



Clinical trial results:

A Randomised, Double Blind, Placebo Controlled, Multicentre Study to Evaluate the Efficacy and Safety of Bevacizumab in Combination With Docetaxel in Comparison With Docetaxel Plus Placebo, as First Line Treatment for Patients With HER2 Negative Metastatic and Locally Recurrent Breast Cancer.

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

| | |
|--------------------------|----------------------------|
| EudraCT number | 2005-003862-40 |
| Trial protocol | ES BE AT GB SE PT DE LT IT |
| Global end of trial date | 24 October 2013 |

Results information

| | |
|-----------------------------------|----------------------------------------------------------------------------------|
| Result version number | v2 (current) |
| This version publication date | 15 July 2016 |
| First version publication date | 07 August 2015 |
| Version creation reason | • Correction of full data set Data QC after the system unavailability period. |
| Summary attachment (see zip file) | BO17708_ClinicalTrials.gov receipt (BO17708_CTg results receipt_22Jul15_RF.pdf) |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | BO17708 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00333775 |
| 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. HoffmannLa Roche AG, F. HoffmannLa Roche AG, +41 616878333, global.trial_information@roche.com |
| Scientific contact | F. HoffmannLa Roche AG, F. HoffmannLa 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 | No |

| |
|--------------------------------|
| 1901/2006 apply to this trial? |
|--------------------------------|

Notes:

Results analysis stage

| | |
|------------------------------------------------------|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 24 October 2013 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|-----------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 24 October 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

This study evaluated the efficacy and safety of 2 doses of Avastin in combination with docetaxel, versus docetaxel plus placebo, in patients with metastatic HER2 negative breast cancer who were candidates for taxane-based chemotherapy but who had not received prior chemotherapy for metastatic disease. A total of 736 participants were enrolled between March 2006 and April 2007. The last-patient, last-visit was in October 2013.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

| | |
|-----------------------------------------------------------|---------------|
| Actual start date of recruitment | 15 March 2006 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy |
| Long term follow-up duration | 24 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Portugal: 6 |
| Country: Number of subjects enrolled | Spain: 60 |
| Country: Number of subjects enrolled | Sweden: 8 |
| Country: Number of subjects enrolled | United Kingdom: 35 |
| Country: Number of subjects enrolled | Austria: 31 |
| Country: Number of subjects enrolled | Belgium: 42 |
| Country: Number of subjects enrolled | France: 116 |
| Country: Number of subjects enrolled | Germany: 54 |
| Country: Number of subjects enrolled | Italy: 43 |
| Country: Number of subjects enrolled | Lithuania: 8 |
| Country: Number of subjects enrolled | Australia: 66 |
| Country: Number of subjects enrolled | Brazil: 33 |
| Country: Number of subjects enrolled | Canada: 71 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | China: 6 |
| Country: Number of subjects enrolled | Mexico: 18 |
| Country: Number of subjects enrolled | Netherlands: 9 |
| Country: Number of subjects enrolled | Panama: 3 |
| Country: Number of subjects enrolled | Poland: 34 |
| Country: Number of subjects enrolled | Romania: 14 |
| Country: Number of subjects enrolled | South Africa: 8 |
| Country: Number of subjects enrolled | Korea, Republic of: 39 |
| Country: Number of subjects enrolled | Switzerland: 3 |
| Country: Number of subjects enrolled | Taiwan: 10 |
| Country: Number of subjects enrolled | Thailand: 19 |
| Worldwide total number of subjects | 736 |
| EEA total number of subjects | 460 |

Notes:

Subjects enrolled per age group

| | |
|-------------------------------------------|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 609 |
| From 65 to 84 years | 127 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

21 participants randomized to the placebo group received bevacizumab 7.5 mg/kg (n=5) or 15.0 mg/kg (n=16). Disposition, baseline characteristics, and end points for these participants are reported according to randomization group; adverse events for these participants are reported according to treatment received.

Period 1

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

Arms

| | |
|------------------------------|----------------------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Docetaxel 100 mg/m ² plus placebo |

Arm description:

Participants received docetaxel 100 mg/m² intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received placebo to bevacizumab intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.

| | |
|----------------------------------------|-----------------------|
| Arm type | Control Arm |
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Emulsion for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Docetaxel was supplied in 2 vials, 1 containing docetaxel and 1 containing a solvent, for intravenous infusion.

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

Dosage and administration details:

Placebo to bevacizumab was supplied as a sterile liquid for intravenous infusion in single-use vials.

| | |
|------------------|------------------------------------------------------------|
| Arm title | Docetaxel 100 mg/m ² plus bevacizumab 7.5 mg/kg |
|------------------|------------------------------------------------------------|

Arm description:

Participants received docetaxel 100 mg/m² intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 7.5 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal

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

| | |
|----------------------------------------|-----------------------|
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Emulsion for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Docetaxel was supplied in 2 vials, 1 containing docetaxel and 1 containing a solvent, for intravenous infusion.

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

Dosage and administration details:

Bevacizumab was supplied as a sterile liquid for intravenous infusion in single-use vials.

| | |
|------------------|-------------------------------------------------------------|
| Arm title | Docetaxel 100 mg/m ² plus bevacizumab 15.0 mg/kg |
|------------------|-------------------------------------------------------------|

Arm description:

Participants received docetaxel 100 mg/m² intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 15.0 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.

| | |
|----------------------------------------|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Emulsion for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Docetaxel was supplied in 2 vials, 1 containing docetaxel and 1 containing a solvent, for intravenous infusion.

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

Dosage and administration details:

Bevacizumab was supplied as a sterile liquid for intravenous infusion in single-use vials.

| Number of subjects in period 1 | Docetaxel 100 mg/m ² plus placebo | Docetaxel 100 mg/m ² plus bevacizumab 7.5 mg/kg | Docetaxel 100 mg/m ² plus bevacizumab 15.0 mg/kg |
|---------------------------------|----------------------------------------------|------------------------------------------------------------|-------------------------------------------------------------|
| | | | |
| Started | 241 | 248 | 247 |
| Received Treatment | 238 | 247 | 245 |
| Completed | 0 | 0 | 0 |
| Not completed | 241 | 248 | 247 |
| Death | 144 | 149 | 143 |
| In follow-up when study stopped | 87 | 92 | 96 |
| Lost to follow-up | 10 | 7 | 8 |

Baseline characteristics

Reporting groups

| | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|
| Reporting group title | Docetaxel 100 mg/m ² plus placebo |
| Reporting group description: Participants received docetaxel 100 mg/m ² intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received placebo to bevacizumab intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal. | |
| Reporting group title | Docetaxel 100 mg/m ² plus bevacizumab 7.5 mg/kg |
| Reporting group description: Participants received docetaxel 100 mg/m ² intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 7.5 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal | |
| Reporting group title | Docetaxel 100 mg/m ² plus bevacizumab 15.0 mg/kg |
| Reporting group description: Participants received docetaxel 100 mg/m ² intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 15.0 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal. | |

| Reporting group values | Docetaxel 100 mg/m ² plus placebo | Docetaxel 100 mg/m ² plus bevacizumab 7.5 mg/kg | Docetaxel 100 mg/m ² plus bevacizumab 15.0 mg/kg |
|-------------------------------------------------------------------------|----------------------------------------------|------------------------------------------------------------|-------------------------------------------------------------|
| Number of subjects | 241 | 248 | 247 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 203 | 207 | 199 |
| From 65-84 years | 38 | 41 | 48 |
| Age continuous Units: years arithmetic mean standard deviation | 53.5 ± 10.47 | 53.9 ± 10.61 | 53.6 ± 10.78 |
| Gender categorical Units: Subjects | | | |
| Female | 241 | 248 | 247 |

| Reporting group values | Total | | |
|-------------------------------------------------------------------------|-------|--|--|
| Number of subjects | 736 | | |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 609 | | |
| From 65-84 years | 127 | | |
| Age continuous Units: years arithmetic mean standard deviation | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 736 | | |

End points

End points reporting groups

| | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|
| Reporting group title | Docetaxel 100 mg/m ² plus placebo |
| Reporting group description: Participants received docetaxel 100 mg/m ² intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received placebo to bevacizumab intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal. | |
| Reporting group title | Docetaxel 100 mg/m ² plus bevacizumab 7.5 mg/kg |
| Reporting group description: Participants received docetaxel 100 mg/m ² intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 7.5 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal | |
| Reporting group title | Docetaxel 100 mg/m ² plus bevacizumab 15.0 mg/kg |
| Reporting group description: Participants received docetaxel 100 mg/m ² intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 15.0 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal. | |

Primary: Progression-free Survival

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| End point title | Progression-free Survival |
| End point description: Progression-free survival was evaluated using Response Evaluation Criteria In Solid Tumors (RECIST 1.0). Progression-free survival was defined as the time from randomization to the time of the first documented disease progression or death, whichever occurred first. Disease progression was defined as $\geq 20\%$ increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since treatment started or the unequivocal progression of existing non-target lesions, or appearance of new lesion(s). | |
| Intent-to-treat population: All randomized participants, regardless of whether they received study drug or not. | |
| End point type | Primary |
| End point timeframe: Baseline to the 15 Sep 2008 cut-off date (up to 2 years, 6 months) | |

| End point values | Docetaxel 100 mg/m ² plus placebo | Docetaxel 100 mg/m ² plus bevacizumab 7.5 mg/kg | Docetaxel 100 mg/m ² plus bevacizumab 15.0 mg/kg | |
|----------------------------------|----------------------------------------------|------------------------------------------------------------|-------------------------------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 241 | 248 | 247 | |
| Units: months | | | | |
| median (confidence interval 95%) | 8 (7.2 to 8.3) | 8.7 (8.2 to 9.9) | 8.8 (8.4 to 10.2) | |

Statistical analyses

| | |
|-----------------------------------------|-----------------------------------------------------------------------------------------------------------|
| Statistical analysis title | Docetaxel 100 mg/m ² Plus Bevacizumab 7.5 mg/kg |
| Comparison groups | Docetaxel 100 mg/m ² plus bevacizumab 7.5 mg/kg v Docetaxel 100 mg/m ² plus placebo |
| Number of subjects included in analysis | 489 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0318 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.79 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.63 |
| upper limit | 0.98 |

| | |
|-----------------------------------------|------------------------------------------------------------------------------------------------------------|
| Statistical analysis title | Docetaxel 100 mg/m ² plus bevacizumab 15.0 mg/kg |
| Comparison groups | Docetaxel 100 mg/m ² plus bevacizumab 15.0 mg/kg v Docetaxel 100 mg/m ² plus placebo |
| Number of subjects included in analysis | 488 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0036 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.72 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.57 |
| upper limit | 0.9 |

Secondary: Percentage of Participants With a Complete Response or a Partial Response

| | |
|-----------------|---------------------------------------------------------------------------|
| End point title | Percentage of Participants With a Complete Response or a Partial Response |
|-----------------|---------------------------------------------------------------------------|

End point description:

Responses were evaluated using the Response Evaluation Criteria in Solid Tumors. A complete response was defined as the disappearance of all target lesions or the disappearance of all non-target lesions and normalization of tumor marker level. A partial response was defined as at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter.

Intent-to-treat population: All randomized participants, regardless of whether they received study drug or not. Only participants with measurable disease at Baseline were included in the analysis.

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

End point timeframe:

Baseline to the 15 Sep 2008 cut-off date (up to 2 years, 6 months)

| End point values | Docetaxel 100 mg/m ² plus placebo | Docetaxel 100 mg/m ² plus bevacizumab 7.5 mg/kg | Docetaxel 100 mg/m ² plus bevacizumab 15.0 mg/kg | |
|-----------------------------------|----------------------------------------------|------------------------------------------------------------|-------------------------------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 207 | 201 | 206 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Complete response | 1 (0.1 to 3.4) | 3 (1.1 to 6.4) | 1 (0.1 to 3.5) | |
| Partial response | 43.5 (36.6 to 50.5) | 52.2 (45.1 to 59.3) | 62.1 (55.1 to 68.8) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

| | |
|-----------------|----------------------|
| End point title | Duration of Response |
|-----------------|----------------------|

End point description:

Duration of response was defined as the time from the first documented complete response or partial response to disease progression or death. A complete response was defined as the disappearance of all target lesions or the disappearance of all non-target lesions and normalization of tumor marker level. A partial response was defined as at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter. Responses were evaluated using the Response Evaluation Criteria in Solid Tumors.

Intent-to-treat population: All randomized participants, regardless of whether they received study drug or not. Only participants with measurable disease at Baseline who had a complete response or a partial response were included in the analysis.

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

End point timeframe:

Baseline to the 15 September 2008 cut-off date (up to 2 years, 6 months)

| End point values | Docetaxel 100 mg/m ² plus placebo | Docetaxel 100 mg/m ² plus bevacizumab 7.5 mg/kg | Docetaxel 100 mg/m ² plus bevacizumab 15.0 mg/kg | |
|----------------------------------|----------------------------------------------|------------------------------------------------------------|-------------------------------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 92 ^[1] | 111 | 130 | |
| Units: months | | | | |
| median (confidence interval 95%) | 6.4 (5.8 to 6.9) | 7.2 (6.4 to 9.1) | 7 (6.4 to 8.5) | |

Notes:

[1] - Only participants with complete response or a partial response were included in the analysis.

Statistical analyses

Secondary: Time to Treatment Failure

| | |
|-----------------|---------------------------|
| End point title | Time to Treatment Failure |
|-----------------|---------------------------|

End point description:

Time to treatment failure was defined as time from randomization to the date of disease progression, death, or withdrawal of treatment due to an adverse event, withdrawal of informed consent, insufficient therapeutic response, refusal of treatment/failure to co-operate, or failure to return, whichever occurred first.

Intent-to-treat population: All randomized participants, regardless of whether they received study drug or not.

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

End point timeframe:

Baseline to the 15 September 2008 cut-off date (up to 2 years, 6 months)

| End point values | Docetaxel 100 mg/m ² plus placebo | Docetaxel 100 mg/m ² plus bevacizumab 7.5 mg/kg | Docetaxel 100 mg/m ² plus bevacizumab 15.0 mg/kg | |
|----------------------------------|----------------------------------------------|------------------------------------------------------------|-------------------------------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 241 | 248 | 247 | |
| Units: months | | | | |
| median (confidence interval 95%) | 6.1 (5.6 to 7) | 7 (6.1 to 7.7) | 7.7 (7.1 to 8) | |

Statistical analyses

| | |
|-----------------------------------------|-----------------------------------------------------------------------------------------------------------|
| Statistical analysis title | Docetaxel 100 mg/m ² Plus Bevacizumab 7.5 mg/kg |
| Comparison groups | Docetaxel 100 mg/m ² plus placebo v Docetaxel 100 mg/m ² plus bevacizumab 7.5 mg/kg |
| Number of subjects included in analysis | 489 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1105 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.69 |
| upper limit | 1.04 |

| | |
|-----------------------------------|-------------------------------------------------------------|
| Statistical analysis title | Docetaxel 100 mg/m ² Plus Bevacizumab 15.0 mg/kg |
|-----------------------------------|-------------------------------------------------------------|

| | |
|-----------------------------------------|------------------------------------------------------------------------------------------------------------|
| Comparison groups | Docetaxel 100 mg/m ² plus placebo v Docetaxel 100 mg/m ² plus bevacizumab 15.0 mg/kg |
| Number of subjects included in analysis | 488 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0241 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.79 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.65 |
| upper limit | 0.97 |

Secondary: Overall Survival

| | |
|-------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| End point title | Overall Survival |
| End point description: | |
| Overall survival was defined as the time from randomization to death from any cause. | |
| Intent-to-treat population: All randomized participants, regardless of whether they received study drug or not. | |
| 999 = Due to the low number of events, the median and lower and/or upper limits of the 95% confidence interval could not be reliably estimated. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to the 15 Sep 2008 cut-off date (up to 2 years, 6 months) | |

| End point values | Docetaxel 100 mg/m ² plus placebo | Docetaxel 100 mg/m ² plus bevacizumab 7.5 mg/kg | Docetaxel 100 mg/m ² plus bevacizumab 15.0 mg/kg | |
|----------------------------------|----------------------------------------------|------------------------------------------------------------|-------------------------------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 241 | 248 | 247 | |
| Units: months | | | | |
| median (confidence interval 95%) | 999 (999 to 999) | 999 (15.7 to 999) | 999 (14.9 to 999) | |

Statistical analyses

| | |
|----------------------------|-----------------------------------------------------------------------------------------------------------|
| Statistical analysis title | Docetaxel 100 mg/m ² Plus Bevacizumab 7.5 mg/kg |
| Comparison groups | Docetaxel 100 mg/m ² plus placebo v Docetaxel 100 mg/m ² plus bevacizumab 7.5 mg/kg |

| | |
|-----------------------------------------|-------------------|
| Number of subjects included in analysis | 489 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6962 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.62 |
| upper limit | 1.37 |

| | |
|-----------------------------------------|------------------------------------------------------------------------------------------------------------|
| Statistical analysis title | Docetaxel 100 mg/m ² Plus Bevacizumab 15.0 mg/kg |
| Comparison groups | Docetaxel 100 mg/m ² plus placebo v Docetaxel 100 mg/m ² plus bevacizumab 15.0 mg/kg |
| Number of subjects included in analysis | 488 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0765 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.68 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.45 |
| upper limit | 1.04 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to the 24 Oct 2013 cut-off date (up to and 21 day(s) after last dose)

Adverse event reporting additional description:

Safety population: All randomized participants exposed to study medication.

21 participants randomized to the placebo group received bevacizumab 7.5 mg/kg (n=5) or 15.0 mg/kg (n=16). Adverse events for these participants are reported according to treatment received.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 16.1 |

Reporting groups

| | |
|-----------------------|----------------------------------------------|
| Reporting group title | Docetaxel 100 mg/m ² plus placebo |
|-----------------------|----------------------------------------------|

Reporting group description:

Participants received docetaxel 100 mg/m² intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received placebo to bevacizumab intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.

| | |
|-----------------------|-------------------------------------------------------------|
| Reporting group title | Docetaxel 100 mg/m ² plus bevacizumab 15.0 mg/kg |
|-----------------------|-------------------------------------------------------------|

Reporting group description:

Participants received docetaxel 100 mg/m² intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 15.0 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.

| | |
|-----------------------|------------------------------------------------------------|
| Reporting group title | Docetaxel 100 mg/m ² plus bevacizumab 7.5 mg/kg |
|-----------------------|------------------------------------------------------------|

Reporting group description:

Participants received docetaxel 100 mg/m² intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 7.5 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.

| Serious adverse events | Docetaxel 100 mg/m ² plus placebo | Docetaxel 100 mg/m ² plus bevacizumab 15.0 mg/kg | Docetaxel 100 mg/m ² plus bevacizumab 7.5 mg/kg |
|---------------------------------------------------------------------|----------------------------------------------|-------------------------------------------------------------|------------------------------------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 82 / 217 (37.79%) | 120 / 261 (45.98%) | 106 / 252 (42.06%) |
| number of deaths (all causes) | 7 | 4 | 6 |
| number of deaths resulting from adverse events | 5 | 4 | 2 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Colon cancer | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Inflammatory carcinoma of the breast | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-hodgkin's lymphoma | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 2 / 261 (0.77%) | 2 / 252 (0.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 2 / 217 (0.92%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Microangiopathy | | | |
| subjects affected / exposed | 2 / 217 (0.92%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Embolism venous | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Flushing | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Jugular vein thrombosis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Phlebitis | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Venous thrombosis | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Central venous catheter removal | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vertebroplasty | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 217 (1.38%) | 7 / 261 (2.68%) | 6 / 252 (2.38%) |
| occurrences causally related to treatment / all | 2 / 3 | 6 / 9 | 3 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthenia | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 4 / 261 (1.53%) | 6 / 252 (2.38%) |
| occurrences causally related to treatment / all | 0 / 1 | 4 / 5 | 6 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 2 / 261 (0.77%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 2 / 217 (0.92%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 2 / 252 (0.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Catheter related complication | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Face oedema | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ill defined disorder | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Impaired healing | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inflammation | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multi-organ failure | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Oedema | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Hypersensitivity | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 217 (0.00%) | 2 / 261 (0.77%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine prolapse | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 217 (0.92%) | 3 / 261 (1.15%) | 3 / 252 (1.19%) |
| occurrences causally related to treatment / all | 4 / 4 | 2 / 3 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 3 / 261 (1.15%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 3 / 217 (1.38%) | 2 / 261 (0.77%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Pneumothorax | | | |
| subjects affected / exposed | 3 / 217 (1.38%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthmatic crisis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung disorder | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nasal septum ulceration | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mood altered | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 2 / 217 (0.92%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|-------------------------------------------------------------------------|-----------------|-----------------|-----------------|
| Dislocation of joint prosthesis subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Joint dislocation subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Narcotic intoxication subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Procedural complication subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal fracture subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound dehiscence subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wrist fracture subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders Atrial fibrillation subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arrhythmia | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arteriospasm coronary | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrioventricular block first degree | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachycardia paroxysmal | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 3 / 261 (1.15%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 3 / 252 (1.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorder | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Cauda equina syndrome | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Convulsion | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cranial nerve palsies multiple | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |

| | | | |
|-------------------------------------------------|------------------|-------------------|-------------------|
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Migraine | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 21 / 217 (9.68%) | 37 / 261 (14.18%) | 29 / 252 (11.51%) |
| occurrences causally related to treatment / all | 23 / 23 | 44 / 44 | 31 / 32 |
| deaths causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 4 / 217 (1.84%) | 18 / 261 (6.90%) | 13 / 252 (5.16%) |
| occurrences causally related to treatment / all | 4 / 4 | 18 / 19 | 14 / 14 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 3 / 252 (1.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaemia | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Visual acuity reduced | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vitreous detachment | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 217 (1.38%) | 8 / 261 (3.07%) | 6 / 252 (2.38%) |
| occurrences causally related to treatment / all | 2 / 4 | 5 / 8 | 4 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 217 (1.84%) | 2 / 261 (0.77%) | 3 / 252 (1.19%) |
| occurrences causally related to treatment / all | 2 / 4 | 2 / 2 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 4 / 261 (1.53%) | 3 / 252 (1.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 4 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 3 / 261 (1.15%) | 2 / 252 (0.79%) |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 3 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 2 / 261 (0.77%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 2 / 217 (0.92%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis erosive | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 2 / 252 (0.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Nausea | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 2 / 261 (0.77%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal fissure | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticular perforation | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enteritis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterocolitis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric perforation | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis haemorrhagic | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroduodenal ulcer | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal perforation | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Gastrointestinal ulcer | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal perforation | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine perforation | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Pancreatitis necrotising | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Biliary colic | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholangitis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic pain | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Hepatorenal failure | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Jaundice cholestatic | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Skin toxicity | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stevens–Johnson syndrome | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Renal colic | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 2 / 261 (0.77%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Back pain | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Infection | | | |
| subjects affected / exposed | 5 / 217 (2.30%) | 2 / 261 (0.77%) | 3 / 252 (1.19%) |
| occurrences causally related to treatment / all | 5 / 5 | 1 / 2 | 2 / 3 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 2 / 217 (0.92%) | 2 / 261 (0.77%) | 3 / 252 (1.19%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 4 / 217 (1.84%) | 1 / 261 (0.38%) | 2 / 252 (0.79%) |
| occurrences causally related to treatment / all | 2 / 4 | 1 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenic infection | | | |
| subjects affected / exposed | 2 / 217 (0.92%) | 1 / 261 (0.38%) | 2 / 252 (0.79%) |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal abscess | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 217 (0.00%) | 2 / 261 (0.77%) | 2 / 252 (0.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Central line infection | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 2 / 261 (0.77%) | 2 / 252 (0.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 3 / 252 (1.19%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 2 / 261 (0.77%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridial infection | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paronychia | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 2 / 261 (0.77%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative wound infection | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 217 (0.92%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 2 / 252 (0.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal infection | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anorectal infection | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis perforated | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis infective | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacterial sepsis | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast abscess | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Catheter bacteraemia | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Catheter related infection | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Catheter sepsis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endophthalmitis | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis viral | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung abscess | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung infection | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nail bed infection | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Periodontal infection | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonsillar abscess | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Purulent discharge | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stent related infection | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound infection | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 3 / 252 (1.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypercalcaemia | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 217 (0.92%) | 1 / 261 (0.38%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 0 / 261 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fluid retention | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 261 (0.38%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Docetaxel 100 mg/m ² plus placebo | Docetaxel 100 mg/m ² plus bevacizumab 15.0 mg/kg | Docetaxel 100 mg/m ² plus bevacizumab 7.5 mg/kg |
|-------------------------------------------------------|----------------------------------------------|-------------------------------------------------------------|------------------------------------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 216 / 217 (99.54%) | 260 / 261 (99.62%) | 251 / 252 (99.60%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 32 / 217 (14.75%) | 66 / 261 (25.29%) | 44 / 252 (17.46%) |
| occurrences (all) | 41 | 88 | 60 |

| | | | |
|------------------------------------------------------|-------------------|--------------------|--------------------|
| Hot flush | | | |
| subjects affected / exposed | 16 / 217 (7.37%) | 19 / 261 (7.28%) | 16 / 252 (6.35%) |
| occurrences (all) | 21 | 23 | 16 |
| Flushing | | | |
| subjects affected / exposed | 12 / 217 (5.53%) | 19 / 261 (7.28%) | 15 / 252 (5.95%) |
| occurrences (all) | 20 | 44 | 42 |
| Lymphoedema | | | |
| subjects affected / exposed | 15 / 217 (6.91%) | 8 / 261 (3.07%) | 19 / 252 (7.54%) |
| occurrences (all) | 16 | 13 | 20 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 96 / 217 (44.24%) | 109 / 261 (41.76%) | 105 / 252 (41.67%) |
| occurrences (all) | 186 | 226 | 213 |
| Asthenia | | | |
| subjects affected / exposed | 83 / 217 (38.25%) | 97 / 261 (37.16%) | 88 / 252 (34.92%) |
| occurrences (all) | 173 | 202 | 183 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 48 / 217 (22.12%) | 78 / 261 (29.89%) | 87 / 252 (34.52%) |
| occurrences (all) | 72 | 135 | 171 |
| Oedema peripheral | | | |
| subjects affected / exposed | 89 / 217 (41.01%) | 61 / 261 (23.37%) | 63 / 252 (25.00%) |
| occurrences (all) | 122 | 73 | 84 |
| Pyrexia | | | |
| subjects affected / exposed | 45 / 217 (20.74%) | 63 / 261 (24.14%) | 61 / 252 (24.21%) |
| occurrences (all) | 64 | 87 | 98 |
| Oedema | | | |
| subjects affected / exposed | 32 / 217 (14.75%) | 21 / 261 (8.05%) | 12 / 252 (4.76%) |
| occurrences (all) | 34 | 23 | 13 |
| Pain | | | |
| subjects affected / exposed | 20 / 217 (9.22%) | 16 / 261 (6.13%) | 16 / 252 (6.35%) |
| occurrences (all) | 20 | 18 | 19 |
| Chest pain | | | |
| subjects affected / exposed | 19 / 217 (8.76%) | 20 / 261 (7.66%) | 10 / 252 (3.97%) |
| occurrences (all) | 23 | 22 | 10 |
| Malaise | | | |

| | | | |
|--------------------------------------------------|----------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 6 / 217 (2.76%) 8 | 15 / 261 (5.75%) 15 | 10 / 252 (3.97%) 12 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Epistaxis | | | |
| subjects affected / exposed | 47 / 217 (21.66%) | 128 / 261 (49.04%) | 123 / 252 (48.81%) |
| occurrences (all) | 81 | 302 | 287 |
| Cough | | | |
| subjects affected / exposed | 42 / 217 (19.35%) | 61 / 261 (23.37%) | 67 / 252 (26.59%) |
| occurrences (all) | 59 | 83 | 84 |
| Dyspnoea | | | |
| subjects affected / exposed | 49 / 217 (22.58%) | 60 / 261 (22.99%) | 44 / 252 (17.46%) |
| occurrences (all) | 57 | 70 | 58 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 19 / 217 (8.76%) | 38 / 261 (14.56%) | 26 / 252 (10.32%) |
| occurrences (all) | 37 | 54 | 40 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 19 / 217 (8.76%) | 28 / 261 (10.73%) | 27 / 252 (10.71%) |
| occurrences (all) | 26 | 38 | 40 |
| Dysphonia | | | |
| subjects affected / exposed | 10 / 217 (4.61%) | 28 / 261 (10.73%) | 24 / 252 (9.52%) |
| occurrences (all) | 25 | 32 | 47 |
| Pleural effusion | | | |
| subjects affected / exposed | 13 / 217 (5.99%) | 17 / 261 (6.51%) | 10 / 252 (3.97%) |
| occurrences (all) | 13 | 18 | 10 |
| Nasal dryness | | | |
| subjects affected / exposed | 3 / 217 (1.38%) | 12 / 261 (4.60%) | 13 / 252 (5.16%) |
| occurrences (all) | 4 | 14 | 22 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 34 / 217 (15.67%) | 35 / 261 (13.41%) | 31 / 252 (12.30%) |
| occurrences (all) | 44 | 50 | 38 |
| Depression | | | |
| subjects affected / exposed | 11 / 217 (5.07%) | 13 / 261 (4.98%) | 13 / 252 (5.16%) |
| occurrences (all) | 12 | 14 | 14 |
| Anxiety | | | |

| | | | |
|--------------------------------------------------|-----------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 8 / 217 (3.69%) 11 | 16 / 261 (6.13%) 20 | 11 / 252 (4.37%) 11 |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 12 / 217 (5.53%) | 30 / 261 (11.49%) | 29 / 252 (11.51%) |
| occurrences (all) | 12 | 31 | 30 |
| Weight increased | | | |
| subjects affected / exposed | 16 / 217 (7.37%) | 7 / 261 (2.68%) | 5 / 252 (1.98%) |
| occurrences (all) | 17 | 7 | 6 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 56 / 217 (25.81%) | 79 / 261 (30.27%) | 86 / 252 (34.13%) |
| occurrences (all) | 113 | 183 | 198 |
| Dysgeusia | | | |
| subjects affected / exposed | 59 / 217 (27.19%) | 63 / 261 (24.14%) | 77 / 252 (30.56%) |
| occurrences (all) | 89 | 99 | 120 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 60 / 217 (27.65%) | 63 / 261 (24.14%) | 67 / 252 (26.59%) |
| occurrences (all) | 78 | 78 | 90 |
| Paraesthesia | | | |
| subjects affected / exposed | 40 / 217 (18.43%) | 51 / 261 (19.54%) | 46 / 252 (18.25%) |
| occurrences (all) | 45 | 64 | 71 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 30 / 217 (13.82%) | 26 / 261 (9.96%) | 35 / 252 (13.89%) |
| occurrences (all) | 37 | 33 | 44 |
| Dizziness | | | |
| subjects affected / exposed | 25 / 217 (11.52%) | 31 / 261 (11.88%) | 26 / 252 (10.32%) |
| occurrences (all) | 34 | 50 | 35 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 11 / 217 (5.07%) | 6 / 261 (2.30%) | 2 / 252 (0.79%) |
| occurrences (all) | 14 | 10 | 2 |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 44 / 217 (20.28%) | 53 / 261 (20.31%) | 51 / 252 (20.24%) |
| occurrences (all) | 102 | 118 | 114 |
| Anaemia | | | |

| | | | |
|---------------------------------------------------------------------------------------------|---------------------------|---------------------------|---------------------------|
| subjects affected / exposed occurrences (all) | 37 / 217 (17.05%) 46 | 32 / 261 (12.26%) 45 | 34 / 252 (13.49%) 47 |
| Leukopenia subjects affected / exposed occurrences (all) | 14 / 217 (6.45%) 23 | 20 / 261 (7.66%) 33 | 21 / 252 (8.33%) 38 |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 10 / 217 (4.61%) 11 | 15 / 261 (5.75%) 19 | 11 / 252 (4.37%) 13 |
| Eye disorders Lacrimation increased subjects affected / exposed occurrences (all) | 63 / 217 (29.03%) 78 | 120 / 261 (45.98%) 149 | 114 / 252 (45.24%) 141 |
| Conjunctivitis subjects affected / exposed occurrences (all) | 11 / 217 (5.07%) 13 | 39 / 261 (14.94%) 43 | 16 / 252 (6.35%) 18 |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) | 106 / 217 (48.85%) 206 | 140 / 261 (53.64%) 345 | 143 / 252 (56.75%) 339 |
| Nausea subjects affected / exposed occurrences (all) | 117 / 217 (53.92%) 243 | 132 / 261 (50.57%) 299 | 115 / 252 (45.63%) 265 |
| Stomatitis subjects affected / exposed occurrences (all) | 60 / 217 (27.65%) 112 | 115 / 261 (44.06%) 282 | 127 / 252 (50.40%) 294 |
| Constipation subjects affected / exposed occurrences (all) | 64 / 217 (29.49%) 117 | 77 / 261 (29.50%) 124 | 89 / 252 (35.32%) 195 |
| Vomiting subjects affected / exposed occurrences (all) | 59 / 217 (27.19%) 88 | 75 / 261 (28.74%) 142 | 64 / 252 (25.40%) 135 |
| Abdominal pain subjects affected / exposed occurrences (all) | 39 / 217 (17.97%) 58 | 58 / 261 (22.22%) 101 | 45 / 252 (17.86%) 84 |
| Dyspepsia | | | |

| | | | |
|---------------------------------------------|--------------------|--------------------|--------------------|
| subjects affected / exposed | 27 / 217 (12.44%) | 43 / 261 (16.48%) | 36 / 252 (14.29%) |
| occurrences (all) | 37 | 74 | 56 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 34 / 217 (15.67%) | 32 / 261 (12.26%) | 24 / 252 (9.52%) |
| occurrences (all) | 43 | 39 | 29 |
| Haemorrhoids | | | |
| subjects affected / exposed | 14 / 217 (6.45%) | 22 / 261 (8.43%) | 22 / 252 (8.73%) |
| occurrences (all) | 16 | 35 | 31 |
| Toothache | | | |
| subjects affected / exposed | 13 / 217 (5.99%) | 14 / 261 (5.36%) | 13 / 252 (5.16%) |
| occurrences (all) | 13 | 16 | 15 |
| Dysphagia | | | |
| subjects affected / exposed | 12 / 217 (5.53%) | 13 / 261 (4.98%) | 13 / 252 (5.16%) |
| occurrences (all) | 36 | 26 | 26 |
| Dry mouth | | | |
| subjects affected / exposed | 8 / 217 (3.69%) | 12 / 261 (4.60%) | 15 / 252 (5.95%) |
| occurrences (all) | 10 | 15 | 19 |
| Gingivitis | | | |
| subjects affected / exposed | 4 / 217 (1.84%) | 16 / 261 (6.13%) | 11 / 252 (4.37%) |
| occurrences (all) | 8 | 19 | 14 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 154 / 217 (70.97%) | 183 / 261 (70.11%) | 181 / 252 (71.83%) |
| occurrences (all) | 157 | 192 | 189 |
| Nail disorder | | | |
| subjects affected / exposed | 87 / 217 (40.09%) | 118 / 261 (45.21%) | 118 / 252 (46.83%) |
| occurrences (all) | 93 | 125 | 127 |
| Palmar–plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 47 / 217 (21.66%) | 70 / 261 (26.82%) | 80 / 252 (31.75%) |
| occurrences (all) | 58 | 103 | 116 |
| Rash | | | |
| subjects affected / exposed | 43 / 217 (19.82%) | 47 / 261 (18.01%) | 43 / 252 (17.06%) |
| occurrences (all) | 61 | 90 | 58 |
| Dry skin | | | |

| | | | |
|-------------------------------------------------|-------------------|-------------------|-------------------|
| subjects affected / exposed | 32 / 217 (14.75%) | 25 / 261 (9.58%) | 33 / 252 (13.10%) |
| occurrences (all) | 34 | 29 | 34 |
| Erythema | | | |
| subjects affected / exposed | 20 / 217 (9.22%) | 33 / 261 (12.64%) | 26 / 252 (10.32%) |
| occurrences (all) | 45 | 63 | 64 |
| Pruritus | | | |
| subjects affected / exposed | 19 / 217 (8.76%) | 23 / 261 (8.81%) | 28 / 252 (11.11%) |
| occurrences (all) | 28 | 29 | 39 |
| Onycholysis | | | |
| subjects affected / exposed | 9 / 217 (4.15%) | 25 / 261 (9.58%) | 21 / 252 (8.33%) |
| occurrences (all) | 9 | 26 | 21 |
| Skin exfoliation | | | |
| subjects affected / exposed | 11 / 217 (5.07%) | 20 / 261 (7.66%) | 21 / 252 (8.33%) |
| occurrences (all) | 15 | 31 | 25 |
| Nail toxicity | | | |
| subjects affected / exposed | 15 / 217 (6.91%) | 12 / 261 (4.60%) | 16 / 252 (6.35%) |
| occurrences (all) | 15 | 12 | 16 |
| Skin hyperpigmentation | | | |
| subjects affected / exposed | 8 / 217 (3.69%) | 10 / 261 (3.83%) | 14 / 252 (5.56%) |
| occurrences (all) | 9 | 10 | 18 |
| Renal and urinary disorders | | | |
| Proteinuria | | | |
| subjects affected / exposed | 8 / 217 (3.69%) | 24 / 261 (9.20%) | 12 / 252 (4.76%) |
| occurrences (all) | 10 | 38 | 15 |
| Musculoskeletal and connective tissue disorders | | | |
| Myalgia | | | |
| subjects affected / exposed | 80 / 217 (36.87%) | 88 / 261 (33.72%) | 82 / 252 (32.54%) |
| occurrences (all) | 199 | 181 | 195 |
| Arthralgia | | | |
| subjects affected / exposed | 48 / 217 (22.12%) | 90 / 261 (34.48%) | 74 / 252 (29.37%) |
| occurrences (all) | 92 | 137 | 155 |
| Pain in extremity | | | |
| subjects affected / exposed | 37 / 217 (17.05%) | 44 / 261 (16.86%) | 56 / 252 (22.22%) |
| occurrences (all) | 54 | 69 | 96 |
| Back pain | | | |

| | | | |
|-----------------------------------|-------------------|-------------------|-------------------|
| subjects affected / exposed | 45 / 217 (20.74%) | 44 / 261 (16.86%) | 36 / 252 (14.29%) |
| occurrences (all) | 54 | 51 | 48 |
| Bone pain | | | |
| subjects affected / exposed | 38 / 217 (17.51%) | 42 / 261 (16.09%) | 35 / 252 (13.89%) |
| occurrences (all) | 47 | 65 | 58 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 23 / 217 (10.60%) | 36 / 261 (13.79%) | 34 / 252 (13.49%) |
| occurrences (all) | 30 | 57 | 53 |
| Neck pain | | | |
| subjects affected / exposed | 8 / 217 (3.69%) | 17 / 261 (6.51%) | 14 / 252 (5.56%) |
| occurrences (all) | 9 | 21 | 17 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 13 / 217 (5.99%) | 12 / 261 (4.60%) | 12 / 252 (4.76%) |
| occurrences (all) | 14 | 12 | 14 |
| Muscular weakness | | | |
| subjects affected / exposed | 9 / 217 (4.15%) | 9 / 261 (3.45%) | 16 / 252 (6.35%) |
| occurrences (all) | 9 | 10 | 17 |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 23 / 217 (10.60%) | 28 / 261 (10.73%) | 22 / 252 (8.73%) |
| occurrences (all) | 33 | 42 | 29 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 14 / 217 (6.45%) | 35 / 261 (13.41%) | 20 / 252 (7.94%) |
| occurrences (all) | 21 | 49 | 34 |
| Urinary tract infection | | | |
| subjects affected / exposed | 18 / 217 (8.29%) | 20 / 261 (7.66%) | 27 / 252 (10.71%) |
| occurrences (all) | 26 | 30 | 32 |
| Influenza | | | |
| subjects affected / exposed | 12 / 217 (5.53%) | 15 / 261 (5.75%) | 26 / 252 (10.32%) |
| occurrences (all) | 18 | 20 | 43 |
| Rhinitis | | | |
| subjects affected / exposed | 9 / 217 (4.15%) | 18 / 261 (6.90%) | 11 / 252 (4.37%) |
| occurrences (all) | 9 | 23 | 15 |
| Sinusitis | | | |
| subjects affected / exposed | 8 / 217 (3.69%) | 19 / 261 (7.28%) | 10 / 252 (3.97%) |
| occurrences (all) | 8 | 25 | 11 |

| | | | |
|------------------------------------|-------------------|-------------------|-------------------|
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 58 / 217 (26.73%) | 85 / 261 (32.57%) | 78 / 252 (30.95%) |
| occurrences (all) | 97 | 133 | 132 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 10 May 2006 | <p>The following changes were made to the protocol at the request of the Paul Ehrlich Institute, Germany:</p> <ul style="list-style-type: none">– Investigators were provided with a retrospective analysis of the bleeding risk of full dose anti-coagulated patients receiving bevacizumab.– Investigators were provided with a clear definition of full dose anticoagulation.– ensured that full dose anti-coagulated patients were within the therapeutic ranges and data was collected on the stability of full dose anti-coagulation therapy at baseline or once initiated during study treatment.– Guidance provided on treatment of patients receiving full dose anti-coagulation who suffered from a bleeding event medication.– The 20 patients receiving full dose anti-coagulation to be followed by DSMB were better defined.– for Germany, it was required that patients must have received prior treatment with anthracyclines or alkylating agents in the neo/adjuvant setting.• Text was added that appropriate diagnostic and therapeutic medical treatment including accurate antihypertensive treatment was mandatory for patients developing signs and symptoms of Reversible Posterior Leukoencephalopathy Syndrome• The study title was changed to reflect the study patient population since not only metastatic breast cancer patients were allowed but also locally recurrent breast cancer patients.• The schedule of assessments was changed to accommodate the changes requested by the Paul Ehrlich Institute• The footnotes to Table 2 - were updated• Protocol text was changed to include patients who had received prior neoadjuvant chemotherapy and radiotherapy as this was allowed in addition to patients who had received prior adjuvant chemotherapy and radiotherapy.• Text on study drug management was modified to allow the site to destroy the trial drugs after being used.• The informed consent was updated |
| 19 September 2006 | <ul style="list-style-type: none">• A washout period for hormone therapy was included in order to reflect the situation of a patient on endocrine treatment as part of an adjuvant treatment. The washout period was reduced from three weeks to two weeks in order to appreciate the fact that such a long treatment interruption may be inappropriate for patients.• Upon the recommendation of DSMB, text on the use of prophylactic antibiotics during Cycle 1 of docetaxel administration for febrile neutropenia prevention was added, and text was added in case of specific chemotherapy adverse event occurrences.• Typographical errors were corrected.• Missing sample procedures following protocol amendment B for patient management of patients on full-dose anticoagulant treatment at study entry was added, and tumor tissue handling and storage was clarified. |

| | |
|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 24 November 2006 | <ul style="list-style-type: none"> • The protocol was updated to be in line with the latest version of the docetaxel SmPC. • In order to avoid bias at the time of the study's primary endpoint analysis due to a substantial amount of unblinding requests being made, patients considered for treatment with bevacizumab in the open-label phase of the study were allowed to enter into the post-study phase without unblinding, regardless of the first-line treatment (placebo or bevacizumab). • Clarification was given for the assessment of the lesions situated in a previously irradiated area. • Typographical errors were corrected. |
| 10 January 2008 | <ul style="list-style-type: none"> • The text was changed to allow bevacizumab to be given for longer than 32 cycles (96 weeks) until confirmed disease progression, unacceptable toxicity (requiring discontinuation of study treatment) or withdrawal at patient request. • If the analysis of this study (BO17708) showed significant improvements in efficacy, patients randomized to placebo that met specific eligibility criteria were allowed to receive bevacizumab. • Information on how post-study safety data would be analyzed was added. • The procedure for enrollment in the post-study phase was clarified |
| 24 July 2013 | <ul style="list-style-type: none"> • Reason for Change: Text changed from RPLS to PRES to reflect current terminology • Reason for Change: Changes made in this Version H of the protocol have been made to the "end of study" definition with thorough consideration to balance the need for long-term treatment with the organizational goal to reduce drug development costs. Other changes have been made to provide adverse event reporting instructions and contact information for patients continuing in the Optional Post-Study Phase. Overall, additional minor administrative changes have also been made to improve clarity and consistency. This amendment represents cumulative changes to the original protocol. This change affects the Synopsis, Section 3.4, Section 3.5, Section 5.3, Section 6.1, Section 7.2.2, and Appendix 15 <ul style="list-style-type: none"> o Synopsis - Length of Study o Section 3.4 End of Study o Section 3.5 Provision of Bevacizumab for Patients Randomized to the Placebo Arm o Section 5.3 End of Treatment and Follow-up Assessments o Section 6.1 Dose and Schedule of Docetaxel and Bevacizumab/Placebo o Section 7.2.2 Follow-up of Adverse Events o Appendix 15 Treatment and Assessment Schedule for Optional Post-Study Phase • Reason for Change: Instructions were added to clarify how adverse events should be reported following approval of Protocol Amendment H or site closure. <ul style="list-style-type: none"> o All clinical adverse events (AE) encountered during the clinical study will be reported on the AE form of the eCRF. Intensity of adverse events will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 (see Appendix 8) and reported in detail as indicated on the eCRF. If an adverse event occurs which is not contained in the CTC AE v3.0, the five-point scale below will be used. Any treatment-related AEs occurring after approval of the Protocol Amendment H or site closure should be reported through the commercial spontaneous AEs reporting system. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

