



## Clinical trial results:

### A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Bevacizumab, and Associated Biomarkers, in Combination With Paclitaxel Compared With Paclitaxel Plus Placebo as First-Line Treatment of Patients With HER2-Negative Metastatic Breast Cancer

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2011-005335-97   |
| Trial protocol           | DE BE GB IT BG   |
| Global end of trial date | 21 November 2017 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 02 December 2018 |
| First version publication date | 29 April 2016    |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | GO25632 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01663727 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | F. Hoffmann-La Roche AG   |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070  |
| Public contact               | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |
| Scientific contact           | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.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                       | 21 November 2017 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 30 November 2014 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 21 November 2017 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy of bevacizumab + paclitaxel compared with placebo + paclitaxel as first-line treatment in participants with HER2-negative metastatic breast cancer (MBC) as measured by: - Progression-free survival (PFS) based on investigator tumor assessment in the intent-to-treat (ITT) participants population (co-primary endpoint). - PFS based on investigator tumor assessment in ITT participants with high baseline plasma VEGF-A levels (co-primary endpoint).

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP) according to the regulations and procedures. This study was conducted in accordance with GCP and investigators were trained according to applicable Sponsor Standard Operating Procedures.

Background therapy: -

Evidence for comparator: -

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

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 16          |
| Country: Number of subjects enrolled | Belgium: 24            |
| Country: Number of subjects enrolled | Bulgaria: 14           |
| Country: Number of subjects enrolled | Chile: 7               |
| Country: Number of subjects enrolled | Germany: 6             |
| Country: Number of subjects enrolled | Italy: 11              |
| Country: Number of subjects enrolled | Japan: 54              |
| Country: Number of subjects enrolled | Korea, Republic of: 38 |
| Country: Number of subjects enrolled | Panama: 28             |
| Country: Number of subjects enrolled | Romania: 27            |
| Country: Number of subjects enrolled | Russian Federation: 46 |
| Country: Number of subjects enrolled | South Africa: 16       |
| Country: Number of subjects enrolled | Ukraine: 57            |
| Country: Number of subjects enrolled | United Kingdom: 33     |
| Country: Number of subjects enrolled | United States: 104     |
| Worldwide total number of subjects   | 481                    |
| EEA total number of subjects         | 115                    |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 378 |
| From 65 to 84 years                       | 102 |
| 85 years and over                         | 1   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 596 participants were screened of whom 115 were screen failures and 481 participants were randomized.

### 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          |

### Arms

|                              |                    |
|------------------------------|--------------------|
| Are arms mutually exclusive? | Yes                |
| <b>Arm title</b>             | Paclitaxel+Placebo |

Arm description:

Participants received paclitaxel 90 mg/m<sup>2</sup> IV on Days 1, 8 and 15 and placebo matched to bevacizumab IV infusion on Days 1 and 15 of a 28 day cycle until progressive disease, treatment limiting toxicity or death.

|  |                                       |
|--|---------------------------------------|
| Arm type                               | Placebo                               |
| 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:

The dose of paclitaxel was based on the participant's weight at each administration.

|  |                                       |
|--|---------------------------------------|
| 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:

The placebo dose was based on the participant's most recent weight taken within 7 days of the first study drug dose (Cycle 1, Day 1) and remained the same throughout the study.

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | Paclitaxel+ Bevacizumab |
|------------------|-------------------------|

Arm description:

Participants received paclitaxel 90 mg/m<sup>2</sup> IV on Days 1, 8 and 15 and bevacizumab IV 10 mg/kg on Days 1 and 15 of a 28 day cycle until progressive disease, treatment limiting toxicity or death.

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

The bevacizumab dose was based on the participant's most recent weight taken within 7 days of the first study drug dose (Cycle 1, Day 1) and remained the same

throughout the study.

|  |                                       |
|--|---------------------------------------|
| 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:

The dose of paclitaxel was based on the participant's weight at each administration.

| <b>Number of subjects in period 1</b>     | Paclitaxel+Placebo | Paclitaxel+Bevacizumab |
|---|--------------------|------------------------|
| Started                                   | 242                | 239                    |
| Completed                                 | 0                  | 1                      |
| Not completed                             | 242                | 238                    |
| Consent withdrawn by subject              | 18                 | 25                     |
| Death                                     | 161                | 155                    |
| Withdrawal prior to dosing.               | 1                  | -                      |
| Participant Withdrawal and Adverse Event. | 1                  | -                      |
| Study Terminated                          | 51                 | 50                     |
| Lost to follow-up                         | 10                 | 8                      |

## Baseline characteristics

### Reporting groups

|   |                         |
|---|-------------------------|
| Reporting group title   | Paclitaxel+Placebo      |
| Reporting group description:<br>Participants received paclitaxel 90 mg/m <sup>2</sup> IV on Days 1, 8 and 15 and placebo matched to bevacizumab IV infusion on Days 1 and 15 of a 28 day cycle until progressive disease, treatment limiting toxicity or death. |                         |
| Reporting group title   | Paclitaxel+ Bevacizumab |
| Reporting group description:<br>Participants received paclitaxel 90 mg/m <sup>2</sup> IV on Days 1, 8 and 15 and bevacizumab IV 10 mg/kg on Days 1 and 15 of a 28 day cycle until progressive disease, treatment limiting toxicity or death.                    |                         |

| Reporting group values                             | Paclitaxel+Placebo | Paclitaxel+ Bevacizumab | Total |
|--|--------------------|-------------------------|-------|
| Number of subjects                                 | 242                | 239                     | 481   |
| Age categorical<br>Units: Subjects                 |                    |                         |       |
| In utero   | 0                  | 0                       | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0                  | 0                       | 0     |
| Newborns (0-27 days)                               | 0                  | 0                       | 0     |
| Infants and toddlers (28 days-23 months)           | 0                  | 0                       | 0     |
| Children (2-11 years)                              | 0                  | 0                       | 0     |
| Adolescents (12-17 years)                          | 0                  | 0                       | 0     |
| Adults (18-64 years)                               | 196                | 182                     | 378   |
| From 65-84 years                                   | 46                 | 56                      | 102   |
| 85 years and over                                  | 0                  | 1                       | 1     |
| Age Continuous<br>Units: years                     |                    |                         |       |
| arithmetic mean                                    | 54.7               | 55.8                    |       |
| standard deviation                                 | ± 10.7             | ± 11.5                  | -     |
| Sex: Female, Male<br>Units: Subjects               |                    |                         |       |
| Female   | 237                | 236                     | 473   |
| Male   | 5                  | 3                       | 8     |

## End points

### End points reporting groups

|   |                         |
|---|-------------------------|
| Reporting group title   | Paclitaxel+Placebo      |
| Reporting group description:<br>Participants received paclitaxel 90 mg/m <sup>2</sup> IV on Days 1, 8 and 15 and placebo matched to bevacizumab IV infusion on Days 1 and 15 of a 28 day cycle until progressive disease, treatment limiting toxicity or death. |                         |
| Reporting group title   | Paclitaxel+ Bevacizumab |
| Reporting group description:<br>Participants received paclitaxel 90 mg/m <sup>2</sup> IV on Days 1, 8 and 15 and bevacizumab IV 10 mg/kg on Days 1 and 15 of a 28 day cycle until progressive disease, treatment limiting toxicity or death.                    |                         |

### Primary: Percentage of participants with Progression or death in Intent-to-Treat (ITT) Population

|                 |   |
|-----------------|---|
| End point title | Percentage of participants with Progression or death in Intent-to-Treat (ITT) Population <sup>[1]</sup> |
|-----------------|---|

#### End point description:

Tumor assessment was performed as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) by investigator. Disease progression was defined as at least 20 percent (%) increase in the sum of diameters of target lesions compared to smallest sum of diameters on-study and absolute increase of at least 5 millimeter (mm), unequivocal progression of existing non-target lesions, or presence of new lesions. ITT population included all participants randomized to study treatment irrespective of whether the assigned treatment was actually received.

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

#### End point timeframe:

Baseline, every 8 weeks until documented disease progression, death or clinical cut-off (up to 117.7 weeks)

#### Notes:

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

Justification: The endpoint was qualitative in nature. Hence, no statistical analysis is provided.

| End point values                  | Paclitaxel+Placebo | Paclitaxel+Bevacizumab |  |  |
|-----------------------------------|--------------------|------------------------|--|--|
| Subject group type                | Reporting group    | Reporting group        |  |  |
| Number of subjects analysed       | 242                | 239                    |  |  |
| Units: percentage of participants |                    |                        |  |  |
| number (not applicable)           | 69.4               | 63.6                   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Progression free survival (PFS) in ITT Population

|                 |   |
|-----------------|---|
| End point title | Progression free survival (PFS) in ITT Population |
|-----------------|---|

#### End point description:

PFS was defined as the interval between the date of randomization and the first documentation of progressive disease or death from any cause. Tumor assessment was performed as per RECIST v1.1 by investigator. Disease progression was defined as at least 20% increase in the sum of diameters of target

lesions compared to smallest sum of diameters on-study and absolute increase of at least 5 mm, unequivocal progression of existing non-target lesions, or presence of new lesions. PFS was estimated using Kaplan Meier method. ITT population included all participants randomized to study treatment irrespective of whether the assigned treatment was actually received.

|   |         |
|---|---------|
| End point type  | Primary |
| End point timeframe:  |         |
| Baseline, every 8 weeks until documented disease progression, death or clinical cut-off (up to 117.7 weeks) |         |

| End point values                 | Paclitaxel+Placebo | Paclitaxel+Bevacizumab |  |  |
|----------------------------------|--------------------|------------------------|--|--|
| Subject group type               | Reporting group    | Reporting group        |  |  |
| Number of subjects analysed      | 242                | 239                    |  |  |
| Units: months                    |                    |                        |  |  |
| median (confidence interval 95%) | 8.8 (7.4 to 9.3)   | 11.0 (9.5 to 12.2)     |  |  |

## Statistical analyses

| Statistical analysis title  | Paclitaxel+Bevacizumab vs. Paclitaxel+Placebo |
|---|---|
| Statistical analysis description:   |   |
| Stratified analysis: Stratification factors were plasma VEGF-A level (low/high), prior adjuvant chemotherapy (yes/no) and estrogen receptor / progesterone receptor status (positive, negative). Hazards ratio was estimated by Cox regression. |   |
| Comparison groups   | Paclitaxel+ Bevacizumab v Paclitaxel+Placebo  |
| Number of subjects included in analysis   | 481   |
| Analysis specification  | Pre-specified                                 |
| Analysis type   | superiority                                   |
| P-value   | = 0.0007                                      |
| Method  | Logrank                                       |
| Parameter estimate  | Hazard ratio (HR)                             |
| Point estimate  | 0.68  |
| Confidence interval   |   |
| level   | Other: 99 %                                   |
| sides   | 2-sided                                       |
| lower limit   | 0.51  |
| upper limit   | 0.91  |

| Statistical analysis title  | Paclitaxel+ Bevacizumab vs. Paclitaxel+Placebo |
|---|--|
| Statistical analysis description:                                     |  |
| Unstratified Analysis. Hazards ratio was estimated by Cox regression. |  |
| Comparison groups   | Paclitaxel+Placebo v Paclitaxel+ Bevacizumab   |



|   |                   |
|---|-------------------|
| Number of subjects included in analysis | 481               |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | superiority       |
| P-value                                 | = 0.0046          |
| Method                                  | Logrank           |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 0.73              |
| Confidence interval                     |                   |
| level                                   | Other: 99 %       |
| sides                                   | 2-sided           |
| lower limit                             | 0.55              |
| upper limit                             | 0.97              |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Paclitaxel+ Bevacizumab vs. Paclitaxel+Placebo |
|-----------------------------------|--|

Statistical analysis description:

A stratified multivariate Cox regression model, including treatment, VEGF-A level, and interaction between treatment and VEGF-A level (low, high) as factors was used to estimate the interaction p-value of the treatment with VEGF-A level for PFS. Analysis for the interaction of treatment effect with the plasma VEGF-A levels was a secondary objective.

|   |  |
|---|--|
| Comparison groups                       | Paclitaxel+Placebo v Paclitaxel+ Bevacizumab |
| Number of subjects included in analysis | 481  |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | superiority                                  |
| P-value                                 | = 0.4619                                     |
| Method                                  | Wald Test                                    |

### **Primary: Percentage of participants with Progression or death in high baseline plasma vascular endothelial growth factor-A (VEGF-A) ITT population**

|                 |  |
|-----------------|--|
| End point title | Percentage of participants with Progression or death in high baseline plasma vascular endothelial growth factor-A (VEGF-A) ITT population <sup>[2]</sup> |
|-----------------|--|

End point description:

Tumor assessment was performed as per RECIST v1.1 by investigator. Disease progression was defined as at least 20% increase in the sum of diameters of target lesions compared to smallest sum of diameters on-study and absolute increase of at least 5 mm, unequivocal progression of existing non-target lesions, or presence of new lesions. High baseline plasma VEGF-A ITT population: All participants randomized to study treatment with high baseline plasma VEGF-A levels (VEGF-A levels greater than or equal to 5.05 picograms per milliliter), irrespective of whether the assigned treatment was actually received.

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

End point timeframe:

Baseline, every 8 weeks until documented disease progression, death or clinical cut-off (up to 111.3 weeks)

Notes:

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

Justification: The endpoint was qualitative in nature. Hence, no statistical analysis is provided.

| End point values                  | Paclitaxel+Placebo | Paclitaxel+Bevacizumab |  |  |
|-----------------------------------|--------------------|------------------------|--|--|
| Subject group type                | Reporting group    | Reporting group        |  |  |
| Number of subjects analysed       | 124                | 120                    |  |  |
| Units: percentage of participants |                    |                        |  |  |
| number (not applicable)           | 75.0               | 70.8                   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: PFS in high baseline plasma VEGF-A ITT population

|                 |   |
|-----------------|---|
| End point title | PFS in high baseline plasma VEGF-A ITT population |
|-----------------|---|

End point description:

PFS was defined as the interval between the date of randomization and the first documentation of progressive disease or death from any cause. Tumor assessment was performed as per RECIST v1.1 by investigator. Disease progression was defined as at least 20% increase in the sum of diameters of target lesions compared to smallest sum of diameters on-study and absolute increase of at least 5 mm, unequivocal progression of existing non-target lesions, or presence of new lesions. PFS was estimated using Kaplan Meier method.

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

End point timeframe:

Baseline, every 8 weeks until documented disease progression, death or clinical cut-off (up to 111.3 weeks)

| End point values                 | Paclitaxel+Placebo | Paclitaxel+Bevacizumab |  |  |
|----------------------------------|--------------------|------------------------|--|--|
| Subject group type               | Reporting group    | Reporting group        |  |  |
| Number of subjects analysed      | 124                | 120                    |  |  |
| Units: months                    |                    |                        |  |  |
| median (confidence interval 95%) | 7.3 (5.6 to 8.7)   | 9.6 (9.0 to 11.0)      |  |  |

## Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Paclitaxel+ Bevacizumab vs. Paclitaxel+Placebo |
|----------------------------|--|

Statistical analysis description:

Stratified analysis: Stratification factors were prior adjuvant chemotherapy (yes/no) and estrogen receptor / progesterone receptor status (positive, negative). Hazards ratio was estimated by Cox regression.

|                   |  |
|-------------------|--|
| Comparison groups | Paclitaxel+Placebo v Paclitaxel+ Bevacizumab |
|-------------------|--|

|   |                   |
|---|-------------------|
| Number of subjects included in analysis | 244               |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | superiority       |
| P-value                                 | = 0.0038          |
| Method                                  | Logrank           |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 0.64              |
| Confidence interval                     |                   |
| level                                   | Other: 96 %       |
| sides                                   | 2-sided           |
| lower limit                             | 0.47              |
| upper limit                             | 0.88              |

|   |  |
|---|--|
| <b>Statistical analysis title</b>                                     | Paclitaxel+ Bevacizumab vs. Paclitaxel+Placebo |
| Statistical analysis description:                                     |  |
| Unstratified analysis. Hazards ratio was estimated by Cox regression. |  |
| Comparison groups   | Paclitaxel+Placebo v Paclitaxel+ Bevacizumab   |
| Number of subjects included in analysis                               | 244  |
| Analysis specification  | Pre-specified                                  |
| Analysis type   | superiority                                    |
| P-value   | = 0.0101                                       |
| Method  | Logrank  |
| Parameter estimate  | Hazard ratio (HR)                              |
| Point estimate  | 0.68   |
| Confidence interval   |  |
| level   | Other: 96 %                                    |
| sides   | 2-sided  |
| lower limit   | 0.5  |
| upper limit   | 0.93   |

|  |  |
|--|--|
| <b>Secondary: Percentage of Participants Who Died - ITT population</b> |  |
| End point title  | Percentage of Participants Who Died - ITT population |
| End point description:   |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| From randomization till death or clinical cut-off (up to 244 weeks)    |  |

| End point values                  | Paclitaxel+Placebo | Paclitaxel+Bevacizumab |  |  |
|-----------------------------------|--------------------|------------------------|--|--|
| Subject group type                | Reporting group    | Reporting group        |  |  |
| Number of subjects analysed       | 242                | 239                    |  |  |
| Units: percentage of participants |                    |                        |  |  |
| number (not applicable)           | 64.9               | 64.0                   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Survival (OS) - ITT Population

|  |  |
|--|--|
| End point title  | Overall Survival (OS) - ITT Population |
| End point description:   |  |
| OS was defined as the interval between the date of randomization and death from any cause. OS was estimated using Kaplan Meier method. Analysis was performed on ITT population. |  |
| End point type   | Secondary                              |
| End point timeframe:   |  |
| From randomization till death or clinical cut-off (up to 244 weeks)  |  |

| End point values                 | Paclitaxel+Placebo  | Paclitaxel+Bevacizumab |  |  |
|----------------------------------|---------------------|------------------------|--|--|
| Subject group type               | Reporting group     | Reporting group        |  |  |
| Number of subjects analysed      | 242                 | 239                    |  |  |
| Units: months                    |                     |                        |  |  |
| median (confidence interval 95%) | 25.8 (21.8 to 30.2) | 28.8 (22.8 to 32.8)    |  |  |

## Statistical analyses

|  |  |
|--|--|
| Statistical analysis title   | Paclitaxel+ Bevacizumab vs. Paclitaxel+Placebo |
| Statistical analysis description:  |  |
| Stratified analysis: Stratification factors were plasma VEGF-A level (low/high), prior adjuvant chemotherapy (yes/no) and estrogen receptor / progesterone receptor status (positive, negative). |  |
| Comparison groups  | Paclitaxel+Placebo v Paclitaxel+ Bevacizumab   |
| Number of subjects included in analysis  | 481  |
| Analysis specification   | Pre-specified                                  |
| Analysis type  | superiority                                    |
| P-value  | = 0.5877                                       |
| Method   | Logrank  |
| Parameter estimate   | Hazard ratio (HR)                              |
| Point estimate   | 0.94   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.75    |
| upper limit         | 1.18    |

|   |  |
|---|--|
| <b>Statistical analysis title</b>                           | Paclitaxel+ Bevacizumab vs. Paclitaxel+Placebo |
| Statistical analysis description:<br>Unstratified analysis. |  |
| Comparison groups   | Paclitaxel+Placebo v Paclitaxel+ Bevacizumab   |
| Number of subjects included in analysis                     | 481  |
| Analysis specification                                      | Pre-specified                                  |
| Analysis type   | superiority                                    |
| P-value   | = 0.8004                                       |
| Method  | Logrank  |
| Parameter estimate  | Hazard ratio (HR)                              |
| Point estimate  | 0.97   |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | 0.78   |
| upper limit   | 1.21   |

## Secondary: Percentage of Participants Who Died - High Baseline Plasma VEGF-A ITT Population

|   |  |
|---|--|
| End point title   | Percentage of Participants Who Died - High Baseline Plasma VEGF-A ITT Population |
| End point description:<br>Analysis was performed on high baseline plasma VEGF-A ITT Population. |  |
| End point type  | Secondary  |
| End point timeframe:<br>From randomization till death or clinical cut-off (up to 244 weeks)     |  |

| End point values                  | Paclitaxel+Placebo | Paclitaxel+Bevacizumab |  |  |
|-----------------------------------|--------------------|------------------------|--|--|
| Subject group type                | Reporting group    | Reporting group        |  |  |
| Number of subjects analysed       | 124                | 120                    |  |  |
| Units: percentage of participants |                    |                        |  |  |
| number (not applicable)           | 74.2               | 71.1                   |  |  |

## Statistical analyses

**Secondary: OS - High Baseline Plasma VEGF-A ITT Population**

|  |   |
|--|---|
| End point title  | OS - High Baseline Plasma VEGF-A ITT Population |
| End point description:<br>OS was defined as the interval between the date of randomization and death from any cause. OS was estimated using Kaplan Meier method. |   |
| End point type   | Secondary                                       |
| End point timeframe:<br>From randomization till death or clinical cut-off (up to 244 weeks)  |   |

| End point values                 | Paclitaxel+Placebo  | Paclitaxel+Bevacizumab |  |  |
|----------------------------------|---------------------|------------------------|--|--|
| Subject group type               | Reporting group     | Reporting group        |  |  |
| Number of subjects analysed      | 124                 | 120                    |  |  |
| Units: months                    |                     |                        |  |  |
| median (confidence interval 95%) | 19.4 (16.5 to 25.0) | 22.8 (18.2 to 31.6)    |  |  |

**Statistical analyses**

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Paclitaxel+ Bevacizumab vs. Paclitaxel+Placebo |
| Statistical analysis description:<br>Stratified analysis: Stratification factors were prior adjuvant chemotherapy (yes/no) and estrogen receptor / progesterone receptor status (positive, negative). |  |
| Comparison groups   | Paclitaxel+Placebo v Paclitaxel+ Bevacizumab   |
| Number of subjects included in analysis   | 244  |
| Analysis specification  | Pre-specified                                  |
| Analysis type   | superiority                                    |
| P-value   | = 0.2745                                       |
| Method  | Logrank  |
| Parameter estimate  | Hazard ratio (HR)                              |
| Point estimate  | 0.85   |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | 0.63   |
| upper limit   | 1.14   |

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | Paclitaxel+ Bevacizumab vs. Paclitaxel+Placebo |
| Statistical analysis description:<br>Unstratified analysis. Hazards ratio was estimated by Cox regression. |  |
| Comparison groups  | Paclitaxel+Placebo v Paclitaxel+ Bevacizumab   |

|   |                   |
|---|-------------------|
| Number of subjects included in analysis | 244               |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | superiority       |
| P-value                                 | = 0.3616          |
| Method                                  | Logrank           |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 0.87              |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.65              |
| upper limit                             | 1.17              |

## Secondary: Percentage of Participants With an Objective Response - ITT population

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants With an Objective Response - ITT population |
|-----------------|--|

### End point description:

Objective response was defined as having a Complete Response (CR) or Partial Response (PR) according to a RECIST criteria v 1.1. CR was defined as disappearance of all target and non-target lesions and no new lesions, all pathological lymph nodes must have decreased to <10 mm in short axis and normalization of tumor marker level. PR was defined as at least a 30% decrease in the sum of diameters of target lesions (taking as reference the baseline sum diameters), no progression in non-target lesions, and no new lesions. Measurable disease was defined by the presence of at least one measurable lesion by clinical measurement, chest x-ray, computed tomography (CT), or magnetic resonance imaging (MRI). Number of participants analyzed=participants from ITT population with measurable disease at baseline.

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

### End point timeframe:

Baseline, every 8 weeks until documented disease progression, death or clinical cut-off (up to 117.7 weeks)

| End point values                  | Paclitaxel+Placebo    | Paclitaxel+Bevacizumab |  |  |
|-----------------------------------|-----------------------|------------------------|--|--|
| Subject group type                | Reporting group       | Reporting group        |  |  |
| Number of subjects analysed       | 214                   | 202                    |  |  |
| Units: percentage of participants |                       |                        |  |  |
| number (confidence interval 95%)  | 33.2 (26.87 to 39.49) | 54.0 (47.09 to 60.83)  |  |  |

## Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Paclitaxel+ Bevacizumab vs. Paclitaxel+Placebo |
| Comparison groups          | Paclitaxel+Placebo v Paclitaxel+ Bevacizumab   |

|   |                              |
|---|------------------------------|
| Number of subjects included in analysis | 416                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| P-value                                 | < 0.0001                     |
| Method                                  | Fisher                       |
| Parameter estimate                      | Difference in Response Rates |
| Point estimate                          | 20.78                        |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 11.45                        |
| upper limit                             | 30.11                        |

### Secondary: Percentage of Participants With an Objective Response - High Baseline Plasma VEGF-A ITT Population

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants With an Objective Response - High Baseline Plasma VEGF-A ITT Population |
|-----------------|--|

#### End point description:

Objective response was defined as having a CR or PR according to a RECIST criteria v 1.1. CR was defined as disappearance of all target and non-target lesions and no new lesions, all pathological lymph nodes must have decreased to <10 mm in short axis and normalization of tumor marker level. PR was defined as at least a 30% decrease in the sum of diameters of target lesions (taking as reference the baseline sum diameters), no progression in non-target lesions, and no new lesions. Measurable disease was defined by the presence of at least one measurable lesion by clinical measurement, chest x-ray, CT, or MRI. Number of participants analyzed=participants from high baseline plasma VEGF-A ITT population with measurable disease at baseline.

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

#### End point timeframe:

Baseline, every 8 weeks until documented disease progression, death or clinical cut-off (up to 111.3 weeks)

| End point values                  | Paclitaxel+Placebo    | Paclitaxel+Bevacizumab |  |  |
|-----------------------------------|-----------------------|------------------------|--|--|
| Subject group type                | Reporting group       | Reporting group        |  |  |
| Number of subjects analysed       | 116                   | 105                    |  |  |
| Units: percentage of participants |                       |                        |  |  |
| number (confidence interval 95%)  | 32.8 (24.22 to 41.30) | 54.3 (44.76 to 63.81)  |  |  |

### Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Paclitaxel+ Bevacizumab vs. Paclitaxel+Placebo |
| Comparison groups          | Paclitaxel+Placebo v Paclitaxel+ Bevacizumab   |



|   |                              |
|---|------------------------------|
| Number of subjects included in analysis | 221                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| P-value                                 | = 0.0017                     |
| Method                                  | Fisher                       |
| Parameter estimate                      | Difference in Response Rates |
| Point estimate                          | 21.53                        |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 8.73                         |
| upper limit                             | 34.32                        |

## Secondary: Duration of Response - ITT Population

|  |                                       |
|--|---------------------------------------|
| End point title  | Duration of Response - ITT Population |
| End point description:   |                                       |
| Duration of response was defined as the time from the initial date of the objective response to documented disease progression or death (whichever occurred first). Objective response was defined as having a CR or PR according to a RECIST criteria v 1.1. CR was defined as disappearance of all target and non-target lesions and no new lesions, all pathological lymph nodes must have decreased to <10 mm in short axis and normalization of tumor marker level. PR was defined as at least a 30% decrease in the sum of diameters of target lesions (taking as reference the baseline sum diameters), no progression in non-target lesions, and no new lesions. Disease progression was defined as at least 20% increase in the sum of diameters of target lesions compared to smallest sum of diameters on-study and absolute increase of at least 5 mm, unequivocal progression of existing non-target lesions, or presence of new lesions. Analysis was performed using Kaplan Meier method. |                                       |
| End point type   | Secondary                             |
| End point timeframe:   |                                       |
| Baseline, every 8 weeks until documented disease progression or clinical cut-off (up to 117.7 weeks)   |                                       |

| End point values                 | Paclitaxel+Placebo | Paclitaxel+Bevacizumab |  |  |
|----------------------------------|--------------------|------------------------|--|--|
| Subject group type               | Reporting group    | Reporting group        |  |  |
| Number of subjects analysed      | 71                 | 109                    |  |  |
| Units: months                    |                    |                        |  |  |
| median (confidence interval 95%) | 9.2 (7.4 to 11.5)  | 9.5 (7.8 to 12.4)      |  |  |

## Statistical analyses

|  |  |
|--|--|
| Statistical analysis title   | Paclitaxel+ Bevacizumab vs. Paclitaxel+Placebo |
| Statistical analysis description:  |  |
| Stratified analysis: Stratification factors were plasma VEGF-A level (low/high), prior adjuvant chemotherapy (yes/no) and estrogen receptor / progesterone receptor status (positive, negative). |  |
| Comparison groups  | Paclitaxel+Placebo v Paclitaxel+ Bevacizumab   |

|   |                   |
|---|-------------------|
| Number of subjects included in analysis | 180               |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | superiority       |
| P-value                                 | = 0.2737          |
| Method                                  | Logrank           |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 0.8               |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.54              |
| upper limit                             | 1.19              |

|   |  |
|---|--|
| <b>Statistical analysis title</b>                                     | Paclitaxel+ Bevacizumab vs. Paclitaxel+Placebo |
| Statistical analysis description:                                     |  |
| Unstratified analysis. Hazards ratio was estimated by Cox regression. |  |
| Comparison groups   | Paclitaxel+Placebo v Paclitaxel+ Bevacizumab   |
| Number of subjects included in analysis                               | 180  |
| Analysis specification  | Pre-specified                                  |
| Analysis type   | superiority                                    |
| P-value   | = 0.2959                                       |
| Method  | Logrank  |
| Parameter estimate  | Hazard ratio (HR)                              |
| Point estimate  | 0.82   |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | 0.56   |
| upper limit   | 1.19   |

## Secondary: Duration of Response - High Baseline Plasma VEGF-A ITT Population

|                 |   |
|-----------------|---|
| End point title | Duration of Response - High Baseline Plasma VEGF-A ITT Population |
|-----------------|---|

End point description:

Duration of response was defined as the time from the initial date of the objective response to documented disease progression or death (whichever occurred first). Objective response was defined as having a CR or PR according to a RECIST criteria v 1.1. CR was defined as disappearance of all target and non-target lesions and no new lesions, all pathological lymph nodes must have decreased to <10 mm in short axis and normalization of tumor marker level. PR was defined as at least a 30% decrease in the sum of diameters of target lesions (taking as reference the baseline sum diameters), no progression in non-target lesions, and no new lesions. Disease progression was defined at least 20% increase in the sum of diameters of target lesions compared to smallest sum of diameters on-study and absolute increase of at least 5 mm, unequivocal progression of existing non-target lesions, or presence of new lesions. Analysis was performed using Kaplan Meier method.

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

End point timeframe:

Baseline, every 8 weeks until documented disease progression or clinical cut-off (up to 111.3 weeks)

| <b>End point values</b>          | Paclitaxel+Placebo | Paclitaxel+Bevacizumab |  |  |
|----------------------------------|--------------------|------------------------|--|--|
| Subject group type               | Reporting group    | Reporting group        |  |  |
| Number of subjects analysed      | 38                 | 57                     |  |  |
| Units: months                    |                    |                        |  |  |
| median (confidence interval 95%) | 7.2 (5.6 to 9.5)   | 8.1 (7.1 to 11.1)      |  |  |

## Statistical analyses

| <b>Statistical analysis title</b>   | Paclitaxel+ Bevacizumab vs. Paclitaxel+Placebo |
|---|--|
| Statistical analysis description:   |  |
| Stratified analysis: Stratification factors were prior adjuvant chemotherapy (yes/no) and estrogen receptor / progesterone receptor status (positive, negative). Hazards ratio was estimated by Cox regression. |  |
| Comparison groups   | Paclitaxel+Placebo v Paclitaxel+ Bevacizumab   |
| Number of subjects included in analysis   | 95   |
| Analysis specification  | Pre-specified                                  |
| Analysis type   | superiority                                    |
| P-value   | = 0.1783                                       |
| Method  | Logrank  |
| Parameter estimate  | Hazard ratio (HR)                              |
| Point estimate  | 0.7  |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | 0.41   |
| upper limit   | 1.18   |

| <b>Statistical analysis title</b>                                     | Paclitaxel+ Bevacizumab vs. Paclitaxel+Placebo |
|---|--|
| Statistical analysis description:                                     |  |
| Unstratified analysis. Hazards ratio was estimated by Cox regression. |  |
| Comparison groups   | Paclitaxel+Placebo v Paclitaxel+ Bevacizumab   |
| Number of subjects included in analysis                               | 95   |
| Analysis specification  | Pre-specified                                  |
| Analysis type   | superiority                                    |
| P-value   | = 0.2429                                       |
| Method  | Logrank  |
| Parameter estimate  | Hazard ratio (HR)                              |
| Point estimate  | 0.74   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.45    |
| upper limit         | 1.22    |

### Secondary: Percentage of Participants Who were Alive at 1 Year - ITT Population

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants Who were Alive at 1 Year - ITT Population |
|-----------------|--|

End point description:

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

End point timeframe:

1 year

| End point values                  | Paclitaxel+Placebo | Paclitaxel+Bevacizumab |  |  |
|-----------------------------------|--------------------|------------------------|--|--|
| Subject group type                | Reporting group    | Reporting group        |  |  |
| Number of subjects analysed       | 242                | 239                    |  |  |
| Units: percentage of participants |                    |                        |  |  |
| number (not applicable)           | 80.94              | 82.47                  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Secondary: Percentage of Participants Who were Alive at 1 Year - High Baseline Plasma VEGF-A ITT Population

|                 |   |
|-----------------|---|
| End point title | Secondary: Percentage of Participants Who were Alive at 1 Year - High Baseline Plasma VEGF-A ITT Population |
|-----------------|---|

End point description:

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

End point timeframe:

1 year

| <b>End point values</b>           | Paclitaxel+Placebo | Paclitaxel+Bevacizumab |  |  |
|-----------------------------------|--------------------|------------------------|--|--|
| Subject group type                | Reporting group    | Reporting group        |  |  |
| Number of subjects analysed       | 124                | 120                    |  |  |
| Units: percentage of participants |                    |                        |  |  |
| number (not applicable)           | 69.27              | 80.96                  |  |  |

### Statistical analyses

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug through 30 days after the last dose of study drug or clinical cut-off (up to 115.1 weeks)

Adverse event reporting additional description:

Safety population: All randomized participants who received at least one full or partial dose of any component of the study treatment (bevacizumab, placebo, or paclitaxel).

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

### Reporting groups

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

Reporting group description:

Participants received paclitaxel 90 mg/m<sup>2</sup> IV on Days 1, 8 and 15 and placebo matched to bevacizumab IV infusion on Days 1 and 15 of a 28 day cycle until progressive disease, treatment limiting toxicity or death.

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

Reporting group description:

Participants received paclitaxel 90 mg/m<sup>2</sup> IV on Days 1, 8 and 15 and bevacizumab IV 10 mg/kg on Days 1 and 15 of a 28 day cycle until progressive disease, treatment limiting toxicity or death.

| Serious adverse events  | Paclitaxel+Placebo | Paclitaxel+ Bevacizumab |  |
|---|--------------------|-------------------------|--|
| Total subjects affected by serious adverse events                   |                    |                         |  |
| subjects affected / exposed   | 45 / 233 (19.31%)  | 66 / 238 (27.73%)       |  |
| number of deaths (all causes)                                       | 162                | 161                     |  |
| number of deaths resulting from adverse events                      |                    |                         |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                         |  |
| Cancer pain   |                    |                         |  |
| subjects affected / exposed   | 1 / 233 (0.43%)    | 0 / 238 (0.00%)         |  |
| occurrences causally related to treatment / all                     | 0 / 1              | 0 / 0                   |  |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 0                   |  |
| Gastric cancer  |                    |                         |  |
| subjects affected / exposed   | 1 / 233 (0.43%)    | 0 / 238 (0.00%)         |  |
| occurrences causally related to treatment / all                     | 1 / 1              | 0 / 0                   |  |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 0                   |  |
| Vascular disorders  |                    |                         |  |
| Aortic stenosis   |                    |                         |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Deep vein thrombosis                                 |                 |                 |  |
| subjects affected / exposed                          | 2 / 233 (0.86%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Embolism venous                                      |                 |                 |  |
| subjects affected / exposed                          | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Superior vena cava syndrome                          |                 |                 |  |
| subjects affected / exposed                          | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Venous thrombosis limb                               |                 |                 |  |
| subjects affected / exposed                          | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| ARTERIAL THROMBOSIS                                  |                 |                 |  |
| subjects affected / exposed                          | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Death  |                 |                 |  |
| subjects affected / exposed                          | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 1           |  |
| Asthenia   |                 |                 |  |
| subjects affected / exposed                          | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Influenza like illness                               |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mucosal inflammation                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Malaise   |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyrexia   |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sudden death                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| CATHETER SITE ERYTHEMA                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Immune system disorders                         |                 |                 |  |
| Drug hypersensitivity                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| ANAPHYLACTIC REACTION                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Bronchospasm                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleural effusion                                |                 |                 |  |
| subjects affected / exposed                     | 2 / 233 (0.86%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyspnoea  |                 |                 |  |
| subjects affected / exposed                     | 2 / 233 (0.86%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| Pneumonitis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumothorax                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary embolism                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 4 / 238 (1.68%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 4 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary oedema                                |                 |                 |  |
| subjects affected / exposed                     | 2 / 233 (0.86%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Urine output decreased                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural                |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| complications                                   |                 |                 |  |
| Femoral neck fracture                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Femur fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 2 / 238 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Humerus fracture                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 2 / 238 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hip fracture                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| ROAD TRAFFIC ACCIDENT                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| STERNAL FRACTURE                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| WOUND DEHISCENCE                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Left ventricular dysfunction                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| ACUTE CORONARY SYNDROME                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| CARDIAC FAILURE CONGESTIVE                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Cerebral ischaemia                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dementia  |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dizziness                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hemiparesis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Speech disorder                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal cord compression                         |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Loss of consciousness                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Syncope   |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 3 / 238 (1.26%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Anaemia   |                 |                 |  |
| subjects affected / exposed                     | 2 / 233 (0.86%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 2 / 3           | 3 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Leukopenia                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neutropenia                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Febrile neutropenia                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 4 / 238 (1.68%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 4 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eye disorders                                   |                 |                 |  |
| Optic nerve disorder                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Visual acuity reduced                           |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| CATARACT  |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Abdominal distension                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal pain                                  |                 |                 |  |
| subjects affected / exposed                     | 4 / 233 (1.72%) | 2 / 238 (0.84%) |  |
| occurrences causally related to treatment / all | 1 / 6           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colitis   |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Constipation                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diarrhoea                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 2 / 238 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Duodenal obstruction                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyspepsia                                       |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric ulcer                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enteritis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric varices haemorrhage                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric ulcer haemorrhage                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematochezia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nausea  |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 4 / 238 (1.68%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vomiting  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 3 / 233 (1.29%) | 4 / 238 (1.68%) |  |
| occurrences causally related to treatment / all | 2 / 3           | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Small intestinal obstruction                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Bile duct obstruction                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystitis acute                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystitis                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gallbladder pain                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic failure                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 3 / 238 (1.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 2 / 2           |  |
| Hyperbilirubinaemia                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Pain of skin                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin haemorrhage                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Cystitis haemorrhagic                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematuria                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Back pain                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 4 / 238 (1.68%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neck pain                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteonecrosis of jaw                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Abdominal wall abscess                          |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abscess   |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abscess limb                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Appendicitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 2 / 238 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 4 / 238 (1.68%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystitis infective                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colonic abscess                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cystitis  |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device related infection                        |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 233 (0.86%) | 3 / 238 (1.26%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device related sepsis                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Influenza                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 2 / 238 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung infection                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pharyngotonsillitis                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peritonitis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 3 / 233 (1.29%) | 4 / 238 (1.68%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Sepsis  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 233 (0.43%) | 2 / 238 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Septic shock                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia necrotising                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sepsis syndrome                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound infection bacterial                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 2 / 238 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infection                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| VIRAL INFECTION                                 |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| CATHETER SITE INFECTION                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| KLEBSIELLA SEPSIS                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| SOFT TISSUE INFECTION                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| URINARY TRACT INFECTION BACTERIAL               |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Decreased appetite                              |                 |                 |  |
| subjects affected / exposed                     | 2 / 233 (0.86%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Type 2 diabetes mellitus                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 233 (0.43%) | 0 / 238 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| HYPOKALAEMIA                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| HYPONATRAEMIA                                   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>LACTIC ACIDOSIS</b>                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 233 (0.00%) | 1 / 238 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                           | <b>Paclitaxel+Placebo</b> | <b>Paclitaxel+Bevacizumab</b> |  |
|---|---------------------------|-------------------------------|--|
| Total subjects affected by non-serious adverse events       |                           |                               |  |
| subjects affected / exposed                                 | 225 / 233 (96.57%)        | 230 / 238 (96.64%)            |  |
| <b>Vascular disorders</b>                                   |                           |                               |  |
| Hypertension  |                           |                               |  |
| subjects affected / exposed                                 | 30 / 233 (12.88%)         | 73 / 238 (30.67%)             |  |
| occurrences (all)   | 83                        | 109                           |  |
| Hot flush   |                           |                               |  |
| subjects affected / exposed                                 | 10 / 233 (4.29%)          | 15 / 238 (6.30%)              |  |
| occurrences (all)   | 30                        | 17                            |  |
| <b>General disorders and administration site conditions</b> |                           |                               |  |
| Asthenia  |                           |                               |  |
| subjects affected / exposed                                 | 36 / 233 (15.45%)         | 32 / 238 (13.45%)             |  |
| occurrences (all)   | 50                        | 62                            |  |
| Fatigue   |                           |                               |  |
| subjects affected / exposed                                 | 74 / 233 (31.76%)         | 88 / 238 (36.97%)             |  |
| occurrences (all)   | 123                       | 156                           |  |
| Pyrexia   |                           |                               |  |
| subjects affected / exposed                                 | 28 / 233 (12.02%)         | 34 / 238 (14.29%)             |  |
| occurrences (all)   | 37                        | 59                            |  |
| Oedema peripheral   |                           |                               |  |
| subjects affected / exposed                                 | 42 / 233 (18.03%)         | 41 / 238 (17.23%)             |  |
| occurrences (all)   | 57                        | 56                            |  |
| <b>Respiratory, thoracic and mediastinal disorders</b>      |                           |                               |  |

|                                      |                   |                   |  |
|--------------------------------------|-------------------|-------------------|--|
| Dyspnoea                             |                   |                   |  |
| subjects affected / exposed          | 30 / 233 (12.88%) | 33 / 238 (13.87%) |  |
| occurrences (all)                    | 33                | 41                |  |
| Cough                                |                   |                   |  |
| subjects affected / exposed          | 30 / 233 (12.88%) | 43 / 238 (18.07%) |  |
| occurrences (all)                    | 38                | 59                |  |
| Epistaxis                            |                   |                   |  |
| subjects affected / exposed          | 48 / 233 (20.60%) | 97 / 238 (40.76%) |  |
| occurrences (all)                    | 77                | 158               |  |
| Dysphonia                            |                   |                   |  |
| subjects affected / exposed          | 5 / 233 (2.15%)   | 19 / 238 (7.98%)  |  |
| occurrences (all)                    | 5                 | 24                |  |
| Oropharyngeal pain                   |                   |                   |  |
| subjects affected / exposed          | 14 / 233 (6.01%)  | 18 / 238 (7.56%)  |  |
| occurrences (all)                    | 15                | 23                |  |
| Rhinorrhoea                          |                   |                   |  |
| subjects affected / exposed          | 3 / 233 (1.29%)   | 20 / 238 (8.40%)  |  |
| occurrences (all)                    | 4                 | 26                |  |
| Psychiatric disorders                |                   |                   |  |
| Anxiety                              |                   |                   |  |
| subjects affected / exposed          | 15 / 233 (6.44%)  | 8 / 238 (3.36%)   |  |
| occurrences (all)                    | 15                | 8                 |  |
| Insomnia                             |                   |                   |  |
| subjects affected / exposed          | 20 / 233 (8.58%)  | 35 / 238 (14.71%) |  |
| occurrences (all)                    | 24                | 46                |  |
| Investigations                       |                   |                   |  |
| Aspartate aminotransferase increased |                   |                   |  |
| subjects affected / exposed          | 16 / 233 (6.87%)  | 21 / 238 (8.82%)  |  |
| occurrences (all)                    | 19                | 32                |  |
| Alanine aminotransferase increased   |                   |                   |  |
| subjects affected / exposed          | 17 / 233 (7.30%)  | 21 / 238 (8.82%)  |  |
| occurrences (all)                    | 21                | 37                |  |
| Neutrophil count decreased           |                   |                   |  |
| subjects affected / exposed          | 20 / 233 (8.58%)  | 15 / 238 (6.30%)  |  |
| occurrences (all)                    | 100               | 56                |  |
| White blood cell count decreased     |                   |                   |  |

|   |                          |                          |  |
|---|--------------------------|--------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                  | 16 / 233 (6.87%)<br>84   | 21 / 238 (8.82%)<br>87   |  |
| WEIGHT DECREASED<br>subjects affected / exposed<br>occurrences (all)              | 5 / 233 (2.15%)<br>5     | 12 / 238 (5.04%)<br>13   |  |
| Nervous system disorders  |                          |                          |  |
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)                     | 22 / 233 (9.44%)<br>24   | 33 / 238 (13.87%)<br>43  |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)                      | 44 / 233 (18.88%)<br>71  | 51 / 238 (21.43%)<br>85  |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                     | 24 / 233 (10.30%)<br>25  | 28 / 238 (11.76%)<br>33  |  |
| Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all)         | 50 / 233 (21.46%)<br>67  | 47 / 238 (19.75%)<br>72  |  |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)                  | 17 / 233 (7.30%)<br>21   | 12 / 238 (5.04%)<br>14   |  |
| Peripheral sensory neuropathy<br>subjects affected / exposed<br>occurrences (all) | 84 / 233 (36.05%)<br>107 | 92 / 238 (38.66%)<br>129 |  |
| Blood and lymphatic system disorders  |                          |                          |  |
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)                    | 14 / 233 (6.01%)<br>42   | 17 / 238 (7.14%)<br>41   |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)                       | 39 / 233 (16.74%)<br>82  | 39 / 238 (16.39%)<br>63  |  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)                   | 50 / 233 (21.46%)<br>124 | 77 / 238 (32.35%)<br>254 |  |
| Gastrointestinal disorders  |                          |                          |  |

|  |                    |                    |  |
|--|--------------------|--------------------|--|
| Abdominal pain                         |                    |                    |  |
| subjects affected / exposed            | 17 / 233 (7.30%)   | 20 / 238 (8.40%)   |  |
| occurrences (all)                      | 30                 | 27                 |  |
| Abdominal pain upper                   |                    |                    |  |
| subjects affected / exposed            | 13 / 233 (5.58%)   | 13 / 238 (5.46%)   |  |
| occurrences (all)                      | 14                 | 16                 |  |
| Diarrhoea                              |                    |                    |  |
| subjects affected / exposed            | 72 / 233 (30.90%)  | 88 / 238 (36.97%)  |  |
| occurrences (all)                      | 128                | 189                |  |
| Constipation                           |                    |                    |  |
| subjects affected / exposed            | 50 / 233 (21.46%)  | 67 / 238 (28.15%)  |  |
| occurrences (all)                      | 70                 | 108                |  |
| Dyspepsia                              |                    |                    |  |
| subjects affected / exposed            | 16 / 233 (6.87%)   | 23 / 238 (9.66%)   |  |
| occurrences (all)                      | 20                 | 40                 |  |
| Toothache                              |                    |                    |  |
| subjects affected / exposed            | 8 / 233 (3.43%)    | 15 / 238 (6.30%)   |  |
| occurrences (all)                      | 9                  | 16                 |  |
| Nausea                                 |                    |                    |  |
| subjects affected / exposed            | 75 / 233 (32.19%)  | 99 / 238 (41.60%)  |  |
| occurrences (all)                      | 205                | 310                |  |
| Stomatitis                             |                    |                    |  |
| subjects affected / exposed            | 26 / 233 (11.16%)  | 42 / 238 (17.65%)  |  |
| occurrences (all)                      | 35                 | 75                 |  |
| Vomiting                               |                    |                    |  |
| subjects affected / exposed            | 36 / 233 (15.45%)  | 47 / 238 (19.75%)  |  |
| occurrences (all)                      | 63                 | 96                 |  |
| Skin and subcutaneous tissue disorders |                    |                    |  |
| Alopecia                               |                    |                    |  |
| subjects affected / exposed            | 145 / 233 (62.23%) | 140 / 238 (58.82%) |  |
| occurrences (all)                      | 159                | 149                |  |
| Nail discolouration                    |                    |                    |  |
| subjects affected / exposed            | 18 / 233 (7.73%)   | 33 / 238 (13.87%)  |  |
| occurrences (all)                      | 18                 | 37                 |  |
| Nail disorder                          |                    |                    |  |



|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 13 / 233 (5.58%)  | 13 / 238 (5.46%)  |  |
| occurrences (all)                               | 13                | 14                |  |
| Dry skin  |                   |                   |  |
| subjects affected / exposed                     | 7 / 233 (3.00%)   | 18 / 238 (7.56%)  |  |
| occurrences (all)                               | 7                 | 20                |  |
| Onychomadesis                                   |                   |                   |  |
| subjects affected / exposed                     | 6 / 233 (2.58%)   | 15 / 238 (6.30%)  |  |
| occurrences (all)                               | 6                 | 17                |  |
| Pruritis  |                   |                   |  |
| subjects affected / exposed                     | 10 / 233 (4.29%)  | 15 / 238 (6.30%)  |  |
| occurrences (all)                               | 12                | 17                |  |
| Rash  |                   |                   |  |
| subjects affected / exposed                     | 31 / 233 (13.30%) | 58 / 238 (24.37%) |  |
| occurrences (all)                               | 36                | 113               |  |
| Renal and urinary disorders                     |                   |                   |  |
| Proteinuria                                     |                   |                   |  |
| subjects affected / exposed                     | 26 / 233 (11.16%) | 32 / 238 (13.45%) |  |
| occurrences (all)                               | 33                | 53                |  |
| Musculoskeletal and connective tissue disorders |                   |                   |  |
| Arthralgia                                      |                   |                   |  |
| subjects affected / exposed                     | 53 / 233 (22.75%) | 53 / 238 (22.27%) |  |
| occurrences (all)                               | 86                | 91                |  |
| Bone pain                                       |                   |                   |  |
| subjects affected / exposed                     | 20 / 233 (8.58%)  | 11 / 238 (4.62%)  |  |
| occurrences (all)                               | 32                | 17                |  |
| Pain in extremity                               |                   |                   |  |
| subjects affected / exposed                     | 21 / 233 (9.01%)  | 23 / 238 (9.66%)  |  |
| occurrences (all)                               | 23                | 32                |  |
| Back pain                                       |                   |                   |  |
| subjects affected / exposed                     | 31 / 233 (13.30%) | 26 / 238 (10.92%) |  |
| occurrences (all)                               | 42                | 32                |  |
| Myalgia   |                   |                   |  |
| subjects affected / exposed                     | 28 / 233 (12.02%) | 43 / 238 (18.07%) |  |
| occurrences (all)                               | 60                | 83                |  |
| NECK PAIN                                       |                   |                   |  |

|   |                         |                         |  |
|---|-------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                      | 3 / 233 (1.29%)<br>5    | 12 / 238 (5.04%)<br>13  |  |
| MUSCULOSKELETAL PAIN<br>subjects affected / exposed<br>occurrences (all)              | 5 / 233 (2.15%)<br>8    | 12 / 238 (5.04%)<br>14  |  |
| Infections and infestations   |                         |                         |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                   | 36 / 233 (15.45%)<br>65 | 24 / 238 (10.08%)<br>54 |  |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)                        | 12 / 233 (5.15%)<br>12  | 11 / 238 (4.62%)<br>14  |  |
| Paronychia<br>subjects affected / exposed<br>occurrences (all)                        | 7 / 233 (3.00%)<br>9    | 13 / 238 (5.46%)<br>13  |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 11 / 233 (4.72%)<br>14  | 25 / 238 (10.50%)<br>26 |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)           | 16 / 233 (6.87%)<br>22  | 35 / 238 (14.71%)<br>47 |  |
| SINUSITIS<br>subjects affected / exposed<br>occurrences (all)                         | 8 / 233 (3.43%)<br>12   | 12 / 238 (5.04%)<br>15  |  |
| Metabolism and nutrition disorders  |                         |                         |  |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)                      | 10 / 233 (4.29%)<br>13  | 15 / 238 (6.30%)<br>22  |  |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)                | 42 / 233 (18.03%)<br>65 | 55 / 238 (23.11%)<br>91 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 24 April 2012     | The protocol was amended to reflect the updated development plans for the VEGF-A assay. In Study GO25632, the IMPACT platform and assay was to be used to support participant enrollment while the new in vitro diagnostic (IVD) assay for clinical use was being developed and validated in parallel with the study. A bridging study was to be conducted to validate the newly developed IVD assay using the IMPACT measurements from Study BO17708 (AVADO) as a reference. - A list of possible VEGF-A testing sites was added in order to clarify which countries the samples might be sent to for VEGF-A testing. - To clarify treatment guidelines in that bevacizumab/placebo treatment could continue until disease progression in the event that paclitaxel was discontinued.  |
| 04 October 2012   | To clarify regarding contraceptive use and the designation of paclitaxel as a study drug. Paclitaxel specific exclusion criteria to reflect IMP designation. Thus, depending on local classification, paclitaxel could either be considered a NIMP or an IMP. - A section was added on the addition of an IRF to demonstrate, through a sensitivity analysis, the robustness of the investigator-determined PFS according to RECIST. - Modifications were made to the internal monitoring committee (replaced by the iDMC), with details of the periodic review of unblinded safety data.   |
| 18 October 2013   | The definition of the end of the study was amended to the date when 394 deaths in the ITT population have been observed. This follow-up OS analysis is expected to occur approximately 5.2 years after 326 progression-free survival events have occurred (i.e., approximately 6.5 years after the first participant was randomized). - An interaction test of treatment effect (PFS) with the VEGF-A level was included as a secondary endpoint. - Participants who were still receiving bevacizumab at the end of the study were to be offered participation in the Avastin Long-Term Extension study (AvaLTE. Protocol MO25757) if this study was approved in the participant's country. The objectives of Study MO25757 are to provide continued bevacizumab therapy as a single agent or in combination with an anti-cancer drug to participants with cancer who were previously enrolled in a bevacizumab study sponsored by F Hoffmann-La Roche Ltd. and Genentech Inc. and who derived benefit from the therapy administered. |
| 14 September 2015 | The protocol was amended to include an additional interim analysis for overall survival (OS) when the original projected number of events at the time of the primary progression free survival (PFS) analysis has been observed.  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported