Intravenous use                                |
| Dosage and administration details:  |  |
| Trebananib administered by IV infusion weekly   |  |
| Investigational medicinal product name  | Paclitaxel                                     |
| Investigational medicinal product code  |  |
| Other name  |  |
| Pharmaceutical forms  | Concentrate for solution for infusion          |
| Routes of administration  | Intravenous use                                |
| Dosage and administration details:  |  |
| Paclitaxel 90 mg/m <sup>2</sup> administered as a $\geq$ 1-hour IV infusion on Weeks 1, 2, and 3 of every 4-week cycle.   |  |

|  |                                       |
|--|---------------------------------------|
| Investigational medicinal product name | Bevacizumab                           |
| Investigational medicinal product code |                                       |
| Other name                             | Avastin                               |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Bevacizumab 10 mg/kg administered as a 90-minute IV infusion on Weeks 1 and 3 of each 4-week cycle.

|                  |                                     |
|------------------|-------------------------------------|
| <b>Arm title</b> | OL Trebananib 10 mg/kg + Paclitaxel |
|------------------|-------------------------------------|

Arm description:

Subjects received open-label (OL) trebananib 10 mg/kg administered as an IV infusion weekly and paclitaxel 90 mg/m<sup>2</sup> IV infusion on Weeks 1, 2, and 3 of every 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death.

|  |                                       |
|--|---------------------------------------|
| Arm type                               | Experimental                          |
| Investigational medicinal product name | Trebananib                            |
| Investigational medicinal product code | AMG 386                               |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Trebananib administered by IV infusion weekly

|  |                                       |
|--|---------------------------------------|
| Investigational medicinal product name | Paclitaxel                            |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Paclitaxel 90 mg/m<sup>2</sup> administered as a ≥ 1-hour IV infusion on Weeks 1, 2, and 3 of every 4-week cycle.

| Number of subjects in period 1 | Placebo + Paclitaxel + Bevacizumab | Trebananib 3 mg/kg + Paclitaxel + Bevacizumab | Trebananib 10 mg/kg + Paclitaxel + Bevacizumab |
|--------------------------------|------------------------------------|---|--|
|                                |                                    |   |  |
| Started                        | 58                                 | 57  | 56   |
| Received study drug            | 58                                 | 57  | 55   |
| Completed                      | 58                                 | 57  | 55   |
| Not completed                  | 0                                  | 0   | 1  |
| Did not receive study drug     | -                                  | -   | 1  |

| Number of subjects in period 1 | OL Trebananib 10 mg/kg + Paclitaxel |
|--------------------------------|-------------------------------------|
| Started                        | 57                                  |
| Received study drug            | 56                                  |
| Completed                      | 56                                  |
| Not completed                  | 1                                   |
| Did not receive study drug     | 1                                   |



## Baseline characteristics

### Reporting groups

|   |  |
|---|--|
| Reporting group title   | Placebo + Paclitaxel + Bevacizumab             |
| Reporting group description:  |  |
| Subjects received blinded placebo administered as an IV infusion weekly, paclitaxel 90 mg/m <sup>2</sup> IV infusion on Weeks 1, 2, and 3 of every 4-week cycle and bevacizumab 10 mg/kg IV on Weeks 1 and 3 of each 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death.             |  |
| Reporting group title   | Trebananib 3 mg/kg + Paclitaxel + Bevacizumab  |
| Reporting group description:  |  |
| Subjects received blinded trebananib 3 mg/kg administered as an IV infusion weekly, paclitaxel 90 mg/m <sup>2</sup> IV infusion on Weeks 1, 2, and 3 of every 4-week cycle and bevacizumab 10 mg/kg IV on Weeks 1 and 3 of each 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death.  |  |
| Reporting group title   | Trebananib 10 mg/kg + Paclitaxel + Bevacizumab |
| Reporting group description:  |  |
| Subjects received blinded trebananib 10 mg/kg administered as an IV infusion weekly, paclitaxel 90 mg/m <sup>2</sup> IV infusion on Weeks 1, 2, and 3 of every 4-week cycle and bevacizumab 10 mg/kg IV on Weeks 1 and 3 of each 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death. |  |
| Reporting group title   | OL Trebananib 10 mg/kg + Paclitaxel            |
| Reporting group description:  |  |
| Subjects received open-label (OL) trebananib 10 mg/kg administered as an IV infusion weekly and paclitaxel 90 mg/m <sup>2</sup> IV infusion on Weeks 1, 2, and 3 of every 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death.  |  |

| Reporting group values             | Placebo + Paclitaxel + Bevacizumab | Trebananib 3 mg/kg + Paclitaxel + Bevacizumab | Trebananib 10 mg/kg + Paclitaxel + Bevacizumab |
|------------------------------------|------------------------------------|---|--|
| Number of subjects                 | 58                                 | 57  | 56   |
| Age categorical<br>Units: Subjects |                                    |   |  |

|                                       |        |        |        |
|---------------------------------------|--------|--------|--------|
| Age continuous<br>Units: years        |        |        |        |
| arithmetic mean                       | 51.4   | 56.2   | 55.1   |
| standard deviation                    | ± 11.1 | ± 10.6 | ± 10.5 |
| Gender categorical<br>Units: Subjects |        |        |        |
| Female                                | 58     | 57     | 56     |
| Male                                  | 0      | 0      | 0      |
| Race<br>Units: Subjects               |        |        |        |
| White or Caucasian                    | 48     | 55     | 45     |
| Black or African American             | 2      | 0      | 1      |
| Hispanic or Latino                    | 1      | 0      | 2      |
| Asian                                 | 6      | 2      | 7      |
| Other                                 | 1      | 0      | 1      |
| Extent of Disease<br>Units: Subjects  |        |        |        |
| ≤ 3 metastatic sites                  | 48     | 47     | 47     |



|   |    |    |    |
|---|----|----|----|
| ≥ 3 metastatic sites                              | 10 | 10 | 9  |
| Prior Adjuvant Taxane Exposure<br>Units: Subjects |    |    |    |
| Yes   | 14 | 15 | 14 |
| No  | 44 | 42 | 42 |

|                                    |                                     |       |  |
|------------------------------------|-------------------------------------|-------|--|
| <b>Reporting group values</b>      | OL Trebananib 10 mg/kg + Paclitaxel | Total |  |
| Number of subjects                 | 57                                  | 228   |  |
| Age categorical<br>Units: Subjects |                                     |       |  |

|   |                |     |  |
|---|----------------|-----|--|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 52.9<br>± 11.8 | -   |  |
| Gender categorical<br>Units: Subjects                                   |                |     |  |
| Female  | 57             | 228 |  |
| Male  | 0              | 0   |  |
| Race<br>Units: Subjects   |                |     |  |
| White or Caucasian  | 52             | 200 |  |
| Black or African American   | 1              | 4   |  |
| Hispanic or Latino  | 0              | 3   |  |
| Asian   | 4              | 19  |  |
| Other   | 0              | 2   |  |
| Extent of Disease<br>Units: Subjects                                    |                |     |  |
| ≤ 3 metastatic sites  | 44             | 186 |  |
| ≥ 3 metastatic sites  | 13             | 42  |  |
| Prior Adjuvant Taxane Exposure<br>Units: Subjects                       |                |     |  |
| Yes   | 14             | 57  |  |
| No  | 43             | 171 |  |

## End points

### End points reporting groups

|   |  |
|---|--|
| Reporting group title   | Placebo + Paclitaxel + Bevacizumab             |
| Reporting group description:<br>Subjects received blinded placebo administered as an IV infusion weekly, paclitaxel 90 mg/m <sup>2</sup> IV infusion on Weeks 1, 2, and 3 of every 4-week cycle and bevacizumab 10 mg/kg IV on Weeks 1 and 3 of each 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death.             |  |
| Reporting group title   | Trebananib 3 mg/kg + Paclitaxel + Bevacizumab  |
| Reporting group description:<br>Subjects received blinded trebananib 3 mg/kg administered as an IV infusion weekly, paclitaxel 90 mg/m <sup>2</sup> IV infusion on Weeks 1, 2, and 3 of every 4-week cycle and bevacizumab 10 mg/kg IV on Weeks 1 and 3 of each 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death.  |  |
| Reporting group title   | Trebananib 10 mg/kg + Paclitaxel + Bevacizumab |
| Reporting group description:<br>Subjects received blinded trebananib 10 mg/kg administered as an IV infusion weekly, paclitaxel 90 mg/m <sup>2</sup> IV infusion on Weeks 1, 2, and 3 of every 4-week cycle and bevacizumab 10 mg/kg IV on Weeks 1 and 3 of each 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death. |  |
| Reporting group title   | OL Trebananib 10 mg/kg + Paclitaxel            |
| Reporting group description:<br>Subjects received open-label (OL) trebananib 10 mg/kg administered as an IV infusion weekly and paclitaxel 90 mg/m <sup>2</sup> IV infusion on Weeks 1, 2, and 3 of every 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death.  |  |

### Primary: Progression-free Survival

|  |                           |
|--|---------------------------|
| End point title  | Progression-free Survival |
| End point description:<br>The time from the randomization date to the date of disease progression per modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 criteria assessed by the investigator or death from any cause. Progression-free survival was analyzed using the Kaplan-Meier method. Subjects not meeting the criteria for disease progression by the data cutoff date were censored at the last evaluable disease assessment date. |                           |
| End point type   | Primary                   |
| End point timeframe:<br>Radiological assessments were performed every 8 weeks throughout the treatment period. Data are reported as of the cut-off date of 22 March 2013; median time on study was 118 weeks.  |                           |

| End point values                 | Placebo + Paclitaxel + Bevacizumab | Trebananib 3 mg/kg + Paclitaxel + Bevacizumab | Trebananib 10 mg/kg + Paclitaxel + Bevacizumab | OL Trebananib 10 mg/kg + Paclitaxel |
|----------------------------------|------------------------------------|---|--|-------------------------------------|
| Subject group type               | Reporting group                    | Reporting group                               | Reporting group                                | Reporting group                     |
| Number of subjects analysed      | 58                                 | 57  | 56   | 57                                  |
| Units: months                    |                                    |   |  |                                     |
| median (confidence interval 80%) | 12.7 (10.8 to 14.6)                | 9.2 (7.1 to 12.9)                             | 12.8 (10.9 to 14.5)                            | 8.6 (7.5 to 12.8)                   |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Blinded Trebananib Combined Versus Placebo  |
| Statistical analysis description:<br>A Cox regression model stratified by adjuvant taxane exposure (yes or no) and number of metastatic sites ( $\leq 3$ or $> 3$ ) was used to estimate the hazard ratio and 2-sided 80% confidence intervals (CI) for both blinded trebananib + paclitaxel + bevacizumab dose groups combined versus placebo + paclitaxel + bevacizumab.<br>A hazard ratio of $< 1.0$ indicates a lower average event rate and longer time to event for the trebananib treatment group relative to the placebo group. |   |
| Comparison groups   | Trebananib 3 mg/kg + Paclitaxel + Bevacizumab v Placebo + Paclitaxel + Bevacizumab v Trebananib 10 mg/kg + Paclitaxel + Bevacizumab |
| Number of subjects included in analysis   | 171   |
| Analysis specification  | Pre-specified   |
| Analysis type   | superiority   |
| P-value   | = 0.532   |
| Method  | Regression, Cox   |
| Parameter estimate  | Hazard ratio (HR)   |
| Point estimate  | 1.118   |
| Confidence interval   |   |
| level   | Other: 80 %   |
| sides   | 2-sided   |
| lower limit   | 0.889   |
| upper limit   | 1.407   |

## Secondary: Objective Response Rate

|  |                         |
|--|-------------------------|
| End point title  | Objective Response Rate |
| End point description:<br>Objective Response Rate (ORR) defined as either a confirmed complete response (CR) or partial response (PR) per modified RECIST (v 1.0) criteria (responder). A confirmed CR requires 2 assessments of CR at least 28 days apart. A confirmed PR requires 2 assessments at least 28 days apart of PR or CR. All subjects who did not meet the criteria for an objective response by the analysis cutoff date were considered non-responders.<br>The analysis of ORR was conducted on the Evaluable for Tumor Response analysis set consist of all subjects in the ITT analysis set with at least 1 unidimensionally measurable lesion at baseline per modified RECIST v 1.0. |                         |
| End point type   | Secondary               |
| End point timeframe:<br>Radiological assessments were performed every 8 weeks throughout the treatment period. Data are reported as of the cut-off date of 22 March 2013; median time on study was 118 weeks.  |                         |

| End point values                 | Placebo +<br>Paclitaxel +<br>Bevacizumab | Trebananib 3<br>mg/kg +<br>Paclitaxel +<br>Bvacizumab | Trebananib 10<br>mg/kg +<br>Paclitaxel +<br>Bvacizumab | OL Trebananib<br>10 mg/kg +<br>Paclitaxel |
|----------------------------------|--|---|--|---|
| Subject group type               | Reporting group                          | Reporting group                                       | Reporting group  | Reporting group                           |
| Number of subjects analysed      | 42                                       | 49  | 41   | 46  |
| Units: percentage of subjects    |  |   |  |   |
| number (confidence interval 80%) | 59.5 (48.5 to<br>69.9)                   | 49 (39 to 59)   | 70.7 (59.8 to<br>80.1)                                 | 45.7 (35.5 to<br>56.1)                    |

## Statistical analyses

| Statistical analysis title   | Trebananib Combined vs Placebo Response Rates   |
|--|---|
| Statistical analysis description:  |   |
| Wilson's score method with continuity correction was used to calculate 80% confidence intervals for the difference in response rates between both trebananib + paclitaxel + bevacizumab dose groups combined and the placebo + paclitaxel + bevacizumab group. |   |
| Comparison groups  | Placebo + Paclitaxel + Bevacizumab v Trebananib 3 mg/kg + Paclitaxel + Bevacizumab v Trebananib 10 mg/kg + Paclitaxel + Bevacizumab |
| Number of subjects included in analysis  | 132   |
| Analysis specification   | Pre-specified   |
| Analysis type  | superiority   |
| Parameter estimate   | Difference in response rates  |
| Point estimate   | -0.6  |
| Confidence interval  |   |
| level  | Other: 80 %   |
| sides  | 2-sided   |
| lower limit  | -13.2   |
| upper limit  | 12.4  |

## Secondary: Duration of Response

|  |                      |
|--|----------------------|
| End point title  | Duration of Response |
| End point description:   |                      |
| Calculated only for those subjects with an objective response as the time from the first objective response (subsequently confirmed within no less than 4 weeks) to first observed disease progression per modified-RECIST criteria or death due to any cause. |                      |
| Subjects not meeting these criteria by the analysis data cutoff date were censored at their last evaluable disease assessment date. Duration of response was analyzed using the Kaplan-Meier method.   |                      |
| End point type   | Secondary            |
| End point timeframe:   |                      |
| Radiological assessments were performed every 8 weeks throughout the treatment period. Data are reported as of the primary analysis cut-off date of 17 May 2010; median time on study was 66 weeks.  |                      |

| End point values                 | Placebo +<br>Paclitaxel +<br>Bevacizumab | Trebananib 3<br>mg/kg +<br>Paclitaxel +<br>Bvacizumab | Trebananib 10<br>mg/kg +<br>Paclitaxel +<br>Bvacizumab | OL Trebananib<br>10 mg/kg +<br>Paclitaxel |
|----------------------------------|--|---|--|---|
| Subject group type               | Reporting group                          | Reporting group                                       | Reporting group  | Reporting group                           |
| Number of subjects analysed      | 25                                       | 25  | 29   | 21  |
| Units: months                    |  |   |  |   |
| median (confidence interval 80%) | 9 (7.4 to 9.4)                           | 11 (7.4 to 11.2)                                      | 9.6 (7.9 to 11.2)                                      | 7.4 (6 to 12.9)                           |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Survival

|   |                  |
|---|------------------|
| End point title   | Overall Survival |
| End point description:<br>Time from the randomization date to the date of death from any cause. Subjects who had not died by the analysis data cutoff date were censored at their last contact date. Overall survival was analyzed using the Kaplan-Meier method. |                  |
| End point type  | Secondary        |
| End point timeframe:<br>Data are reported as of the cut-off date of 22 March 2013; median time on study was 118 weeks.  |                  |

| End point values                 | Placebo +<br>Paclitaxel +<br>Bvacizumab | Trebananib 3<br>mg/kg +<br>Paclitaxel +<br>Bvacizumab | Trebananib 10<br>mg/kg +<br>Paclitaxel +<br>Bvacizumab | OL Trebananib<br>10 mg/kg +<br>Paclitaxel |
|----------------------------------|---|---|--|---|
| Subject group type               | Reporting group                         | Reporting group                                       | Reporting group  | Reporting group                           |
| Number of subjects analysed      | 58                                      | 57  | 56   | 57  |
| Units: months                    |   |   |  |   |
| median (confidence interval 80%) | 35.1 (25 to 37.3)                       | 27.1 (24.2 to 35.1)                                   | 28.5 (24.5 to 32.3)                                    | 30.7 (25.1 to 34.9)                       |

## Statistical analyses

|   |   |
|---|---|
| Statistical analysis title  | Blinded Trebananib Combined Versus Placebo  |
| Statistical analysis description:<br>A Cox regression model stratified by adjuvant taxane exposure (yes or no) and number of metastatic sites ( $\leq 3$ or $> 3$ ) was used to estimate the hazard ratio and 2-sided 80% confidence intervals (CI) for both blinded trebananib + paclitaxel + bevacizumab dose groups combined versus placebo + paclitaxel + bevacizumab.<br>A hazard ratio of $< 1.0$ indicates a lower average event rate and longer time to event for the trebananib treatment group relative to the placebo group. |   |
| Comparison groups   | Placebo + Paclitaxel + Bevacizumab v Trebananib 3 mg/kg + Paclitaxel + Bevacizumab v Trebananib 10 mg/kg + Paclitaxel + Bevacizumab |

|   |                   |
|---|-------------------|
| Number of subjects included in analysis | 171               |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | superiority       |
| P-value                                 | = 0.81            |
| Method                                  | Regression, Cox   |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 1.046             |
| Confidence interval                     |                   |
| level                                   | Other: 80 %       |
| sides                                   | 2-sided           |
| lower limit                             | 0.823             |
| upper limit                             | 1.33              |

## Secondary: Time to Response

|  |                  |
|--|------------------|
| End point title  | Time to Response |
| End point description:   |                  |
| Time from randomization date to first objective response (subsequently confirmed within no less than 4 weeks); subjects with a best response of Stable Disease (SD) at their last evaluable assessment date were censored at this date and subjects with all other categories of best response while on study were censored at the maximum observed time to a first confirmed response among all responders. Time to response was analyzed using the Kaplan-Meier method for subjects with a confirmed objective response. |                  |
| End point type   | Secondary        |
| End point timeframe:   |                  |
| Radiological assessments were performed every 8 weeks throughout the treatment period. Data are reported as of the primary analysis cut-off date of 17 May 2010; median time on study was 66 weeks.  |                  |

| End point values                      | Placebo +<br>Paclitaxel +<br>Bevacizumab | Trebananib 3<br>mg/kg +<br>Paclitaxel +<br>Bevacizumab | Trebananib 10<br>mg/kg +<br>Paclitaxel +<br>Bevacizumab | OL Trebananib<br>10 mg/kg +<br>Paclitaxel |
|---------------------------------------|--|--|---|---|
| Subject group type                    | Reporting group                          | Reporting group  | Reporting group   | Reporting group                           |
| Number of subjects analysed           | 25                                       | 25   | 29  | 21  |
| Units: weeks                          |  |  |   |   |
| median (inter-quartile range (Q1-Q3)) | 8.7 (7.6 to 15.9)                        | 8.1 (7.7 to 17)  | 8 (7.6 to 15.1)   | 15.3 (7.6 to 16.4)                        |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in Tumor Burden

|  |                        |
|--|------------------------|
| End point title  | Change in Tumor Burden |
| End point description:   |                        |
| Reduction in tumor burden was measured as the maximum percent reduction from Baseline (or, for subjects without a reduction, the minimum increase from Baseline) in the sum of the longest diameters (SLD) of target lesions. For each subject the maximum percent reduction in SLD from baseline to the post-baseline nadir was identified, and the mean of these values was then calculated. |                        |

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| Radiological assessments were performed every 8 weeks throughout the treatment period. Data are reported as of the primary analysis cut-off date of 17 May 2010; median time on study was 66 weeks. |           |

| End point values                      | Placebo +<br>Paclitaxel +<br>Bevacizumab | Trebananib 3<br>mg/kg +<br>Paclitaxel +<br>Bvacizumab | Trebananib 10<br>mg/kg +<br>Paclitaxel +<br>Bvacizumab | OL Trebananib<br>10 mg/kg +<br>Paclitaxel |
|---------------------------------------|--|---|--|---|
| Subject group type                    | Reporting group                          | Reporting group                                       | Reporting group  | Reporting group                           |
| Number of subjects analysed           | 40 <sup>[1]</sup>                        | 44 <sup>[2]</sup>                                     | 40 <sup>[3]</sup>                                      | 41 <sup>[4]</sup>                         |
| Units: percent reduction              |  |   |  |   |
| median (inter-quartile range (Q1-Q3)) | -50.3 (-66.3 to<br>-28.2)                | -49.1 (-65.5 to<br>-22.3)                             | -52 (-76.8 to -<br>34.1)                               | -41.1 (-59.5 to<br>-16.4)                 |

Notes:

[1] - Subjects with available data

[2] - Subjects with available data

[3] - Subjects with available data

[4] - Subjects with available data

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects With Adverse Events

|   |  |
|---|--|
| End point title   | Number of Subjects With Adverse Events |
| End point description:  |  |
| Related, trebananib-related, paclitaxel-related, and bevacizumab-related adverse events are those events for which the investigator considered there to be a reasonable possibility that the event may have been caused by the study treatment, trebananib, paclitaxel, or bevacizumab respectively. The intensity of each adverse event was graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. |  |
| End point type  | Secondary                              |
| End point timeframe:  |  |
| From first dose until 30 days after last dose of any study therapy. Median duration of trebananib/placebo treatment was 9.0, 6.0, 9.0 and 8.0 months in each treatment group respectively.  |  |

| End point values            | Placebo +<br>Paclitaxel +<br>Bvacizumab | Trebananib 3<br>mg/kg +<br>Paclitaxel +<br>Bvacizumab | Trebananib 10<br>mg/kg +<br>Paclitaxel +<br>Bvacizumab | OL Trebananib<br>10 mg/kg +<br>Paclitaxel |
|-----------------------------|---|---|--|---|
| Subject group type          | Reporting group                         | Reporting group                                       | Reporting group  | Reporting group                           |
| Number of subjects analysed | 58 <sup>[5]</sup>                       | 57 <sup>[6]</sup>                                     | 55 <sup>[7]</sup>                                      | 56 <sup>[8]</sup>                         |
| Units: subjects             |   |   |  |   |
| Any adverse event (AE)      | 58                                      | 57  | 55   | 56  |
| Worst grade of 3            | 37                                      | 35  | 40   | 30  |
| Worst grade of 4            | 9                                       | 8   | 4  | 3   |
| Worst grade of 5            | 1                                       | 3   | 1  | 4   |
| Serious adverse event (SAE) | 21                                      | 24  | 13   | 18  |

|  |    |    |    |    |
|--|----|----|----|----|
| Leading to discontinuation from therapy or study | 9  | 12 | 9  | 3  |
| Any treatment-related adverse event              | 57 | 57 | 52 | 51 |
| Treatment-related worst grade of 3               | 30 | 29 | 37 | 23 |
| Treatment-related worst grade of 4               | 10 | 7  | 3  | 3  |
| Treatment-related worst grade of 5               | 0  | 2  | 0  | 0  |
| Serious treatment-related AE                     | 12 | 13 | 8  | 6  |
| Treatment-related leading to discontinuation     | 5  | 11 | 7  | 0  |

Notes:

[5] - All randomized subjects who received at least 1 dose of trebananib or paclitaxel or bevacizumab.

[6] - All randomized subjects who received at least 1 dose of trebananib or paclitaxel or bevacizumab.

[7] - All randomized subjects who received at least 1 dose of trebananib or paclitaxel or bevacizumab.

[8] - All randomized subjects who received at least 1 dose of trebananib or paclitaxel.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects with Grade 3 or Higher Laboratory Toxicities

|                 |   |
|-----------------|---|
| End point title | Number of Subjects with Grade 3 or Higher Laboratory Toxicities |
|-----------------|---|

End point description:

Textbook laboratory ranges were utilized to determine National Cancer Institute Common Toxicity Criteria version 3.0 (CTC) grades.

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

End point timeframe:

From first dose of study treatment until the last dose, until the data cut-off date of 22 March 2013.

| End point values                         | Placebo + Paclitaxel + Bevacizumab | Trebananib 3 mg/kg + Paclitaxel + Bevacizumab | Trebananib 10 mg/kg + Paclitaxel + Bevacizumab | OL Trebananib 10 mg/kg + Paclitaxel |
|--|------------------------------------|---|--|-------------------------------------|
| Subject group type                       | Reporting group                    | Reporting group                               | Reporting group                                | Reporting group                     |
| Number of subjects analysed              | 58                                 | 57  | 55   | 56                                  |
| Units: subjects                          |                                    |   |  |                                     |
| Alanine amino transferase increased      | 3                                  | 2   | 0  | 1                                   |
| Albumin decreased                        | 0                                  | 0   | 0  | 1                                   |
| Alkaline phosphatase increased           | 0                                  | 2   | 3  | 1                                   |
| Aspartate amino transferase increased    | 2                                  | 3   | 2  | 2                                   |
| Calcium decreased                        | 0                                  | 0   | 3  | 0                                   |
| Glucose increased                        | 3                                  | 0   | 4  | 2                                   |
| Glucose decreased                        | 1                                  | 0   | 0  | 0                                   |
| Magnesium increased                      | 1                                  | 1   | 1  | 2                                   |
| Magnesium decreased                      | 1                                  | 1   | 0  | 0                                   |
| Phosphorus decreased                     | 3                                  | 3   | 0  | 2                                   |
| Potassium increased                      | 1                                  | 0   | 2  | 1                                   |
| Potassium decreased                      | 1                                  | 0   | 3  | 1                                   |
| Sodium decreased                         | 0                                  | 2   | 1  | 1                                   |
| Hemoglobin decreased                     | 0                                  | 0   | 1  | 2                                   |
| International normalized ratio increased | 1                                  | 0   | 1  | 0                                   |



|                                       |    |    |    |    |
|---------------------------------------|----|----|----|----|
| Lymphocytes decreased                 | 18 | 12 | 9  | 10 |
| Partial thromboplastin time increased | 2  | 5  | 1  | 3  |
| Platelets decreased                   | 1  | 1  | 1  | 1  |
| Segmented neutrophils decreased       | 2  | 0  | 0  | 2  |
| Total neutrophils decreased           | 13 | 8  | 14 | 11 |
| White blood cells decreased           | 17 | 12 | 9  | 11 |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Trebananib/Placebo, Paclitaxel and/or Bevacizumab Cycles Administered

|                 |   |
|-----------------|---|
| End point title | Number of Trebananib/Placebo, Paclitaxel and/or Bevacizumab Cycles Administered |
|-----------------|---|

End point description:

Two subjects randomized to open label trebananib arm received at least one dose of bevacizumab due to dosing error.

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

End point timeframe:

Up until the cut-off date date of 22 March 2013.

| End point values                      | Placebo +<br>Paclitaxel +<br>Bevacizumab | Trebananib 3<br>mg/kg +<br>Paclitaxel +<br>Bevacizumab | Trebananib 10<br>mg/kg +<br>Paclitaxel +<br>Bevacizumab | OL Trebananib<br>10 mg/kg +<br>Paclitaxel |
|---------------------------------------|--|--|---|---|
| Subject group type                    | Reporting group                          | Reporting group  | Reporting group   | Reporting group                           |
| Number of subjects analysed           | 58                                       | 57   | 55  | 56  |
| Units: cycles                         |  |  |   |   |
| median (inter-quartile range (Q1-Q3)) |  |  |   |   |
| Trebananib / Placebo                  | 9 (5 to 13)                              | 6 (4 to 13)  | 9 (6 to 16)   | 8 (5 to 14)                               |
| Paclitaxel                            | 6 (5 to 9)                               | 6 (4 to 7)   | 6 (4 to 9)  | 6 (5 to 8)                                |
| Bevacizumab                           | 8.5 (5 to 14)                            | 6 (4 to 13)  | 9 (5 to 16)   | 2.5 (2 to 3)                              |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects with Trebananib/Placebo, Paclitaxel and/or Bevacizumab Dose Modifications

|                 |  |
|-----------------|--|
| End point title | Number of Subjects with Trebananib/Placebo, Paclitaxel and/or Bevacizumab Dose Modifications |
|-----------------|--|

End point description:

If a subject developed a  $\geq$  grade 3 (per CTCAE, version 3.0) toxicity considered to be related to trebananib, placebo, paclitaxel or bevacizumab, then trebananib, placebo paclitaxel or bevacizumab was to be held until the toxicity resolved. One permanent dose reduction of paclitaxel to 65 mg/m<sup>2</sup> was permitted. No dose level reductions for trebananib, placebo or bevacizumab were permitted.

Two subjects randomized to open label trebananib arm received at least one dose of bevacizumab due to dosing error.

|   |           |
|---|-----------|
| End point type                                  | Secondary |
| End point timeframe:                            |           |
| Up until the data cut-off date of 22 March 2013 |           |

| End point values                       | Placebo +<br>Paclitaxel +<br>Bevacizumab | Trebananib 3<br>mg/kg +<br>Paclitaxel +<br>Bevacizumab | Trebananib 10<br>mg/kg +<br>Paclitaxel +<br>Bevacizumab | OL Trebananib<br>10 mg/kg +<br>Paclitaxel |
|--|--|--|---|---|
| Subject group type                     | Reporting group                          | Reporting group  | Reporting group   | Reporting group                           |
| Number of subjects analysed            | 58                                       | 57   | 55  | 56  |
| Units: subjects                        |  |  |   |   |
| Trebananib / placebo dose withholdings | 49                                       | 39   | 47  | 44  |
| Paclitaxel dose withholdings           | 49                                       | 43   | 44  | 46  |
| Paclitaxel dose reductions             | 35                                       | 33   | 30  | 29  |
| Bevacizumab dose withholdings          | 46                                       | 37   | 39  | 2   |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Steady-State Maximum and Minimum Observed Concentration of Trebananib

|                 |  |
|-----------------|--|
| End point title | Steady-State Maximum and Minimum Observed Concentration of Trebananib <sup>[9]</sup> |
|-----------------|--|

End point description:

Steady-state serum concentration of trebananib was measured at the end of infusion (maximum observed serum concentration [C<sub>max</sub>]) at Weeks 5 and 15; and predose (minimum observed serum concentration [C<sub>min</sub>], ie, prior to AMG 386 or placebo, bevacizumab, and paclitaxel infusion) on Weeks 5, 9, and 15. Serum concentration was measured using a validated enzyme-linked immunosorbent (ELISA) assay; The lower limit of quantification (LLOQ) of the serum assay was 20 ng/mL. Only samples collected at the protocol-specified dose regimen were included, and concentrations that were below the LLOQ were set to 0.

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

End point timeframe:

Weeks 5, 9, and 15

Notes:

[9] - 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: Observed Concentration of Trebananib was assessed in the Trebananib treatment groups only.

| End point values              | Trebananib 3<br>mg/kg +<br>Paclitaxel +<br>Bevacizumab | Trebananib 10<br>mg/kg +<br>Paclitaxel +<br>Bevacizumab | OL Trebananib<br>10 mg/kg +<br>Paclitaxel |  |
|-------------------------------|--|---|---|--|
| Subject group type            | Reporting group  | Reporting group   | Reporting group                           |  |
| Number of subjects analysed   | 46   | 45  | 40  |  |
| Units: µg/mL                  |  |   |   |  |
| median (full range (min-max)) |  |   |   |  |

|                                |                     |                      |                      |  |
|--------------------------------|---------------------|----------------------|----------------------|--|
| Cmax at Week 5 (N=44, 43, 40)  | 79 (52.2 to 167)    | 260 (65.2 to 809)    | 270 (125 to 376)     |  |
| Cmax at Week 15 (N=23, 20, 17) | 90.7 (50.5 to 139)  | 296 (107 to 387)     | 294 (122 to 471)     |  |
| Cmin at Week 5 (N=46, 49, 38)  | 3.99 (1.5 to 17.7)  | 14.4 (1.63 to 43)    | 13.8 (0.808 to 30.1) |  |
| Cmin at Week 9 (N=44, 45, 37)  | 4.04 (1.73 to 19.3) | 14.6 (0.613 to 81.8) | 14.6 (0.998 to 40.8) |  |
| Cmin at Week 15 (N=36, 33, 28) | 4.2 (1.38 to 22.6)  | 15.2 (6.43 to 34.7)  | 18 (2.18 to 40.3)    |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Steady-State Maximum and Minimum Observed Concentration of Bevacizumab

|                 |  |
|-----------------|--|
| End point title | Steady-State Maximum and Minimum Observed Concentration of Bevacizumab <sup>[10]</sup> |
|-----------------|--|

End point description:

Steady-state bevacizumab concentration was measured at the end of infusion (maximum observed serum concentration [Cmax]) on Weeks 5, and 15; and predose (minimum observed serum concentration [Cmin], ie, prior to AMG 386 or placebo, bevacizumab, and paclitaxel infusion) at Week 15. Serum bevacizumab samples were not measured in subjects receiving open-label trebaninib. Bevacizumab concentration was measured using a validated indirect ELISA; the LLOQ of the serum assay was 19.5 ng/mL.

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

End point timeframe:

Weeks 5, 9 and 15

Notes:

[10] - 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: Observed Concentration of Bevacizumab was assessed in the Bevacizumab treatment groups only.

| End point values               | Placebo + Paclitaxel + Bevacizumab | Trebananib 3 mg/kg + Paclitaxel + Bevacizumab | Trebananib 10 mg/kg + Paclitaxel + Bevacizumab |  |
|--------------------------------|------------------------------------|---|--|--|
| Subject group type             | Reporting group                    | Reporting group                               | Reporting group                                |  |
| Number of subjects analysed    | 25                                 | 24  | 26   |  |
| Units: µg/mL                   |                                    |   |  |  |
| median (full range (min-max))  |                                    |   |  |  |
| Cmax at Week 15 (N=18, 24, 19) | 491 (232 to 727)                   | 545 (327 to 785)                              | 525 (93.6 to 901)                              |  |
| Cmin at Week 15 (N=25, 24, 26) | 218 (79.7 to 428)                  | 200 (98.5 to 310)                             | 193 (81.7 to 434)                              |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects Who Developed Antibodies to Trebaninib Post-Baseline

|                 |   |
|-----------------|---|
| End point title | Number of Subjects Who Developed Antibodies to Trebaninib Post-Baseline |
|-----------------|---|

End point description:

Samples were first tested in a validated electrochemiluminescent (ECL) immunoassay to detect and confirm the presence of antibodies capable of binding to trebaninib. Samples that were positive in the immunoassay were then further tested in a validated ECL receptor-binding assay to measure neutralizing or inhibitory effects of the antibodies in vitro. If a sample was positive in both assays, a subject was defined as positive for neutralizing antibodies. Additionally, if a sample was positive in the immunoassay, but negative in the receptor-binding assay, the sample was defined as positive for binding antibodies.

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

End point timeframe:

Week 1, Week 5, Week 9, Week 23 and every 16 weeks thereafter until the data cut-off date of 22 March 2013.

| End point values               | Placebo +<br>Paclitaxel +<br>Bevacizumab | Trebananib 3<br>mg/kg +<br>Paclitaxel +<br>Bevacizumab | Trebananib 10<br>mg/kg +<br>Paclitaxel +<br>Bevacizumab | OL Trebananib<br>10 mg/kg +<br>Paclitaxel |
|--------------------------------|--|--|---|---|
| Subject group type             | Reporting group                          | Reporting group  | Reporting group   | Reporting group                           |
| Number of subjects analysed    | 56 <sup>[11]</sup>                       | 55 <sup>[12]</sup>                                     | 52 <sup>[13]</sup>                                      | 49 <sup>[14]</sup>                        |
| Units: subjects                |  |  |   |   |
| Binding antibody positive      | 1  | 6  | 2   | 5   |
| Neutralizing antibody positive | 0  | 0  | 0   | 0   |

Notes:

[11] - Subjects with at least one post-baseline immunoassay result

[12] - Subjects with at least one post-baseline immunoassay result

[13] - Subjects with at least one post-baseline immunoassay result

[14] - Subjects with at least one post-baseline immunoassay result

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug until 30 days after the last dose of any study therapy.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

### Reporting groups

|                       |                                    |
|-----------------------|------------------------------------|
| Reporting group title | Placebo + Paclitaxel + Bevacizumab |
|-----------------------|------------------------------------|

Reporting group description:

Subjects received blinded placebo administered as an IV infusion weekly, paclitaxel 90 mg/m<sup>2</sup> IV infusion on Weeks 1, 2, and 3 of every 4-week cycle and bevacizumab 10 mg/kg IV on Weeks 1 and 3 of each 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death.

|                       |   |
|-----------------------|---|
| Reporting group title | Trebananib 3 mg/kg + Paclitaxel + Bevacizumab |
|-----------------------|---|

Reporting group description:

Subjects received blinded trebananib 3 mg/kg administered as an IV infusion weekly, paclitaxel 90 mg/m<sup>2</sup> IV infusion on Weeks 1, 2, and 3 of every 4-week cycle and bevacizumab 10 mg/kg IV on Weeks 1 and 3 of each 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death.

|                       |  |
|-----------------------|--|
| Reporting group title | Trebananib 10 mg/kg + Paclitaxel + Bevacizumab |
|-----------------------|--|

Reporting group description:

Subjects received blinded trebananib 10 mg/kg administered as an IV infusion weekly, paclitaxel 90 mg/m<sup>2</sup> IV infusion on Weeks 1, 2, and 3 of every 4-week cycle and bevacizumab 10 mg/kg IV on Weeks 1 and 3 of each 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death.

|                       |  |
|-----------------------|--|
| Reporting group title | OL Trebananib 10 mg/kg QW + Paclitaxel |
|-----------------------|--|

Reporting group description:

Subjects received open-label (OL) trebananib 10 mg/kg administered as an IV infusion weekly and paclitaxel 90 mg/m<sup>2</sup> IV infusion on Weeks 1, 2, and 3 of every 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death.

| Serious adverse events  | Placebo + Paclitaxel + Bevacizumab | Trebananib 3 mg/kg + Paclitaxel + Bevacizumab | Trebananib 10 mg/kg + Paclitaxel + Bevacizumab |
|---|------------------------------------|---|--|
| Total subjects affected by serious adverse events                   |                                    |   |  |
| subjects affected / exposed   | 21 / 58 (36.21%)                   | 24 / 57 (42.11%)                              | 13 / 55 (23.64%)                               |
| number of deaths (all causes)                                       | 46                                 | 40  | 42   |
| number of deaths resulting from adverse events                      |                                    |   |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                    |   |  |
| BREAST CANCER   |                                    |   |  |
| subjects affected / exposed   | 1 / 58 (1.72%)                     | 0 / 57 (0.00%)                                | 0 / 55 (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  |
| BREAST NEOPLASM   |                                    |   |  |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                                 | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| occurrences causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all                  | 0 / 0          | 0 / 0          | 0 / 1          |
| <b>MALIGNANT PLEURAL EFFUSION</b>                           |                |                |                |
| subjects affected / exposed                                 | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                  | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>METASTASES TO EYE</b>                                    |                |                |                |
| subjects affected / exposed                                 | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                  | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>METASTASES TO MENINGES</b>                               |                |                |                |
| subjects affected / exposed                                 | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 0 / 55 (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>Vascular disorders</b>                                   |                |                |                |
| <b>DEEP VEIN THROMBOSIS</b>                                 |                |                |                |
| subjects affected / exposed                                 | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (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          |
| <b>JUGULAR VEIN THROMBOSIS</b>                              |                |                |                |
| subjects affected / exposed                                 | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 0 / 55 (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>VENOUS THROMBOSIS</b>                                    |                |                |                |
| subjects affected / exposed                                 | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (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>General disorders and administration site conditions</b> |                |                |                |
| <b>CHEST PAIN</b>   |                |                |                |
| subjects affected / exposed                                 | 1 / 58 (1.72%) | 1 / 57 (1.75%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all             | 0 / 1          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all                  | 0 / 0          | 0 / 0          | 0 / 0          |

|   |                |                |                |  |
|---|----------------|----------------|----------------|--|
| CHILLS  |                |                |                |  |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 0 / 55 (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          |  |
| DEVICE DISLOCATION                              |                |                |                |  |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2          | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |  |
| FATIGUE   |                |                |                |  |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (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          |  |
| FEELING OF BODY TEMPERATURE CHANGE              |                |                |                |  |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |  |
| GENERAL PHYSICAL HEALTH DETERIORATION           |                |                |                |  |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |  |
| IMPAIRED HEALING                                |                |                |                |  |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 0 / 55 (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          |  |
| INFLUENZA LIKE ILLNESS                          |                |                |                |  |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (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          |  |
| LOCAL SWELLING                                  |                |                |                |  |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |  |
| PAIN  |                |                |                |  |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (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          |
| PYREXIA   |                |                |                |
| subjects affected / exposed                     | 3 / 58 (5.17%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Immune system disorders                         |                |                |                |
| HYPERSENSITIVITY                                |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| COUGH   |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (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          |
| DYSPNOEA  |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 1 / 55 (1.82%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| DYSPNOEA EXERTIONAL                             |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (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          |
| EPISTAXIS                                       |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| HAEMOPTYSIS                                     |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1          | 0 / 0          |



|   |                |                |                |
|---|----------------|----------------|----------------|
| LUNG INFILTRATION                               |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| NASAL SEPTUM PERFORATION                        |                |                |                |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 0 / 55 (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          |
| PNEUMOTHORAX                                    |                |                |                |
| subjects affected / exposed                     | 2 / 58 (3.45%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| PULMONARY EMBOLISM                              |                |                |                |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 1 / 57 (1.75%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| RESPIRATORY DISTRESS                            |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| RESPIRATORY FAILURE                             |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| Psychiatric disorders                           |                |                |                |
| DEPRESSION                                      |                |                |                |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 0 / 55 (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          |
| SUICIDAL IDEATION                               |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Injury, poisoning and procedural                |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| complications                                   |                |                |                |
| ANKLE FRACTURE                                  |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| FEMORAL NECK FRACTURE                           |                |                |                |
| subjects affected / exposed                     | 2 / 58 (3.45%) | 0 / 57 (0.00%) | 0 / 55 (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          |
| JOINT DISLOCATION                               |                |                |                |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 0 / 55 (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          |
| RIB FRACTURE                                    |                |                |                |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 0 / 55 (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                               |                |                |                |
| ATRIOVENTRICULAR BLOCK SECOND DEGREE            |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| BRADYCARDIA                                     |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (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          |
| CARDIAC FAILURE CONGESTIVE                      |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| CARDIOMYOPATHY                                  |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| LEFT VENTRICULAR DYSFUNCTION                    |                |                |                |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 0 / 55 (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          |
| MITRAL VALVE INCOMPETENCE                       |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| MYOCARDIAL INFARCTION                           |                |                |                |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 0 / 55 (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          |
| SUPRAVENTRICULAR TACHYCARDIA                    |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                |                |                |
| CEREBROVASCULAR ACCIDENT                        |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (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          |
| EPILEPSY  |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (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          |
| HEADACHE  |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (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          |
| MENINGEAL DISORDER                              |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| PARESIS   |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (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          |
| <b>SPEECH DISORDER</b>                          |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (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          |
| <b>Blood and lymphatic system disorders</b>     |                |                |                |
| <b>ANAEMIA</b>                                  |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (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>FEBRILE NEUTROPENIA</b>                      |                |                |                |
| subjects affected / exposed                     | 2 / 58 (3.45%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| 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>LEUKOPENIA</b>                               |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>NEUTROPENIA</b>                              |                |                |                |
| subjects affected / exposed                     | 2 / 58 (3.45%) | 2 / 57 (3.51%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Gastrointestinal disorders</b>               |                |                |                |
| <b>ABDOMINAL PAIN</b>                           |                |                |                |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 0 / 55 (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>ASCITES</b>                                  |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (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>DIARRHOEA</b>                                |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 58 (1.72%) | 2 / 57 (3.51%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 1 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| GASTROINTESTINAL PERFORATION                    |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (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          |
| ILEUS   |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| NAUSEA  |                |                |                |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 2 / 57 (3.51%) | 1 / 55 (1.82%) |
| occurrences causally related to treatment / all | 1 / 1          | 2 / 2          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| PANCREATITIS                                    |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| RECTAL HAEMORRHAGE                              |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (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          |
| SMALL INTESTINAL OBSTRUCTION                    |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (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          |
| VOMITING  |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 3 / 57 (5.26%) | 2 / 55 (3.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 3          | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hepatobiliary disorders                         |                |                |                |
| CHOLECYSTITIS                                   |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 0 / 55 (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          |
| CHOLECYSTITIS ACUTE                             |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| HEPATIC FUNCTION ABNORMAL                       |                |                |                |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 0 / 55 (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          |
| Skin and subcutaneous tissue disorders          |                |                |                |
| DERMATITIS                                      |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| RASH  |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| SUBCUTANEOUS EMPHYSEMA                          |                |                |                |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 0 / 55 (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          |
| Musculoskeletal and connective tissue disorders |                |                |                |
| ARTHRALGIA                                      |                |                |                |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 1 / 57 (1.75%) | 0 / 55 (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          |
| BACK PAIN                                       |                |                |                |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 0 / 55 (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>BONE PAIN</b>                                |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (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          |
| <b>MUSCLE SPASMS</b>                            |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| 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>MUSCULOSKELETAL CHEST PAIN</b>               |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| 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>NECK PAIN</b>                                |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| 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>OSTEONECROSIS</b>                            |                |                |                |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 0 / 55 (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>PAIN IN EXTREMITY</b>                        |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (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>PATHOLOGICAL FRACTURE</b>                    |                |                |                |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 0 / 55 (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>Infections and infestations</b>              |                |                |                |
| <b>ASPERGILLUS INFECTION</b>                    |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| 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>BRONCHOPNEUMONIA</b>                         |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 0 / 55 (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          |
| CATHETER SITE INFECTION                         |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| CELLULITIS                                      |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| DEVICE RELATED INFECTION                        |                |                |                |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 0 / 55 (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          |
| DEVICE RELATED SEPSIS                           |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| GASTROENTERITIS                                 |                |                |                |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 0 / 55 (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          |
| HERPES ZOSTER                                   |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (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          |
| INFECTION                                       |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| LOBAR PNEUMONIA                                 |                |                |                |



|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (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          |
| NAIL INFECTION                                  |                |                |                |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| PNEUMONIA                                       |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| RESPIRATORY TRACT INFECTION                     |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| SEPSIS  |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| SKIN INFECTION                                  |                |                |                |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 0 / 55 (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          |
| URINARY TRACT INFECTION                         |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (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          |
| Metabolism and nutrition disorders              |                |                |                |
| DECREASED APPETITE                              |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (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          |
| DEHYDRATION                                     |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 58 (0.00%) | 1 / 57 (1.75%) | 0 / 55 (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>FLUID RETENTION</b>                          |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>HYPOCALCAEMIA</b>                            |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 57 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|   |  |  |  |
|---|--|--|--|
| <b>Serious adverse events</b>                                       | OL Trebananib 10 mg/kg QW + Paclitaxel |  |  |
| Total subjects affected by serious adverse events                   |  |  |  |
| subjects affected / exposed   | 18 / 56 (32.14%)                       |  |  |
| number of deaths (all causes)                                       | 35                                     |  |  |
| number of deaths resulting from adverse events                      |  |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  |  |  |
| <b>BREAST CANCER</b>  |  |  |  |
| subjects affected / exposed   | 1 / 56 (1.79%)                         |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                                  |  |  |
| deaths causally related to treatment / all                          | 0 / 1                                  |  |  |
| <b>BREAST NEOPLASM</b>  |  |  |  |
| subjects affected / exposed   | 0 / 56 (0.00%)                         |  |  |
| occurrences causally related to treatment / all                     | 0 / 0                                  |  |  |
| deaths causally related to treatment / all                          | 0 / 0                                  |  |  |
| <b>MALIGNANT PLEURAL EFFUSION</b>                                   |  |  |  |
| subjects affected / exposed   | 1 / 56 (1.79%)                         |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                                  |  |  |
| deaths causally related to treatment / all                          | 0 / 0                                  |  |  |
| <b>METASTASES TO EYE</b>  |  |  |  |

|  |                |  |  |
|--|----------------|--|--|
| subjects affected / exposed                          | 1 / 56 (1.79%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| METASTASES TO MENINGES                               |                |  |  |
| subjects affected / exposed                          | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Vascular disorders                                   |                |  |  |
| DEEP VEIN THROMBOSIS                                 |                |  |  |
| subjects affected / exposed                          | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| JUGULAR VEIN THROMBOSIS                              |                |  |  |
| subjects affected / exposed                          | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| VENOUS THROMBOSIS                                    |                |  |  |
| subjects affected / exposed                          | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| General disorders and administration site conditions |                |  |  |
| CHEST PAIN   |                |  |  |
| subjects affected / exposed                          | 1 / 56 (1.79%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| CHILLS   |                |  |  |
| subjects affected / exposed                          | 1 / 56 (1.79%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| DEVICE DISLOCATION                                   |                |  |  |
| subjects affected / exposed                          | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |

|   |                |  |  |  |
|---|----------------|--|--|--|
| FATIGUE   |                |  |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| FEELING OF BODY TEMPERATURE CHANGE              |                |  |  |  |
| subjects affected / exposed                     | 1 / 56 (1.79%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| GENERAL PHYSICAL HEALTH DETERIORATION           |                |  |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| IMPAIRED HEALING                                |                |  |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| INFLUENZA LIKE ILLNESS                          |                |  |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| LOCAL SWELLING                                  |                |  |  |  |
| subjects affected / exposed                     | 1 / 56 (1.79%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| PAIN  |                |  |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| PYREXIA   |                |  |  |  |
| subjects affected / exposed                     | 2 / 56 (3.57%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Immune system disorders                         |                |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| HYPERSENSITIVITY                                |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Respiratory, thoracic and mediastinal disorders |                |  |  |
| COUGH   |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| DYSPNOEA  |                |  |  |
| subjects affected / exposed                     | 1 / 56 (1.79%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |
| DYSPNOEA EXERTIONAL                             |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| EPISTAXIS                                       |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| HAEMOPTYSIS                                     |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| LUNG INFILTRATION                               |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| NASAL SEPTUM PERFORATION                        |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|   |                |  |  |
|---|----------------|--|--|
| PNEUMOTHORAX                                    |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| PULMONARY EMBOLISM                              |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| RESPIRATORY DISTRESS                            |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| RESPIRATORY FAILURE                             |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Psychiatric disorders                           |                |  |  |
| DEPRESSION                                      |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| SUICIDAL IDEATION                               |                |  |  |
| subjects affected / exposed                     | 1 / 56 (1.79%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Injury, poisoning and procedural complications  |                |  |  |
| ANKLE FRACTURE                                  |                |  |  |
| subjects affected / exposed                     | 1 / 56 (1.79%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| FEMORAL NECK FRACTURE                           |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|   |                |  |  |  |
|---|----------------|--|--|--|
| JOINT DISLOCATION                               |                |  |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| RIB FRACTURE                                    |                |  |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Cardiac disorders                               |                |  |  |  |
| ATRIOVENTRICULAR BLOCK SECOND DEGREE            |                |  |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| BRADYCARDIA                                     |                |  |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| CARDIAC FAILURE CONGESTIVE                      |                |  |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| CARDIOMYOPATHY                                  |                |  |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| LEFT VENTRICULAR DYSFUNCTION                    |                |  |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| MITRAL VALVE INCOMPETENCE                       |                |  |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| MYOCARDIAL INFARCTION                           |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| SUPRAVENTRICULAR TACHYCARDIA                    |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Nervous system disorders                        |                |  |  |
| CEREBROVASCULAR ACCIDENT                        |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| EPILEPSY  |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| HEADACHE  |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| MENINGEAL DISORDER                              |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| PARESIS   |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| SPEECH DISORDER                                 |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Blood and lymphatic system disorders            |                |  |  |



|   |                |  |  |
|---|----------------|--|--|
| ANAEMIA   |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| FEBRILE NEUTROPENIA                             |                |  |  |
| subjects affected / exposed                     | 1 / 56 (1.79%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| LEUKOPENIA                                      |                |  |  |
| subjects affected / exposed                     | 1 / 56 (1.79%) |  |  |
| occurrences causally related to treatment / all | 3 / 3          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| NEUTROPENIA                                     |                |  |  |
| subjects affected / exposed                     | 4 / 56 (7.14%) |  |  |
| occurrences causally related to treatment / all | 5 / 6          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastrointestinal disorders                      |                |  |  |
| ABDOMINAL PAIN                                  |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| ASCITES   |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| DIARRHOEA                                       |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| GASTROINTESTINAL PERFORATION                    |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| ILEUS   |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| NAUSEA  |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| PANCREATITIS                                    |                |  |  |
| subjects affected / exposed                     | 1 / 56 (1.79%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| RECTAL HAEMORRHAGE                              |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| SMALL INTESTINAL OBSTRUCTION                    |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| VOMITING  |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hepatobiliary disorders                         |                |  |  |
| CHOLECYSTITIS                                   |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| CHOLECYSTITIS ACUTE                             |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| HEPATIC FUNCTION ABNORMAL                       |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Skin and subcutaneous tissue disorders          |                |  |  |
| DERMATITIS                                      |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| RASH  |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| SUBCUTANEOUS EMPHYSEMA                          |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Musculoskeletal and connective tissue disorders |                |  |  |
| ARTHRALGIA                                      |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| BACK PAIN                                       |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| BONE PAIN                                       |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| MUSCLE SPASMS                                   |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|   |                |  |  |
|---|----------------|--|--|
| MUSCULOSKELETAL CHEST PAIN                      |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| NECK PAIN                                       |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| OSTEONECROSIS                                   |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| PAIN IN EXTREMITY                               |                |  |  |
| subjects affected / exposed                     | 1 / 56 (1.79%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| PATHOLOGICAL FRACTURE                           |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| ASPERGILLUS INFECTION                           |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| BRONCHOPNEUMONIA                                |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| CATHETER SITE INFECTION                         |                |  |  |
| subjects affected / exposed                     | 1 / 56 (1.79%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| CELLULITIS                                      |                |  |  |

|   |                |  |  |  |
|---|----------------|--|--|--|
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| DEVICE RELATED INFECTION                        |                |  |  |  |
| subjects affected / exposed                     | 1 / 56 (1.79%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| DEVICE RELATED SEPSIS                           |                |  |  |  |
| subjects affected / exposed                     | 1 / 56 (1.79%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| GASTROENTERITIS                                 |                |  |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| HERPES ZOSTER                                   |                |  |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| INFECTION                                       |                |  |  |  |
| subjects affected / exposed                     | 2 / 56 (3.57%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| LOBAR PNEUMONIA                                 |                |  |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| NAIL INFECTION                                  |                |  |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| PNEUMONIA                                       |                |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 56 (1.79%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| RESPIRATORY TRACT INFECTION                     |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| SEPSIS  |                |  |  |
| subjects affected / exposed                     | 2 / 56 (3.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 2          |  |  |
| SKIN INFECTION                                  |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| URINARY TRACT INFECTION                         |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Metabolism and nutrition disorders              |                |  |  |
| DECREASED APPETITE                              |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| DEHYDRATION                                     |                |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| FLUID RETENTION                                 |                |  |  |
| subjects affected / exposed                     | 1 / 56 (1.79%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| HYPOCALCAEMIA                                   |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 56 (1.79%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

| <b>Non-serious adverse events</b>                           | Placebo + Paclitaxel<br>+ Bevacizumab | Trebananib 3 mg/kg<br>+ Paclitaxel +<br>Bevacizumab | Trebananib 10<br>mg/kg + Paclitaxel<br>+ Bevacizumab |
|---|---------------------------------------|---|--|
| Total subjects affected by non-serious adverse events       |                                       |   |  |
| subjects affected / exposed                                 | 56 / 58 (96.55%)                      | 57 / 57 (100.00%)                                   | 54 / 55 (98.18%)                                     |
| <b>Vascular disorders</b>                                   |                                       |   |  |
| DEEP VEIN THROMBOSIS  |                                       |   |  |
| subjects affected / exposed                                 | 0 / 58 (0.00%)                        | 0 / 57 (0.00%)                                      | 3 / 55 (5.45%)                                       |
| occurrences (all)   | 0                                     | 0   | 3  |
| FLUSHING  |                                       |   |  |
| subjects affected / exposed                                 | 4 / 58 (6.90%)                        | 3 / 57 (5.26%)                                      | 4 / 55 (7.27%)                                       |
| occurrences (all)   | 23                                    | 8   | 30   |
| HOT FLUSH   |                                       |   |  |
| subjects affected / exposed                                 | 12 / 58 (20.69%)                      | 3 / 57 (5.26%)                                      | 5 / 55 (9.09%)                                       |
| occurrences (all)   | 20                                    | 7   | 8  |
| HYPERTENSION  |                                       |   |  |
| subjects affected / exposed                                 | 22 / 58 (37.93%)                      | 22 / 57 (38.60%)                                    | 24 / 55 (43.64%)                                     |
| occurrences (all)   | 42                                    | 33  | 42   |
| HYPOTENSION   |                                       |   |  |
| subjects affected / exposed                                 | 1 / 58 (1.72%)                        | 1 / 57 (1.75%)                                      | 0 / 55 (0.00%)                                       |
| occurrences (all)   | 1                                     | 1   | 0  |
| LYMPHOEDEMA   |                                       |   |  |
| subjects affected / exposed                                 | 4 / 58 (6.90%)                        | 7 / 57 (12.28%)                                     | 8 / 55 (14.55%)                                      |
| occurrences (all)   | 5                                     | 9   | 10   |
| <b>General disorders and administration site conditions</b> |                                       |   |  |
| ASTHENIA  |                                       |   |  |
| subjects affected / exposed                                 | 19 / 58 (32.76%)                      | 19 / 57 (33.33%)                                    | 17 / 55 (30.91%)                                     |
| occurrences (all)   | 87                                    | 74  | 76   |
| CATHETER SITE PAIN  |                                       |   |  |

|                             |                  |                  |                  |
|-----------------------------|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 58 (1.72%)   | 0 / 57 (0.00%)   | 3 / 55 (5.45%)   |
| occurrences (all)           | 1                | 0                | 3                |
| CHEST DISCOMFORT            |                  |                  |                  |
| subjects affected / exposed | 1 / 58 (1.72%)   | 1 / 57 (1.75%)   | 4 / 55 (7.27%)   |
| occurrences (all)           | 1                | 1                | 5                |
| CHEST PAIN                  |                  |                  |                  |
| subjects affected / exposed | 5 / 58 (8.62%)   | 4 / 57 (7.02%)   | 3 / 55 (5.45%)   |
| occurrences (all)           | 5                | 5                | 6                |
| FACE OEDEMA                 |                  |                  |                  |
| subjects affected / exposed | 0 / 58 (0.00%)   | 3 / 57 (5.26%)   | 6 / 55 (10.91%)  |
| occurrences (all)           | 0                | 5                | 6                |
| FATIGUE                     |                  |                  |                  |
| subjects affected / exposed | 22 / 58 (37.93%) | 33 / 57 (57.89%) | 27 / 55 (49.09%) |
| occurrences (all)           | 40               | 67               | 44               |
| GAIT DISTURBANCE            |                  |                  |                  |
| subjects affected / exposed | 3 / 58 (5.17%)   | 1 / 57 (1.75%)   | 2 / 55 (3.64%)   |
| occurrences (all)           | 3                | 1                | 2                |
| GENERALISED OEDEMA          |                  |                  |                  |
| subjects affected / exposed | 1 / 58 (1.72%)   | 0 / 57 (0.00%)   | 1 / 55 (1.82%)   |
| occurrences (all)           | 1                | 0                | 2                |
| INFLUENZA LIKE ILLNESS      |                  |                  |                  |
| subjects affected / exposed | 4 / 58 (6.90%)   | 1 / 57 (1.75%)   | 4 / 55 (7.27%)   |
| occurrences (all)           | 5                | 1                | 4                |
| MUCOSAL INFLAMMATION        |                  |                  |                  |
| subjects affected / exposed | 13 / 58 (22.41%) | 11 / 57 (19.30%) | 9 / 55 (16.36%)  |
| occurrences (all)           | 21               | 20               | 14               |
| OEDEMA PERIPHERAL           |                  |                  |                  |
| subjects affected / exposed | 11 / 58 (18.97%) | 26 / 57 (45.61%) | 18 / 55 (32.73%) |
| occurrences (all)           | 26               | 55               | 37               |
| PAIN                        |                  |                  |                  |
| subjects affected / exposed | 9 / 58 (15.52%)  | 6 / 57 (10.53%)  | 2 / 55 (3.64%)   |
| occurrences (all)           | 11               | 6                | 3                |
| PYREXIA                     |                  |                  |                  |
| subjects affected / exposed | 11 / 58 (18.97%) | 9 / 57 (15.79%)  | 14 / 55 (25.45%) |
| occurrences (all)           | 19               | 12               | 22               |
| Immune system disorders     |                  |                  |                  |



|   |                                   |                                   |                                   |
|---|-----------------------------------|-----------------------------------|-----------------------------------|
| <p>DRUG HYPERSENSITIVITY</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>3 / 58 (5.17%)</p> <p>3</p>    | <p>1 / 57 (1.75%)</p> <p>1</p>    | <p>1 / 55 (1.82%)</p> <p>2</p>    |
| <p>HYPERSENSITIVITY</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>1 / 58 (1.72%)</p> <p>2</p>    | <p>3 / 57 (5.26%)</p> <p>3</p>    | <p>4 / 55 (7.27%)</p> <p>5</p>    |
| <p>Reproductive system and breast disorders</p> <p>VULVOVAGINAL DRYNESS</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 58 (0.00%)</p> <p>0</p>    | <p>3 / 57 (5.26%)</p> <p>3</p>    | <p>0 / 55 (0.00%)</p> <p>0</p>    |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>COUGH</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>         | <p>20 / 58 (34.48%)</p> <p>40</p> | <p>15 / 57 (26.32%)</p> <p>23</p> | <p>18 / 55 (32.73%)</p> <p>36</p> |
| <p>DYSPHONIA</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>19 / 58 (32.76%)</p> <p>37</p> | <p>8 / 57 (14.04%)</p> <p>10</p>  | <p>11 / 55 (20.00%)</p> <p>13</p> |
| <p>DYSPNOEA</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>11 / 58 (18.97%)</p> <p>20</p> | <p>11 / 57 (19.30%)</p> <p>22</p> | <p>12 / 55 (21.82%)</p> <p>23</p> |
| <p>DYSPNOEA EXERTIONAL</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>6 / 58 (10.34%)</p> <p>10</p>  | <p>3 / 57 (5.26%)</p> <p>5</p>    | <p>4 / 55 (7.27%)</p> <p>5</p>    |
| <p>EPISTAXIS</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>29 / 58 (50.00%)</p> <p>55</p> | <p>35 / 57 (61.40%)</p> <p>53</p> | <p>25 / 55 (45.45%)</p> <p>44</p> |
| <p>NASAL DRYNESS</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>5 / 58 (8.62%)</p> <p>5</p>    | <p>4 / 57 (7.02%)</p> <p>5</p>    | <p>1 / 55 (1.82%)</p> <p>1</p>    |
| <p>OROPHARYNGEAL PAIN</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>11 / 58 (18.97%)</p> <p>17</p> | <p>11 / 57 (19.30%)</p> <p>14</p> | <p>6 / 55 (10.91%)</p> <p>10</p>  |
| <p>PLEURAL EFFUSION</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>0 / 58 (0.00%)</p> <p>0</p>    | <p>4 / 57 (7.02%)</p> <p>4</p>    | <p>3 / 55 (5.45%)</p> <p>4</p>    |
| <p>PRODUCTIVE COUGH</p>   |                                   |                                   |                                   |

|   |                        |                       |                        |
|---|------------------------|-----------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)  | 2 / 58 (3.45%)<br>2    | 2 / 57 (3.51%)<br>2   | 2 / 55 (3.64%)<br>2    |
| RHINORRHOEA<br>subjects affected / exposed<br>occurrences (all)   | 6 / 58 (10.34%)<br>10  | 6 / 57 (10.53%)<br>6  | 10 / 55 (18.18%)<br>13 |
| Psychiatric disorders<br>ANXIETY<br>subjects affected / exposed<br>occurrences (all)                        | 6 / 58 (10.34%)<br>7   | 4 / 57 (7.02%)<br>7   | 6 / 55 (10.91%)<br>6   |
| DEPRESSION<br>subjects affected / exposed<br>occurrences (all)  | 2 / 58 (3.45%)<br>2    | 4 / 57 (7.02%)<br>5   | 5 / 55 (9.09%)<br>5    |
| INSOMNIA<br>subjects affected / exposed<br>occurrences (all)  | 10 / 58 (17.24%)<br>13 | 8 / 57 (14.04%)<br>10 | 9 / 55 (16.36%)<br>10  |
| SLEEP DISORDER<br>subjects affected / exposed<br>occurrences (all)  | 3 / 58 (5.17%)<br>8    | 1 / 57 (1.75%)<br>1   | 1 / 55 (1.82%)<br>1    |
| Investigations<br>ALANINE AMINOTRANSFERASE<br>INCREASED<br>subjects affected / exposed<br>occurrences (all) | 2 / 58 (3.45%)<br>2    | 4 / 57 (7.02%)<br>7   | 3 / 55 (5.45%)<br>4    |
| ASPARTATE AMINOTRANSFERASE<br>INCREASED<br>subjects affected / exposed<br>occurrences (all)                 | 3 / 58 (5.17%)<br>3    | 4 / 57 (7.02%)<br>9   | 2 / 55 (3.64%)<br>2    |
| NEUTROPHIL COUNT DECREASED<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 58 (0.00%)<br>0    | 2 / 57 (3.51%)<br>3   | 4 / 55 (7.27%)<br>9    |
| WEIGHT DECREASED<br>subjects affected / exposed<br>occurrences (all)  | 5 / 58 (8.62%)<br>8    | 6 / 57 (10.53%)<br>12 | 4 / 55 (7.27%)<br>13   |
| WEIGHT INCREASED<br>subjects affected / exposed<br>occurrences (all)  | 1 / 58 (1.72%)<br>2    | 2 / 57 (3.51%)<br>3   | 3 / 55 (5.45%)<br>5    |
| WHITE BLOOD CELL COUNT<br>DECREASED   |                        |                       |                        |

|  |                        |                        |                        |
|--|------------------------|------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all) | 4 / 58 (6.90%)<br>8    | 0 / 57 (0.00%)<br>0    | 2 / 55 (3.64%)<br>6    |
| Cardiac disorders                                |                        |                        |                        |
| PALPITATIONS                                     |                        |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 3 / 58 (5.17%)<br>3    | 0 / 57 (0.00%)<br>0    | 1 / 55 (1.82%)<br>1    |
| TACHYCARDIA                                      |                        |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 1 / 58 (1.72%)<br>1    | 3 / 57 (5.26%)<br>3    | 3 / 55 (5.45%)<br>3    |
| Nervous system disorders                         |                        |                        |                        |
| DIZZINESS  |                        |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 5 / 58 (8.62%)<br>6    | 11 / 57 (19.30%)<br>14 | 8 / 55 (14.55%)<br>11  |
| DYSAESTHESIA                                     |                        |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 3 / 58 (5.17%)<br>3    | 1 / 57 (1.75%)<br>1    | 2 / 55 (3.64%)<br>4    |
| DYSGEUSIA  |                        |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 18 / 58 (31.03%)<br>34 | 10 / 57 (17.54%)<br>15 | 17 / 55 (30.91%)<br>23 |
| HEADACHE   |                        |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 27 / 58 (46.55%)<br>88 | 24 / 57 (42.11%)<br>48 | 16 / 55 (29.09%)<br>43 |
| HYPOAESTHESIA                                    |                        |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 5 / 58 (8.62%)<br>6    | 4 / 57 (7.02%)<br>5    | 4 / 55 (7.27%)<br>4    |
| MEMORY IMPAIRMENT                                |                        |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 4 / 58 (6.90%)<br>4    | 0 / 57 (0.00%)<br>0    | 2 / 55 (3.64%)<br>2    |
| NEUROPATHY PERIPHERAL                            |                        |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 16 / 58 (27.59%)<br>49 | 23 / 57 (40.35%)<br>61 | 19 / 55 (34.55%)<br>68 |
| PARAESTHESIA                                     |                        |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 8 / 58 (13.79%)<br>17  | 10 / 57 (17.54%)<br>19 | 11 / 55 (20.00%)<br>33 |
| PERIPHERAL SENSORY NEUROPATHY                    |                        |                        |                        |

|                                      |                  |                  |                  |
|--------------------------------------|------------------|------------------|------------------|
| subjects affected / exposed          | 10 / 58 (17.24%) | 12 / 57 (21.05%) | 11 / 55 (20.00%) |
| occurrences (all)                    | 24               | 36               | 28               |
| POLYNEUROPATHY                       |                  |                  |                  |
| subjects affected / exposed          | 2 / 58 (3.45%)   | 0 / 57 (0.00%)   | 0 / 55 (0.00%)   |
| occurrences (all)                    | 3                | 0                | 0                |
| SCIATICA                             |                  |                  |                  |
| subjects affected / exposed          | 4 / 58 (6.90%)   | 2 / 57 (3.51%)   | 3 / 55 (5.45%)   |
| occurrences (all)                    | 4                | 2                | 5                |
| SPEECH DISORDER                      |                  |                  |                  |
| subjects affected / exposed          | 0 / 58 (0.00%)   | 3 / 57 (5.26%)   | 0 / 55 (0.00%)   |
| occurrences (all)                    | 0                | 3                | 0                |
| SYNCOPE                              |                  |                  |                  |
| subjects affected / exposed          | 0 / 58 (0.00%)   | 1 / 57 (1.75%)   | 1 / 55 (1.82%)   |
| occurrences (all)                    | 0                | 1                | 1                |
| TREMOR                               |                  |                  |                  |
| subjects affected / exposed          | 0 / 58 (0.00%)   | 1 / 57 (1.75%)   | 5 / 55 (9.09%)   |
| occurrences (all)                    | 0                | 1                | 5                |
| Blood and lymphatic system disorders |                  |                  |                  |
| ANAEMIA                              |                  |                  |                  |
| subjects affected / exposed          | 5 / 58 (8.62%)   | 5 / 57 (8.77%)   | 4 / 55 (7.27%)   |
| occurrences (all)                    | 22               | 7                | 17               |
| LEUKOPENIA                           |                  |                  |                  |
| subjects affected / exposed          | 4 / 58 (6.90%)   | 3 / 57 (5.26%)   | 4 / 55 (7.27%)   |
| occurrences (all)                    | 35               | 6                | 8                |
| NEUTROPENIA                          |                  |                  |                  |
| subjects affected / exposed          | 24 / 58 (41.38%) | 23 / 57 (40.35%) | 19 / 55 (34.55%) |
| occurrences (all)                    | 135              | 61               | 82               |
| Ear and labyrinth disorders          |                  |                  |                  |
| EAR PAIN                             |                  |                  |                  |
| subjects affected / exposed          | 3 / 58 (5.17%)   | 2 / 57 (3.51%)   | 2 / 55 (3.64%)   |
| occurrences (all)                    | 3                | 2                | 3                |
| TINNITUS                             |                  |                  |                  |
| subjects affected / exposed          | 3 / 58 (5.17%)   | 2 / 57 (3.51%)   | 0 / 55 (0.00%)   |
| occurrences (all)                    | 3                | 3                | 0                |
| VERTIGO                              |                  |                  |                  |

|  |                     |                        |                     |
|--|---------------------|------------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 3 / 58 (5.17%)<br>4 | 10 / 57 (17.54%)<br>13 | 2 / 55 (3.64%)<br>2 |
| Eye disorders                                    |                     |                        |                     |
| DRY EYE  |                     |                        |                     |
| subjects affected / exposed                      | 4 / 58 (6.90%)      | 1 / 57 (1.75%)         | 2 / 55 (3.64%)      |
| occurrences (all)                                | 4                   | 1                      | 3                   |
| EYELID OEDEMA                                    |                     |                        |                     |
| subjects affected / exposed                      | 0 / 58 (0.00%)      | 2 / 57 (3.51%)         | 2 / 55 (3.64%)      |
| occurrences (all)                                | 0                   | 2                      | 2                   |
| LACRIMATION INCREASED                            |                     |                        |                     |
| subjects affected / exposed                      | 5 / 58 (8.62%)      | 5 / 57 (8.77%)         | 5 / 55 (9.09%)      |
| occurrences (all)                                | 6                   | 7                      | 5                   |
| VISION BLURRED                                   |                     |                        |                     |
| subjects affected / exposed                      | 1 / 58 (1.72%)      | 3 / 57 (5.26%)         | 4 / 55 (7.27%)      |
| occurrences (all)                                | 1                   | 3                      | 4                   |
| VISUAL ACUITY REDUCED                            |                     |                        |                     |
| subjects affected / exposed                      | 3 / 58 (5.17%)      | 2 / 57 (3.51%)         | 1 / 55 (1.82%)      |
| occurrences (all)                                | 3                   | 2                      | 1                   |
| VISUAL IMPAIRMENT                                |                     |                        |                     |
| subjects affected / exposed                      | 2 / 58 (3.45%)      | 4 / 57 (7.02%)         | 2 / 55 (3.64%)      |
| occurrences (all)                                | 3                   | 4                      | 7                   |
| Gastrointestinal disorders                       |                     |                        |                     |
| ABDOMINAL DISTENSION                             |                     |                        |                     |
| subjects affected / exposed                      | 1 / 58 (1.72%)      | 7 / 57 (12.28%)        | 5 / 55 (9.09%)      |
| occurrences (all)                                | 1                   | 9                      | 5                   |
| ABDOMINAL PAIN                                   |                     |                        |                     |
| subjects affected / exposed                      | 15 / 58 (25.86%)    | 13 / 57 (22.81%)       | 14 / 55 (25.45%)    |
| occurrences (all)                                | 36                  | 17                     | 28                  |
| ABDOMINAL PAIN UPPER                             |                     |                        |                     |
| subjects affected / exposed                      | 13 / 58 (22.41%)    | 11 / 57 (19.30%)       | 8 / 55 (14.55%)     |
| occurrences (all)                                | 19                  | 12                     | 17                  |
| CONSTIPATION                                     |                     |                        |                     |
| subjects affected / exposed                      | 22 / 58 (37.93%)    | 24 / 57 (42.11%)       | 14 / 55 (25.45%)    |
| occurrences (all)                                | 36                  | 31                     | 25                  |
| DENTAL CARIES                                    |                     |                        |                     |

|                                 |                  |                  |                  |
|---------------------------------|------------------|------------------|------------------|
| subjects affected / exposed     | 3 / 58 (5.17%)   | 0 / 57 (0.00%)   | 0 / 55 (0.00%)   |
| occurrences (all)               | 4                | 0                | 0                |
| DIARRHOEA                       |                  |                  |                  |
| subjects affected / exposed     | 35 / 58 (60.34%) | 31 / 57 (54.39%) | 27 / 55 (49.09%) |
| occurrences (all)               | 83               | 59               | 57               |
| DRY MOUTH                       |                  |                  |                  |
| subjects affected / exposed     | 5 / 58 (8.62%)   | 4 / 57 (7.02%)   | 6 / 55 (10.91%)  |
| occurrences (all)               | 7                | 4                | 11               |
| DYSPEPSIA                       |                  |                  |                  |
| subjects affected / exposed     | 11 / 58 (18.97%) | 8 / 57 (14.04%)  | 9 / 55 (16.36%)  |
| occurrences (all)               | 14               | 25               | 16               |
| DYSPHAGIA                       |                  |                  |                  |
| subjects affected / exposed     | 2 / 58 (3.45%)   | 1 / 57 (1.75%)   | 4 / 55 (7.27%)   |
| occurrences (all)               | 4                | 1                | 4                |
| FLATULENCE                      |                  |                  |                  |
| subjects affected / exposed     | 2 / 58 (3.45%)   | 3 / 57 (5.26%)   | 3 / 55 (5.45%)   |
| occurrences (all)               | 2                | 3                | 3                |
| GASTROESOPHAGEAL REFLUX DISEASE |                  |                  |                  |
| subjects affected / exposed     | 5 / 58 (8.62%)   | 3 / 57 (5.26%)   | 5 / 55 (9.09%)   |
| occurrences (all)               | 6                | 4                | 5                |
| GINGIVAL BLEEDING               |                  |                  |                  |
| subjects affected / exposed     | 5 / 58 (8.62%)   | 1 / 57 (1.75%)   | 2 / 55 (3.64%)   |
| occurrences (all)               | 6                | 2                | 2                |
| HAEMORRHOIDS                    |                  |                  |                  |
| subjects affected / exposed     | 3 / 58 (5.17%)   | 6 / 57 (10.53%)  | 3 / 55 (5.45%)   |
| occurrences (all)               | 5                | 6                | 3                |
| NAUSEA                          |                  |                  |                  |
| subjects affected / exposed     | 26 / 58 (44.83%) | 25 / 57 (43.86%) | 34 / 55 (61.82%) |
| occurrences (all)               | 70               | 58               | 90               |
| ORAL PAIN                       |                  |                  |                  |
| subjects affected / exposed     | 0 / 58 (0.00%)   | 3 / 57 (5.26%)   | 1 / 55 (1.82%)   |
| occurrences (all)               | 0                | 5                | 1                |
| STOMATITIS                      |                  |                  |                  |
| subjects affected / exposed     | 13 / 58 (22.41%) | 12 / 57 (21.05%) | 10 / 55 (18.18%) |
| occurrences (all)               | 21               | 16               | 13               |

|  |                  |                  |                  |
|--|------------------|------------------|------------------|
| TOOTHACHE                              |                  |                  |                  |
| subjects affected / exposed            | 2 / 58 (3.45%)   | 3 / 57 (5.26%)   | 4 / 55 (7.27%)   |
| occurrences (all)                      | 2                | 4                | 4                |
| VOMITING                               |                  |                  |                  |
| subjects affected / exposed            | 17 / 58 (29.31%) | 21 / 57 (36.84%) | 19 / 55 (34.55%) |
| occurrences (all)                      | 45               | 37               | 40               |
| Hepatobiliary disorders                |                  |                  |                  |
| HEPATIC PAIN                           |                  |                  |                  |
| subjects affected / exposed            | 1 / 58 (1.72%)   | 2 / 57 (3.51%)   | 1 / 55 (1.82%)   |
| occurrences (all)                      | 1                | 3                | 1                |
| Skin and subcutaneous tissue disorders |                  |                  |                  |
| ACNE                                   |                  |                  |                  |
| subjects affected / exposed            | 4 / 58 (6.90%)   | 5 / 57 (8.77%)   | 4 / 55 (7.27%)   |
| occurrences (all)                      | 8                | 5                | 4                |
| ALOPECIA                               |                  |                  |                  |
| subjects affected / exposed            | 36 / 58 (62.07%) | 35 / 57 (61.40%) | 35 / 55 (63.64%) |
| occurrences (all)                      | 64               | 62               | 53               |
| DERMATITIS ACNEIFORM                   |                  |                  |                  |
| subjects affected / exposed            | 5 / 58 (8.62%)   | 0 / 57 (0.00%)   | 1 / 55 (1.82%)   |
| occurrences (all)                      | 6                | 0                | 1                |
| DRY SKIN                               |                  |                  |                  |
| subjects affected / exposed            | 6 / 58 (10.34%)  | 5 / 57 (8.77%)   | 4 / 55 (7.27%)   |
| occurrences (all)                      | 10               | 5                | 5                |
| ERYTHEMA                               |                  |                  |                  |
| subjects affected / exposed            | 5 / 58 (8.62%)   | 6 / 57 (10.53%)  | 10 / 55 (18.18%) |
| occurrences (all)                      | 9                | 13               | 26               |
| NAIL DISCOLOURATION                    |                  |                  |                  |
| subjects affected / exposed            | 2 / 58 (3.45%)   | 3 / 57 (5.26%)   | 1 / 55 (1.82%)   |
| occurrences (all)                      | 2                | 3                | 2                |
| NAIL DISORDER                          |                  |                  |                  |
| subjects affected / exposed            | 14 / 58 (24.14%) | 20 / 57 (35.09%) | 20 / 55 (36.36%) |
| occurrences (all)                      | 49               | 39               | 47               |
| NAIL TOXICITY                          |                  |                  |                  |
| subjects affected / exposed            | 4 / 58 (6.90%)   | 6 / 57 (10.53%)  | 2 / 55 (3.64%)   |
| occurrences (all)                      | 8                | 11               | 10               |
| PAIN OF SKIN                           |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 58 (1.72%)   | 3 / 57 (5.26%)   | 0 / 55 (0.00%)   |
| occurrences (all)                               | 1                | 3                | 0                |
| PALMAR-PLANTAR<br>ERYTHRODYSAESTHESIA SYNDROME  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 58 (1.72%)   | 1 / 57 (1.75%)   | 2 / 55 (3.64%)   |
| occurrences (all)                               | 2                | 1                | 3                |
| PRURITUS  |                  |                  |                  |
| subjects affected / exposed                     | 6 / 58 (10.34%)  | 7 / 57 (12.28%)  | 12 / 55 (21.82%) |
| occurrences (all)                               | 8                | 9                | 12               |
| RASH  |                  |                  |                  |
| subjects affected / exposed                     | 17 / 58 (29.31%) | 13 / 57 (22.81%) | 13 / 55 (23.64%) |
| occurrences (all)                               | 51               | 17               | 20               |
| SKIN DISCOLOURATION                             |                  |                  |                  |
| subjects affected / exposed                     | 1 / 58 (1.72%)   | 4 / 57 (7.02%)   | 0 / 55 (0.00%)   |
| occurrences (all)                               | 1                | 4                | 0                |
| SKIN FISSURES                                   |                  |                  |                  |
| subjects affected / exposed                     | 2 / 58 (3.45%)   | 0 / 57 (0.00%)   | 0 / 55 (0.00%)   |
| occurrences (all)                               | 2                | 0                | 0                |
| SKIN HYPERPIGMENTATION                          |                  |                  |                  |
| subjects affected / exposed                     | 2 / 58 (3.45%)   | 1 / 57 (1.75%)   | 4 / 55 (7.27%)   |
| occurrences (all)                               | 3                | 1                | 4                |
| Renal and urinary disorders                     |                  |                  |                  |
| DYSURIA   |                  |                  |                  |
| subjects affected / exposed                     | 6 / 58 (10.34%)  | 1 / 57 (1.75%)   | 5 / 55 (9.09%)   |
| occurrences (all)                               | 7                | 1                | 7                |
| PROTEINURIA                                     |                  |                  |                  |
| subjects affected / exposed                     | 3 / 58 (5.17%)   | 2 / 57 (3.51%)   | 3 / 55 (5.45%)   |
| occurrences (all)                               | 5                | 3                | 3                |
| Musculoskeletal and connective tissue disorders |                  |                  |                  |
| ARTHRALGIA                                      |                  |                  |                  |
| subjects affected / exposed                     | 16 / 58 (27.59%) | 22 / 57 (38.60%) | 15 / 55 (27.27%) |
| occurrences (all)                               | 26               | 36               | 29               |
| BACK PAIN                                       |                  |                  |                  |
| subjects affected / exposed                     | 13 / 58 (22.41%) | 15 / 57 (26.32%) | 13 / 55 (23.64%) |
| occurrences (all)                               | 30               | 27               | 17               |
| BONE PAIN                                       |                  |                  |                  |



|                             |                  |                  |                  |
|-----------------------------|------------------|------------------|------------------|
| subjects affected / exposed | 11 / 58 (18.97%) | 3 / 57 (5.26%)   | 6 / 55 (10.91%)  |
| occurrences (all)           | 15               | 5                | 12               |
| MUSCLE FATIGUE              |                  |                  |                  |
| subjects affected / exposed | 0 / 58 (0.00%)   | 1 / 57 (1.75%)   | 2 / 55 (3.64%)   |
| occurrences (all)           | 0                | 1                | 5                |
| MUSCLE SPASMS               |                  |                  |                  |
| subjects affected / exposed | 10 / 58 (17.24%) | 2 / 57 (3.51%)   | 4 / 55 (7.27%)   |
| occurrences (all)           | 12               | 3                | 6                |
| MUSCULAR WEAKNESS           |                  |                  |                  |
| subjects affected / exposed | 4 / 58 (6.90%)   | 3 / 57 (5.26%)   | 2 / 55 (3.64%)   |
| occurrences (all)           | 9                | 3                | 3                |
| MUSCULOSKELETAL CHEST PAIN  |                  |                  |                  |
| subjects affected / exposed | 6 / 58 (10.34%)  | 8 / 57 (14.04%)  | 4 / 55 (7.27%)   |
| occurrences (all)           | 7                | 10               | 4                |
| MUSCULOSKELETAL PAIN        |                  |                  |                  |
| subjects affected / exposed | 9 / 58 (15.52%)  | 6 / 57 (10.53%)  | 7 / 55 (12.73%)  |
| occurrences (all)           | 15               | 8                | 15               |
| MUSCULOSKELETAL STIFFNESS   |                  |                  |                  |
| subjects affected / exposed | 3 / 58 (5.17%)   | 1 / 57 (1.75%)   | 1 / 55 (1.82%)   |
| occurrences (all)           | 4                | 2                | 1                |
| MYALGIA                     |                  |                  |                  |
| subjects affected / exposed | 15 / 58 (25.86%) | 16 / 57 (28.07%) | 13 / 55 (23.64%) |
| occurrences (all)           | 38               | 32               | 35               |
| NECK PAIN                   |                  |                  |                  |
| subjects affected / exposed | 3 / 58 (5.17%)   | 4 / 57 (7.02%)   | 3 / 55 (5.45%)   |
| occurrences (all)           | 4                | 7                | 3                |
| PAIN IN EXTREMITY           |                  |                  |                  |
| subjects affected / exposed | 14 / 58 (24.14%) | 14 / 57 (24.56%) | 9 / 55 (16.36%)  |
| occurrences (all)           | 25               | 24               | 14               |
| SPINAL PAIN                 |                  |                  |                  |
| subjects affected / exposed | 3 / 58 (5.17%)   | 2 / 57 (3.51%)   | 2 / 55 (3.64%)   |
| occurrences (all)           | 4                | 2                | 2                |
| Infections and infestations |                  |                  |                  |
| BRONCHITIS                  |                  |                  |                  |
| subjects affected / exposed | 1 / 58 (1.72%)   | 4 / 57 (7.02%)   | 2 / 55 (3.64%)   |
| occurrences (all)           | 1                | 4                | 2                |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| CELLULITIS                  |                |                |                |
| subjects affected / exposed | 0 / 58 (0.00%) | 2 / 57 (3.51%) | 1 / 55 (1.82%) |
| occurrences (all)           | 0              | 2              | 2              |
| CONJUNCTIVITIS              |                |                |                |
| subjects affected / exposed | 5 / 58 (8.62%) | 3 / 57 (5.26%) | 0 / 55 (0.00%) |
| occurrences (all)           | 7              | 3              | 0              |
| CYSTITIS                    |                |                |                |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 57 (0.00%) | 2 / 55 (3.64%) |
| occurrences (all)           | 1              | 0              | 2              |
| EAR INFECTION               |                |                |                |
| subjects affected / exposed | 3 / 58 (5.17%) | 1 / 57 (1.75%) | 0 / 55 (0.00%) |
| occurrences (all)           | 4              | 1              | 0              |
| FOLLICULITIS                |                |                |                |
| subjects affected / exposed | 4 / 58 (6.90%) | 3 / 57 (5.26%) | 2 / 55 (3.64%) |
| occurrences (all)           | 8              | 3              | 8              |
| FUNGAL INFECTION            |                |                |                |
| subjects affected / exposed | 3 / 58 (5.17%) | 1 / 57 (1.75%) | 0 / 55 (0.00%) |
| occurrences (all)           | 3              | 1              | 0              |
| GASTROENTERITIS             |                |                |                |
| subjects affected / exposed | 4 / 58 (6.90%) | 2 / 57 (3.51%) | 2 / 55 (3.64%) |
| occurrences (all)           | 5              | 2              | 3              |
| GINGIVITIS                  |                |                |                |
| subjects affected / exposed | 3 / 58 (5.17%) | 2 / 57 (3.51%) | 4 / 55 (7.27%) |
| occurrences (all)           | 3              | 7              | 4              |
| HERPES VIRUS INFECTION      |                |                |                |
| subjects affected / exposed | 0 / 58 (0.00%) | 3 / 57 (5.26%) | 1 / 55 (1.82%) |
| occurrences (all)           | 0              | 3              | 1              |
| HORDEOLUM                   |                |                |                |
| subjects affected / exposed | 3 / 58 (5.17%) | 1 / 57 (1.75%) | 1 / 55 (1.82%) |
| occurrences (all)           | 3              | 1              | 2              |
| INFLUENZA                   |                |                |                |
| subjects affected / exposed | 3 / 58 (5.17%) | 1 / 57 (1.75%) | 4 / 55 (7.27%) |
| occurrences (all)           | 6              | 1              | 5              |
| NAIL INFECTION              |                |                |                |
| subjects affected / exposed | 3 / 58 (5.17%) | 0 / 57 (0.00%) | 1 / 55 (1.82%) |
| occurrences (all)           | 4              | 0              | 1              |

|                                    |                  |                 |                  |
|------------------------------------|------------------|-----------------|------------------|
| NASOPHARYNGITIS                    |                  |                 |                  |
| subjects affected / exposed        | 8 / 58 (13.79%)  | 5 / 57 (8.77%)  | 8 / 55 (14.55%)  |
| occurrences (all)                  | 14               | 6               | 8                |
| ORAL CANDIDIASIS                   |                  |                 |                  |
| subjects affected / exposed        | 1 / 58 (1.72%)   | 1 / 57 (1.75%)  | 0 / 55 (0.00%)   |
| occurrences (all)                  | 1                | 1               | 0                |
| ORAL HERPES                        |                  |                 |                  |
| subjects affected / exposed        | 1 / 58 (1.72%)   | 0 / 57 (0.00%)  | 2 / 55 (3.64%)   |
| occurrences (all)                  | 1                | 0               | 3                |
| PHARYNGITIS                        |                  |                 |                  |
| subjects affected / exposed        | 4 / 58 (6.90%)   | 4 / 57 (7.02%)  | 2 / 55 (3.64%)   |
| occurrences (all)                  | 4                | 5               | 2                |
| RESPIRATORY TRACT INFECTION        |                  |                 |                  |
| subjects affected / exposed        | 1 / 58 (1.72%)   | 3 / 57 (5.26%)  | 1 / 55 (1.82%)   |
| occurrences (all)                  | 1                | 5               | 1                |
| RHINITIS                           |                  |                 |                  |
| subjects affected / exposed        | 7 / 58 (12.07%)  | 7 / 57 (12.28%) | 6 / 55 (10.91%)  |
| occurrences (all)                  | 11               | 8               | 8                |
| SINUSITIS                          |                  |                 |                  |
| subjects affected / exposed        | 3 / 58 (5.17%)   | 2 / 57 (3.51%)  | 8 / 55 (14.55%)  |
| occurrences (all)                  | 3                | 2               | 9                |
| TOOTH ABSCESS                      |                  |                 |                  |
| subjects affected / exposed        | 0 / 58 (0.00%)   | 3 / 57 (5.26%)  | 1 / 55 (1.82%)   |
| occurrences (all)                  | 0                | 5               | 1                |
| TOOTH INFECTION                    |                  |                 |                  |
| subjects affected / exposed        | 1 / 58 (1.72%)   | 4 / 57 (7.02%)  | 2 / 55 (3.64%)   |
| occurrences (all)                  | 1                | 5               | 2                |
| UPPER RESPIRATORY TRACT INFECTION  |                  |                 |                  |
| subjects affected / exposed        | 11 / 58 (18.97%) | 4 / 57 (7.02%)  | 8 / 55 (14.55%)  |
| occurrences (all)                  | 23               | 6               | 11               |
| URINARY TRACT INFECTION            |                  |                 |                  |
| subjects affected / exposed        | 7 / 58 (12.07%)  | 6 / 57 (10.53%) | 12 / 55 (21.82%) |
| occurrences (all)                  | 15               | 9               | 17               |
| Metabolism and nutrition disorders |                  |                 |                  |

|                             |                  |                  |                  |
|-----------------------------|------------------|------------------|------------------|
| DECREASED APPETITE          |                  |                  |                  |
| subjects affected / exposed | 17 / 58 (29.31%) | 16 / 57 (28.07%) | 13 / 55 (23.64%) |
| occurrences (all)           | 36               | 27               | 19               |
| DEHYDRATION                 |                  |                  |                  |
| subjects affected / exposed | 1 / 58 (1.72%)   | 4 / 57 (7.02%)   | 2 / 55 (3.64%)   |
| occurrences (all)           | 1                | 4                | 2                |
| HYPERGLYCAEMIA              |                  |                  |                  |
| subjects affected / exposed | 1 / 58 (1.72%)   | 3 / 57 (5.26%)   | 0 / 55 (0.00%)   |
| occurrences (all)           | 1                | 3                | 0                |
| HYPOCALCAEMIA               |                  |                  |                  |
| subjects affected / exposed | 0 / 58 (0.00%)   | 0 / 57 (0.00%)   | 3 / 55 (5.45%)   |
| occurrences (all)           | 0                | 0                | 3                |
| HYPOKALAEMIA                |                  |                  |                  |
| subjects affected / exposed | 3 / 58 (5.17%)   | 2 / 57 (3.51%)   | 1 / 55 (1.82%)   |
| occurrences (all)           | 5                | 3                | 1                |

|   |  |  |  |
|---|--|--|--|
| <b>Non-serious adverse events</b>                     | OL Trebananib 10 mg/kg QW + Paclitaxel |  |  |
| Total subjects affected by non-serious adverse events |  |  |  |
| subjects affected / exposed                           | 54 / 56 (96.43%)                       |  |  |
| Vascular disorders                                    |  |  |  |
| DEEP VEIN THROMBOSIS                                  |  |  |  |
| subjects affected / exposed                           | 0 / 56 (0.00%)                         |  |  |
| occurrences (all)                                     | 0                                      |  |  |
| FLUSHING  |  |  |  |
| subjects affected / exposed                           | 3 / 56 (5.36%)                         |  |  |
| occurrences (all)                                     | 3                                      |  |  |
| HOT FLUSH   |  |  |  |
| subjects affected / exposed                           | 9 / 56 (16.07%)                        |  |  |
| occurrences (all)                                     | 14                                     |  |  |
| HYPERTENSION  |  |  |  |
| subjects affected / exposed                           | 8 / 56 (14.29%)                        |  |  |
| occurrences (all)                                     | 8                                      |  |  |
| HYPOTENSION   |  |  |  |
| subjects affected / exposed                           | 4 / 56 (7.14%)                         |  |  |
| occurrences (all)                                     | 4                                      |  |  |
| LYMPHOEDEMA   |  |  |  |

|  |                  |  |  |
|--|------------------|--|--|
| subjects affected / exposed                          | 9 / 56 (16.07%)  |  |  |
| occurrences (all)                                    | 10               |  |  |
| General disorders and administration site conditions |                  |  |  |
| ASTHENIA   |                  |  |  |
| subjects affected / exposed                          | 23 / 56 (41.07%) |  |  |
| occurrences (all)                                    | 95               |  |  |
| CATHETER SITE PAIN                                   |                  |  |  |
| subjects affected / exposed                          | 2 / 56 (3.57%)   |  |  |
| occurrences (all)                                    | 3                |  |  |
| CHEST DISCOMFORT                                     |                  |  |  |
| subjects affected / exposed                          | 1 / 56 (1.79%)   |  |  |
| occurrences (all)                                    | 1                |  |  |
| CHEST PAIN   |                  |  |  |
| subjects affected / exposed                          | 12 / 56 (21.43%) |  |  |
| occurrences (all)                                    | 22               |  |  |
| FACE OEDEMA  |                  |  |  |
| subjects affected / exposed                          | 7 / 56 (12.50%)  |  |  |
| occurrences (all)                                    | 12               |  |  |
| FATIGUE  |                  |  |  |
| subjects affected / exposed                          | 15 / 56 (26.79%) |  |  |
| occurrences (all)                                    | 29               |  |  |
| GAIT DISTURBANCE                                     |                  |  |  |
| subjects affected / exposed                          | 1 / 56 (1.79%)   |  |  |
| occurrences (all)                                    | 1                |  |  |
| GENERALISED OEDEMA                                   |                  |  |  |
| subjects affected / exposed                          | 4 / 56 (7.14%)   |  |  |
| occurrences (all)                                    | 4                |  |  |
| INFLUENZA LIKE ILLNESS                               |                  |  |  |
| subjects affected / exposed                          | 4 / 56 (7.14%)   |  |  |
| occurrences (all)                                    | 4                |  |  |
| MUCOSAL INFLAMMATION                                 |                  |  |  |
| subjects affected / exposed                          | 2 / 56 (3.57%)   |  |  |
| occurrences (all)                                    | 2                |  |  |
| OEDEMA PERIPHERAL                                    |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 30 / 56 (53.57%) |  |  |
| occurrences (all)                               | 72               |  |  |
| PAIN  |                  |  |  |
| subjects affected / exposed                     | 5 / 56 (8.93%)   |  |  |
| occurrences (all)                               | 5                |  |  |
| PYREXIA   |                  |  |  |
| subjects affected / exposed                     | 10 / 56 (17.86%) |  |  |
| occurrences (all)                               | 18               |  |  |
| Immune system disorders                         |                  |  |  |
| DRUG HYPERSENSITIVITY                           |                  |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%)   |  |  |
| occurrences (all)                               | 0                |  |  |
| HYPERSENSITIVITY                                |                  |  |  |
| subjects affected / exposed                     | 1 / 56 (1.79%)   |  |  |
| occurrences (all)                               | 1                |  |  |
| Reproductive system and breast disorders        |                  |  |  |
| VULVOVAGINAL DRYNESS                            |                  |  |  |
| subjects affected / exposed                     | 1 / 56 (1.79%)   |  |  |
| occurrences (all)                               | 1                |  |  |
| Respiratory, thoracic and mediastinal disorders |                  |  |  |
| COUGH   |                  |  |  |
| subjects affected / exposed                     | 18 / 56 (32.14%) |  |  |
| occurrences (all)                               | 29               |  |  |
| DYSPHONIA                                       |                  |  |  |
| subjects affected / exposed                     | 3 / 56 (5.36%)   |  |  |
| occurrences (all)                               | 4                |  |  |
| DYSPNOEA  |                  |  |  |
| subjects affected / exposed                     | 11 / 56 (19.64%) |  |  |
| occurrences (all)                               | 20               |  |  |
| DYSPNOEA EXERTIONAL                             |                  |  |  |
| subjects affected / exposed                     | 1 / 56 (1.79%)   |  |  |
| occurrences (all)                               | 1                |  |  |
| EPISTAXIS                                       |                  |  |  |
| subjects affected / exposed                     | 10 / 56 (17.86%) |  |  |
| occurrences (all)                               | 16               |  |  |
| NASAL DRYNESS                                   |                  |  |  |

|                                      |                  |  |  |
|--------------------------------------|------------------|--|--|
| subjects affected / exposed          | 0 / 56 (0.00%)   |  |  |
| occurrences (all)                    | 0                |  |  |
| OROPHARYNGEAL PAIN                   |                  |  |  |
| subjects affected / exposed          | 3 / 56 (5.36%)   |  |  |
| occurrences (all)                    | 5                |  |  |
| PLEURAL EFFUSION                     |                  |  |  |
| subjects affected / exposed          | 5 / 56 (8.93%)   |  |  |
| occurrences (all)                    | 6                |  |  |
| PRODUCTIVE COUGH                     |                  |  |  |
| subjects affected / exposed          | 3 / 56 (5.36%)   |  |  |
| occurrences (all)                    | 3                |  |  |
| RHINORRHOEA                          |                  |  |  |
| subjects affected / exposed          | 4 / 56 (7.14%)   |  |  |
| occurrences (all)                    | 5                |  |  |
| Psychiatric disorders                |                  |  |  |
| ANXIETY                              |                  |  |  |
| subjects affected / exposed          | 2 / 56 (3.57%)   |  |  |
| occurrences (all)                    | 2                |  |  |
| DEPRESSION                           |                  |  |  |
| subjects affected / exposed          | 4 / 56 (7.14%)   |  |  |
| occurrences (all)                    | 7                |  |  |
| INSOMNIA                             |                  |  |  |
| subjects affected / exposed          | 12 / 56 (21.43%) |  |  |
| occurrences (all)                    | 17               |  |  |
| SLEEP DISORDER                       |                  |  |  |
| subjects affected / exposed          | 3 / 56 (5.36%)   |  |  |
| occurrences (all)                    | 4                |  |  |
| Investigations                       |                  |  |  |
| ALANINE AMINOTRANSFERASE INCREASED   |                  |  |  |
| subjects affected / exposed          | 1 / 56 (1.79%)   |  |  |
| occurrences (all)                    | 3                |  |  |
| ASPARTATE AMINOTRANSFERASE INCREASED |                  |  |  |
| subjects affected / exposed          | 1 / 56 (1.79%)   |  |  |
| occurrences (all)                    | 2                |  |  |
| NEUTROPHIL COUNT DECREASED           |                  |  |  |

|                                  |                  |  |  |
|----------------------------------|------------------|--|--|
| subjects affected / exposed      | 1 / 56 (1.79%)   |  |  |
| occurrences (all)                | 4                |  |  |
| WEIGHT DECREASED                 |                  |  |  |
| subjects affected / exposed      | 1 / 56 (1.79%)   |  |  |
| occurrences (all)                | 3                |  |  |
| WEIGHT INCREASED                 |                  |  |  |
| subjects affected / exposed      | 4 / 56 (7.14%)   |  |  |
| occurrences (all)                | 5                |  |  |
| WHITE BLOOD CELL COUNT DECREASED |                  |  |  |
| subjects affected / exposed      | 2 / 56 (3.57%)   |  |  |
| occurrences (all)                | 5                |  |  |
| Cardiac disorders                |                  |  |  |
| PALPITATIONS                     |                  |  |  |
| subjects affected / exposed      | 0 / 56 (0.00%)   |  |  |
| occurrences (all)                | 0                |  |  |
| TACHYCARDIA                      |                  |  |  |
| subjects affected / exposed      | 2 / 56 (3.57%)   |  |  |
| occurrences (all)                | 2                |  |  |
| Nervous system disorders         |                  |  |  |
| DIZZINESS                        |                  |  |  |
| subjects affected / exposed      | 6 / 56 (10.71%)  |  |  |
| occurrences (all)                | 11               |  |  |
| DYSAESTHESIA                     |                  |  |  |
| subjects affected / exposed      | 3 / 56 (5.36%)   |  |  |
| occurrences (all)                | 4                |  |  |
| DYSGEUSIA                        |                  |  |  |
| subjects affected / exposed      | 10 / 56 (17.86%) |  |  |
| occurrences (all)                | 13               |  |  |
| HEADACHE                         |                  |  |  |
| subjects affected / exposed      | 17 / 56 (30.36%) |  |  |
| occurrences (all)                | 42               |  |  |
| HYPOAESTHESIA                    |                  |  |  |
| subjects affected / exposed      | 4 / 56 (7.14%)   |  |  |
| occurrences (all)                | 7                |  |  |
| MEMORY IMPAIRMENT                |                  |  |  |



|                                      |                  |  |  |
|--------------------------------------|------------------|--|--|
| subjects affected / exposed          | 0 / 56 (0.00%)   |  |  |
| occurrences (all)                    | 0                |  |  |
| NEUROPATHY PERIPHERAL                |                  |  |  |
| subjects affected / exposed          | 21 / 56 (37.50%) |  |  |
| occurrences (all)                    | 46               |  |  |
| PARAESTHESIA                         |                  |  |  |
| subjects affected / exposed          | 9 / 56 (16.07%)  |  |  |
| occurrences (all)                    | 26               |  |  |
| PERIPHERAL SENSORY NEUROPATHY        |                  |  |  |
| subjects affected / exposed          | 11 / 56 (19.64%) |  |  |
| occurrences (all)                    | 26               |  |  |
| POLYNEUROPATHY                       |                  |  |  |
| subjects affected / exposed          | 3 / 56 (5.36%)   |  |  |
| occurrences (all)                    | 5                |  |  |
| SCIATICA                             |                  |  |  |
| subjects affected / exposed          | 1 / 56 (1.79%)   |  |  |
| occurrences (all)                    | 1                |  |  |
| SPEECH DISORDER                      |                  |  |  |
| subjects affected / exposed          | 0 / 56 (0.00%)   |  |  |
| occurrences (all)                    | 0                |  |  |
| SYNCOPE                              |                  |  |  |
| subjects affected / exposed          | 5 / 56 (8.93%)   |  |  |
| occurrences (all)                    | 5                |  |  |
| TREMOR                               |                  |  |  |
| subjects affected / exposed          | 0 / 56 (0.00%)   |  |  |
| occurrences (all)                    | 0                |  |  |
| Blood and lymphatic system disorders |                  |  |  |
| ANAEMIA                              |                  |  |  |
| subjects affected / exposed          | 8 / 56 (14.29%)  |  |  |
| occurrences (all)                    | 8                |  |  |
| LEUKOPENIA                           |                  |  |  |
| subjects affected / exposed          | 5 / 56 (8.93%)   |  |  |
| occurrences (all)                    | 9                |  |  |
| NEUTROPENIA                          |                  |  |  |
| subjects affected / exposed          | 17 / 56 (30.36%) |  |  |
| occurrences (all)                    | 31               |  |  |

|  |  |  |  |
|--|--|--|--|
| Ear and labyrinth disorders<br>EAR PAIN<br>subjects affected / exposed<br>occurrences (all)<br><br>TINNITUS<br>subjects affected / exposed<br>occurrences (all)<br><br>VERTIGO<br>subjects affected / exposed<br>occurrences (all)   | 1 / 56 (1.79%)<br>1<br><br>1 / 56 (1.79%)<br>1<br><br>3 / 56 (5.36%)<br>6  |  |  |
| Eye disorders<br>DRY EYE<br>subjects affected / exposed<br>occurrences (all)<br><br>EYELID OEDEMA<br>subjects affected / exposed<br>occurrences (all)<br><br>LACRIMATION INCREASED<br>subjects affected / exposed<br>occurrences (all)<br><br>VISION BLURRED<br>subjects affected / exposed<br>occurrences (all)<br><br>VISUAL ACUITY REDUCED<br>subjects affected / exposed<br>occurrences (all)<br><br>VISUAL IMPAIRMENT<br>subjects affected / exposed<br>occurrences (all) | 1 / 56 (1.79%)<br>1<br><br>6 / 56 (10.71%)<br>8<br><br>6 / 56 (10.71%)<br>8<br><br>0 / 56 (0.00%)<br>0<br><br>1 / 56 (1.79%)<br>1<br><br>0 / 56 (0.00%)<br>0 |  |  |
| Gastrointestinal disorders<br>ABDOMINAL DISTENSION<br>subjects affected / exposed<br>occurrences (all)<br><br>ABDOMINAL PAIN<br>subjects affected / exposed<br>occurrences (all)<br><br>ABDOMINAL PAIN UPPER   | 2 / 56 (3.57%)<br>2<br><br>12 / 56 (21.43%)<br>14  |  |  |

|                                  |                  |  |  |
|----------------------------------|------------------|--|--|
| subjects affected / exposed      | 6 / 56 (10.71%)  |  |  |
| occurrences (all)                | 15               |  |  |
| CONSTIPATION                     |                  |  |  |
| subjects affected / exposed      | 13 / 56 (23.21%) |  |  |
| occurrences (all)                | 19               |  |  |
| DENTAL CARIES                    |                  |  |  |
| subjects affected / exposed      | 0 / 56 (0.00%)   |  |  |
| occurrences (all)                | 0                |  |  |
| DIARRHOEA                        |                  |  |  |
| subjects affected / exposed      | 18 / 56 (32.14%) |  |  |
| occurrences (all)                | 39               |  |  |
| DRY MOUTH                        |                  |  |  |
| subjects affected / exposed      | 2 / 56 (3.57%)   |  |  |
| occurrences (all)                | 2                |  |  |
| DYSPEPSIA                        |                  |  |  |
| subjects affected / exposed      | 8 / 56 (14.29%)  |  |  |
| occurrences (all)                | 15               |  |  |
| DYSPHAGIA                        |                  |  |  |
| subjects affected / exposed      | 3 / 56 (5.36%)   |  |  |
| occurrences (all)                | 3                |  |  |
| FLATULENCE                       |                  |  |  |
| subjects affected / exposed      | 2 / 56 (3.57%)   |  |  |
| occurrences (all)                | 2                |  |  |
| GASTROOESOPHAGEAL REFLUX DISEASE |                  |  |  |
| subjects affected / exposed      | 1 / 56 (1.79%)   |  |  |
| occurrences (all)                | 1                |  |  |
| GINGIVAL BLEEDING                |                  |  |  |
| subjects affected / exposed      | 0 / 56 (0.00%)   |  |  |
| occurrences (all)                | 0                |  |  |
| HAEMORRHOIDS                     |                  |  |  |
| subjects affected / exposed      | 4 / 56 (7.14%)   |  |  |
| occurrences (all)                | 4                |  |  |
| NAUSEA                           |                  |  |  |
| subjects affected / exposed      | 26 / 56 (46.43%) |  |  |
| occurrences (all)                | 44               |  |  |

|   |  |  |  |
|---|--|--|--|
| <p>ORAL PAIN</p> <p>subjects affected / exposed</p> <p>1 / 56 (1.79%)</p> <p>occurrences (all)</p> <p>1</p> <p>STOMATITIS</p> <p>subjects affected / exposed</p> <p>3 / 56 (5.36%)</p> <p>occurrences (all)</p> <p>7</p> <p>TOOTHACHE</p> <p>subjects affected / exposed</p> <p>1 / 56 (1.79%)</p> <p>occurrences (all)</p> <p>2</p> <p>VOMITING</p> <p>subjects affected / exposed</p> <p>12 / 56 (21.43%)</p> <p>occurrences (all)</p> <p>15</p>  |  |  |  |
| <p>Hepatobiliary disorders</p> <p>HEPATIC PAIN</p> <p>subjects affected / exposed</p> <p>3 / 56 (5.36%)</p> <p>occurrences (all)</p> <p>4</p>   |  |  |  |
| <p>Skin and subcutaneous tissue disorders</p> <p>ACNE</p> <p>subjects affected / exposed</p> <p>4 / 56 (7.14%)</p> <p>occurrences (all)</p> <p>9</p> <p>ALOPECIA</p> <p>subjects affected / exposed</p> <p>31 / 56 (55.36%)</p> <p>occurrences (all)</p> <p>43</p> <p>DERMATITIS ACNEIFORM</p> <p>subjects affected / exposed</p> <p>0 / 56 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>DRY SKIN</p> <p>subjects affected / exposed</p> <p>5 / 56 (8.93%)</p> <p>occurrences (all)</p> <p>7</p> <p>ERYTHEMA</p> <p>subjects affected / exposed</p> <p>11 / 56 (19.64%)</p> <p>occurrences (all)</p> <p>37</p> <p>NAIL DISCOLOURATION</p> <p>subjects affected / exposed</p> <p>0 / 56 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>NAIL DISORDER</p> |  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 5 / 56 (8.93%)   |  |  |
| occurrences (all)                               | 10               |  |  |
| NAIL TOXICITY                                   |                  |  |  |
| subjects affected / exposed                     | 7 / 56 (12.50%)  |  |  |
| occurrences (all)                               | 20               |  |  |
| PAIN OF SKIN                                    |                  |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%)   |  |  |
| occurrences (all)                               | 0                |  |  |
| PALMAR-PLANTAR<br>ERYTHRODYSAESTHESIA SYNDROME  |                  |  |  |
| subjects affected / exposed                     | 4 / 56 (7.14%)   |  |  |
| occurrences (all)                               | 5                |  |  |
| PRURITUS  |                  |  |  |
| subjects affected / exposed                     | 9 / 56 (16.07%)  |  |  |
| occurrences (all)                               | 13               |  |  |
| RASH  |                  |  |  |
| subjects affected / exposed                     | 12 / 56 (21.43%) |  |  |
| occurrences (all)                               | 17               |  |  |
| SKIN DISCOLOURATION                             |                  |  |  |
| subjects affected / exposed                     | 0 / 56 (0.00%)   |  |  |
| occurrences (all)                               | 0                |  |  |
| SKIN FISSURES                                   |                  |  |  |
| subjects affected / exposed                     | 3 / 56 (5.36%)   |  |  |
| occurrences (all)                               | 3                |  |  |
| SKIN HYPERPIGMENTATION                          |                  |  |  |
| subjects affected / exposed                     | 1 / 56 (1.79%)   |  |  |
| occurrences (all)                               | 1                |  |  |
| Renal and urinary disorders                     |                  |  |  |
| DYSURIA   |                  |  |  |
| subjects affected / exposed                     | 4 / 56 (7.14%)   |  |  |
| occurrences (all)                               | 5                |  |  |
| PROTEINURIA                                     |                  |  |  |
| subjects affected / exposed                     | 2 / 56 (3.57%)   |  |  |
| occurrences (all)                               | 2                |  |  |
| Musculoskeletal and connective tissue disorders |                  |  |  |

|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| ARTHRALGIA                  |                  |  |  |
| subjects affected / exposed | 14 / 56 (25.00%) |  |  |
| occurrences (all)           | 24               |  |  |
| BACK PAIN                   |                  |  |  |
| subjects affected / exposed | 12 / 56 (21.43%) |  |  |
| occurrences (all)           | 23               |  |  |
| BONE PAIN                   |                  |  |  |
| subjects affected / exposed | 7 / 56 (12.50%)  |  |  |
| occurrences (all)           | 8                |  |  |
| MUSCLE FATIGUE              |                  |  |  |
| subjects affected / exposed | 3 / 56 (5.36%)   |  |  |
| occurrences (all)           | 7                |  |  |
| MUSCLE SPASMS               |                  |  |  |
| subjects affected / exposed | 5 / 56 (8.93%)   |  |  |
| occurrences (all)           | 5                |  |  |
| MUSCULAR WEAKNESS           |                  |  |  |
| subjects affected / exposed | 4 / 56 (7.14%)   |  |  |
| occurrences (all)           | 4                |  |  |
| MUSCULOSKELETAL CHEST PAIN  |                  |  |  |
| subjects affected / exposed | 3 / 56 (5.36%)   |  |  |
| occurrences (all)           | 4                |  |  |
| MUSCULOSKELETAL PAIN        |                  |  |  |
| subjects affected / exposed | 4 / 56 (7.14%)   |  |  |
| occurrences (all)           | 6                |  |  |
| MUSCULOSKELETAL STIFFNESS   |                  |  |  |
| subjects affected / exposed | 0 / 56 (0.00%)   |  |  |
| occurrences (all)           | 0                |  |  |
| MYALGIA                     |                  |  |  |
| subjects affected / exposed | 16 / 56 (28.57%) |  |  |
| occurrences (all)           | 31               |  |  |
| NECK PAIN                   |                  |  |  |
| subjects affected / exposed | 1 / 56 (1.79%)   |  |  |
| occurrences (all)           | 1                |  |  |
| PAIN IN EXTREMITY           |                  |  |  |
| subjects affected / exposed | 12 / 56 (21.43%) |  |  |
| occurrences (all)           | 21               |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| SPINAL PAIN                 |                 |  |  |
| subjects affected / exposed | 1 / 56 (1.79%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Infections and infestations |                 |  |  |
| BRONCHITIS                  |                 |  |  |
| subjects affected / exposed | 4 / 56 (7.14%)  |  |  |
| occurrences (all)           | 4               |  |  |
| CELLULITIS                  |                 |  |  |
| subjects affected / exposed | 6 / 56 (10.71%) |  |  |
| occurrences (all)           | 8               |  |  |
| CONJUNCTIVITIS              |                 |  |  |
| subjects affected / exposed | 4 / 56 (7.14%)  |  |  |
| occurrences (all)           | 5               |  |  |
| CYSTITIS                    |                 |  |  |
| subjects affected / exposed | 3 / 56 (5.36%)  |  |  |
| occurrences (all)           | 4               |  |  |
| EAR INFECTION               |                 |  |  |
| subjects affected / exposed | 0 / 56 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| FOLLICULITIS                |                 |  |  |
| subjects affected / exposed | 1 / 56 (1.79%)  |  |  |
| occurrences (all)           | 1               |  |  |
| FUNGAL INFECTION            |                 |  |  |
| subjects affected / exposed | 0 / 56 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| GASTROENTERITIS             |                 |  |  |
| subjects affected / exposed | 1 / 56 (1.79%)  |  |  |
| occurrences (all)           | 1               |  |  |
| GINGIVITIS                  |                 |  |  |
| subjects affected / exposed | 0 / 56 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| HERPES VIRUS INFECTION      |                 |  |  |
| subjects affected / exposed | 1 / 56 (1.79%)  |  |  |
| occurrences (all)           | 1               |  |  |
| HORDEOLUM                   |                 |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 56 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| INFLUENZA                   |                 |  |  |
| subjects affected / exposed | 1 / 56 (1.79%)  |  |  |
| occurrences (all)           | 1               |  |  |
| NAIL INFECTION              |                 |  |  |
| subjects affected / exposed | 1 / 56 (1.79%)  |  |  |
| occurrences (all)           | 1               |  |  |
| NASOPHARYNGITIS             |                 |  |  |
| subjects affected / exposed | 7 / 56 (12.50%) |  |  |
| occurrences (all)           | 11              |  |  |
| ORAL CANDIDIASIS            |                 |  |  |
| subjects affected / exposed | 3 / 56 (5.36%)  |  |  |
| occurrences (all)           | 3               |  |  |
| ORAL HERPES                 |                 |  |  |
| subjects affected / exposed | 3 / 56 (5.36%)  |  |  |
| occurrences (all)           | 5               |  |  |
| PHARYNGITIS                 |                 |  |  |
| subjects affected / exposed | 3 / 56 (5.36%)  |  |  |
| occurrences (all)           | 3               |  |  |
| RESPIRATORY TRACT INFECTION |                 |  |  |
| subjects affected / exposed | 4 / 56 (7.14%)  |  |  |
| occurrences (all)           | 5               |  |  |
| RHINITIS                    |                 |  |  |
| subjects affected / exposed | 3 / 56 (5.36%)  |  |  |
| occurrences (all)           | 3               |  |  |
| SINUSITIS                   |                 |  |  |
| subjects affected / exposed | 4 / 56 (7.14%)  |  |  |
| occurrences (all)           | 5               |  |  |
| TOOTH ABSCESS               |                 |  |  |
| subjects affected / exposed | 1 / 56 (1.79%)  |  |  |
| occurrences (all)           | 1               |  |  |
| TOOTH INFECTION             |                 |  |  |
| subjects affected / exposed | 0 / 56 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| UPPER RESPIRATORY TRACT     |                 |  |  |



|                                    |                  |  |  |
|------------------------------------|------------------|--|--|
| INFECTION                          |                  |  |  |
| subjects affected / exposed        | 7 / 56 (12.50%)  |  |  |
| occurrences (all)                  | 8                |  |  |
| URINARY TRACT INFECTION            |                  |  |  |
| subjects affected / exposed        | 5 / 56 (8.93%)   |  |  |
| occurrences (all)                  | 13               |  |  |
| Metabolism and nutrition disorders |                  |  |  |
| DECREASED APPETITE                 |                  |  |  |
| subjects affected / exposed        | 10 / 56 (17.86%) |  |  |
| occurrences (all)                  | 12               |  |  |
| DEHYDRATION                        |                  |  |  |
| subjects affected / exposed        | 2 / 56 (3.57%)   |  |  |
| occurrences (all)                  | 2                |  |  |
| HYPERGLYCAEMIA                     |                  |  |  |
| subjects affected / exposed        | 2 / 56 (3.57%)   |  |  |
| occurrences (all)                  | 3                |  |  |
| HYPOCALCAEMIA                      |                  |  |  |
| subjects affected / exposed        | 3 / 56 (5.36%)   |  |  |
| occurrences (all)                  | 10               |  |  |
| HYPOKALAEMIA                       |                  |  |  |
| subjects affected / exposed        | 1 / 56 (1.79%)   |  |  |
| occurrences (all)                  | 1                |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date         | Amendment   |
|--------------|---|
| 18 June 2007 | <p>Amendment 1 included the following changes:</p> <ul style="list-style-type: none"><li>• Prior malignancy (other than thyroid cancer, in situ cervical cancer, or basal cell cancer of the skin) was added as an exclusion criterion.</li><li>• Clinical safety and efficacy experience and paclitaxel background were updated.</li><li>• Baseline samples for anti-AMG 386 antibody tests (immunogenicity), biomarkers, and pharmacokinetic tests) were to be taken within 14 days prior to randomization or before dosing on day 1.</li><li>• A MUGA scan or echocardiogram was to be performed on week 1 day 1, week 9, and week 21.</li><li>• Radiological assessments were to include a CT scan or MRI of the chest, abdomen, and pelvis, and the modality selected was to be the same throughout the study.</li><li>• The timing for the 12-lead ECG was defined: on day 1 of week 1, week 4, and week 21, 60 minutes after the completion of the infusion of AMG 386 and after the subject had been supine for at least 5 minutes.</li><li>• Additional blood samples for biomarker development were to be drawn every 4 cycles (16 weeks) after cycle 3 (week 9).</li><li>• All non-serious adverse events that occurred after the subject has signed the ICF were to be captured.</li><li>• Additional statistical analyses included Arm A and/or B relative to Arm D; and Arm C relative to Arm D.</li></ul>  |
| 11 July 2008 | <p>Amendment 2 included the following changes:</p> <ul style="list-style-type: none"><li>• Baseline values and changes from baseline in pharmacogenetic markers were added as an exploratory endpoint.</li><li>• Complete radiology and tumor measurements were to be performed within 28 days prior to randomization.</li><li>• The brain CT or MRI inclusion criterion was changed to head or brain CT or MRI and was to be performed within 28 days before randomization.</li><li>• The echocardiogram or MUGA scan was to be performed within 14 days prior to randomization.</li><li>• aPTT and INR <math>\leq 1.0 \times</math> ULN per institutional laboratory range was added to the PTT laboratory inclusion criterion.</li><li>• Renal function inclusion criterion was amended to include urinary protein quantitative value of <math>\leq 30</math> mg in urinalysis or <math>\leq 1+</math> on dipstick, unless quantitative protein is <math>\leq 1000</math> mg in a 24 hour urine sample.</li><li>• Exceptions were added to the prior malignancy exclusion criterion: malignancy treated with curative intent and with no known active disease present for <math>\geq 3</math> years; adequately treated non-melanomatous skin cancer or lentigo maligna without evidence of disease; adequately treated cervical carcinoma in situ without evidence of disease.</li><li>• Motesanib was added as an excluded medication, and concurrent or prior anticoagulation therapy, excluding aspirin and anti-platelet agents.</li><li>• Concurrent therapy with any hormonal agents must have been discontinued 14 days before randomization.</li><li>• Baseline samples for anti-AMG 386 antibody tests, biomarkers, and PK tests were to be taken before dosing on day 1 cycle 1.</li><li>• Treatment procedures were modified to include weight, CT or MRI of head or brain and bone metastases, and bone scan if a subject developed signs or symptoms suggestive of bony metastasis while on study treatment.</li><li>• Randomization was to be stratified according to adjuvant taxane exposure and number of metastatic sites.</li><li>• Addition of India and Australia.</li><li>• Other clarifications regarding study procedures were added.</li></ul> |

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| 25 February 2009 | <p>The third amendment included the following changes:</p> <ul style="list-style-type: none"> <li>• The echocardiogram or MUGA scan was to be performed within 28 days prior to randomization (previously 14 days).</li> <li>• The sample size consideration for PFS hazard ratio was expanded and clarified.</li> <li>• Plans for two interim analyses of efficacy were changed to one interim analysis, to take place when 75 PFS events (RECIST v 1.0 with modifications progression or death) among subjects in Arms A, B, and C have occurred.</li> <li>• The status of studies listed in the table of clinical safety experience was updated.</li> <li>• The study accrual period was changed from approximately 12 months to approximately 22 months.</li> <li>• It was clarified that investigators could recalculate AMG 386 dose based on subject weight changes per institutional guidelines.</li> <li>• The paclitaxel and bevacizumab dose modification section was updated to include guidelines for dose withholding.</li> <li>• The venous thrombosis toxicity management section was modified to differentiate between symptomatic and asymptomatic grade 4 events.</li> <li>• The safety reporting procedures were expanded and clarified.</li> <li>• The time frame for the primary efficacy analysis was clarified.</li> <li>• The treatment effect statistical analyses were modified.</li> <li>• A description of the use of a peristaltic pump with an in-line filter for AMG 386 infusion was added for consistency with instructions in the Pharmacy Binder.</li> </ul> |
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Notes:

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## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported