



Clinical trial results:

A MULTICENTER, PHASE III, RANDOMIZED, PLACEBO-CONTROLLED TRIAL EVALUATING THE EFFICACY AND SAFETY OF BEVACIZUMAB IN COMBINATION WITH CHEMOTHERAPY REGIMENS IN SUBJECTS WITH PREVIOUSLY UNTREATED METASTATIC BREAST CANCER

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2006-000378-61 |
| Trial protocol | ES GB NL SE GR |
| Global end of trial date | 08 January 2015 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 27 November 2016 |
| First version publication date | 27 November 2016 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | AVF3694g |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00262067 |
| 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 | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |
| Scientific contact | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 08 January 2015 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 08 January 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To determine the clinical benefit of the addition of bevacizumab to standard chemotherapy regimens (taxane or anthracycline based and capecitabine) for previously untreated metastatic breast cancer, as measured by progression-free survival based on investigator tumor assessment.

Protection of trial subjects:

Participants were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the participant and considering the local culture. The participants were provided an emergency medical call center help desk in the case of emergency during the study to ensure the safety.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 15 December 2005 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 6 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--|
| Country: Number of subjects enrolled | United States: 610 |
| Country: Number of subjects enrolled | Ukraine: 82 |
| Country: Number of subjects enrolled | Australia: 55 |
| Country: Number of subjects enrolled | Korea, Democratic People's Republic of: 31 |
| Country: Number of subjects enrolled | Philippines: 25 |
| Country: Number of subjects enrolled | Brazil: 35 |
| Country: Number of subjects enrolled | Taiwan: 12 |
| Country: Number of subjects enrolled | Canada: 28 |
| Country: Number of subjects enrolled | Singapore: 26 |
| Country: Number of subjects enrolled | Mexico: 11 |
| Country: Number of subjects enrolled | Panama: 4 |
| Country: Number of subjects enrolled | Russian Federation: 126 |
| Country: Number of subjects enrolled | Netherlands: 15 |
| Country: Number of subjects enrolled | Spain: 29 |
| Country: Number of subjects enrolled | Sweden: 9 |
| Country: Number of subjects enrolled | United Kingdom: 42 |
| Country: Number of subjects enrolled | France: 60 |

| | |
|--------------------------------------|---------------|
| Country: Number of subjects enrolled | Norway: 2 |
| Country: Number of subjects enrolled | Guatemala: 20 |
| Country: Number of subjects enrolled | Uruguay: 6 |
| Country: Number of subjects enrolled | Peru: 5 |
| Country: Number of subjects enrolled | Greece: 4 |
| Worldwide total number of subjects | 1237 |
| EEA total number of subjects | 161 |

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) | 960 |
| From 65 to 84 years | 277 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This study was conducted from 15 December 2005 to 8 January 2015 in the United States, Europe, and the rest of the world.

Pre-assignment

Screening details:

A total of 1237 participants were enrolled in the United States, Europe, and the rest of the world. Eligible participants were randomized in a 2:1 ratio to receive either chemotherapy plus bevacizumab or chemotherapy plus placebo.

Period 1

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

Arms

| | |
|------------------------------|---------------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Bevacizumab + Taxane or Anthracycline |

Arm description:

Eligible participants were administered Avastin® (bevacizumab) 15 milligrams (mg)/kilogram (kg) intravenously (IV) on Day 1 of every 21-day cycle + either a taxane or anthracycline (minimum 6 cycles and maximum 8 cycles of anthracycline)-based standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Bevacizumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Bevacizumab was packaged in either 5 milliliter (mL) (100 mg) or 20 mL (400 mg) glass vials containing 4 mL or 16 mL of bevacizumab, respectively (25 mg/mL for either vial).

| | |
|------------------|-----------------------------------|
| Arm title | Placebo + Taxane or Anthracycline |
|------------------|-----------------------------------|

Arm description:

Eligible participants were administered bevacizumab matching placebo IV on Day 1 of every 21-day cycle + either a taxane or anthracycline (minimum 6 cycles and maximum 8 cycles of anthracycline)-based standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.

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

Dosage and administration details:

Placebo was a clear to slightly opalescent and sterile liquid ready for intravenous administration.

| | |
|------------------|----------------------------|
| Arm title | Bevacizumab + Capecitabine |
|------------------|----------------------------|

Arm description:

Eligible participants were administered bevacizumab 15 mg/kg IV on Day 1 of every 21-day cycle +

capecitabine standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Bevacizumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Bevacizumab was packaged in either 5 mL (100 mg) or 20 mL (400 mg) glass vials containing 4 mL or 16 mL of bevacizumab, respectively (25 mg/mL for either vial).

| | |
|------------------|------------------------|
| Arm title | Placebo + Capecitabine |
|------------------|------------------------|

Arm description:

Eligible participants were administered bevacizumab matching placebo IV on Day 1 of every 21-day cycle + capecitabine standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.

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

Dosage and administration details:

Placebo was a clear to slightly opalescent and sterile liquid ready for intravenous administration.

| Number of subjects in period 1 | Bevacizumab + Taxane or Anthracycline | Placebo + Taxane or Anthracycline | Bevacizumab + Capecitabine |
|---|---------------------------------------|-----------------------------------|----------------------------|
| | | | |
| Started | 415 | 207 | 409 |
| Completed | 0 | 0 | 0 |
| Not completed | 415 | 207 | 409 |
| Consent withdrawn by subject | 45 | 14 | 25 |
| Physician decision | 46 | 12 | 17 |
| Disease progression | 187 | 146 | 245 |
| >60 days since last administration of BV | 6 | - | - |
| > 60 days since last administration of BV | - | 1 | 8 |
| Death | 14 | 7 | 11 |
| Other | 12 | 6 | 5 |
| Treatment completion | - | - | 1 |
| Adverse event | 63 | 10 | 37 |
| Lost to follow-up | - | 3 | - |
| Not known to have discontinued protocol therapy | 36 | 7 | 55 |
| Not treated | 6 | 1 | 5 |

| | |
|---------------------------------------|-----------|
| Number of subjects in period 1 | Placebo + |
|---------------------------------------|-----------|

| | Capecitabine |
|---|--------------|
| Started | 206 |
| Completed | 0 |
| Not completed | 206 |
| Consent withdrawn by subject | 5 |
| Physician decision | 6 |
| Disease progression | 145 |
| >60 days since last administration of BV | - |
| > 60 days since last administration of BV | 1 |
| Death | 6 |
| Other | 5 |
| Treatment completion | - |
| Adverse event | 11 |
| Lost to follow-up | - |
| Not known to have discontinued protocol therapy | 22 |
| Not treated | 5 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------------------------------|
| Reporting group title | Bevacizumab + Taxane or Anthracycline |
|-----------------------|---------------------------------------|

Reporting group description:

Eligible participants were administered Avastin® (bevacizumab) 15 milligrams (mg)/kilogram (kg) intravenously (IV) on Day 1 of every 21-day cycle + either a taxane or anthracycline (minimum 6 cycles and maximum 8 cycles of anthracycline)-based standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Placebo + Taxane or Anthracycline |
|-----------------------|-----------------------------------|

Reporting group description:

Eligible participants were administered bevacizumab matching placebo IV on Day 1 of every 21-day cycle + either a taxane or anthracycline (minimum 6 cycles and maximum 8 cycles of anthracycline)-based standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.

| | |
|-----------------------|----------------------------|
| Reporting group title | Bevacizumab + Capecitabine |
|-----------------------|----------------------------|

Reporting group description:

Eligible participants were administered bevacizumab 15 mg/kg IV on Day 1 of every 21-day cycle + capecitabine standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.

| | |
|-----------------------|------------------------|
| Reporting group title | Placebo + Capecitabine |
|-----------------------|------------------------|

Reporting group description:

Eligible participants were administered bevacizumab matching placebo IV on Day 1 of every 21-day cycle + capecitabine standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.

| Reporting group values | Bevacizumab + Taxane or Anthracycline | Placebo + Taxane or Anthracycline | Bevacizumab + Capecitabine |
|---------------------------------------|---------------------------------------|-----------------------------------|----------------------------|
| Number of subjects | 415 | 207 | 409 |
| Age categorical Units: Subjects | | | |
| < 40 years | 29 | 14 | 21 |
| 40-64 years | 295 | 160 | 289 |
| ≥ 65 years | 91 | 33 | 99 |
| Gender categorical Units: Subjects | | | |
| Female | 413 | 207 | 408 |
| Male | 2 | 0 | 1 |

| Reporting group values | Placebo + Capecitabine | Total | |
|---------------------------------------|------------------------|-------|--|
| Number of subjects | 206 | 1237 | |
| Age categorical Units: Subjects | | | |
| < 40 years | 15 | 79 | |
| 40-64 years | 137 | 881 | |
| ≥ 65 years | 54 | 277 | |
| Gender categorical Units: Subjects | | | |
| Female | 204 | 1232 | |
| Male | 2 | 5 | |

End points

End points reporting groups

| | |
|-----------------------|---------------------------------------|
| Reporting group title | Bevacizumab + Taxane or Anthracycline |
|-----------------------|---------------------------------------|

Reporting group description:

Eligible participants were administered Avastin® (bevacizumab) 15 milligrams (mg)/kilogram (kg) intravenously (IV) on Day 1 of every 21-day cycle + either a taxane or anthracycline (minimum 6 cycles and maximum 8 cycles of anthracycline)-based standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Placebo + Taxane or Anthracycline |
|-----------------------|-----------------------------------|

Reporting group description:

Eligible participants were administered bevacizumab matching placebo IV on Day 1 of every 21-day cycle + either a taxane or anthracycline (minimum 6 cycles and maximum 8 cycles of anthracycline)-based standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.

| | |
|-----------------------|----------------------------|
| Reporting group title | Bevacizumab + Capecitabine |
|-----------------------|----------------------------|

Reporting group description:

Eligible participants were administered bevacizumab 15 mg/kg IV on Day 1 of every 21-day cycle + capecitabine standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.

| | |
|-----------------------|------------------------|
| Reporting group title | Placebo + Capecitabine |
|-----------------------|------------------------|

Reporting group description:

Eligible participants were administered bevacizumab matching placebo IV on Day 1 of every 21-day cycle + capecitabine standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.

| | |
|----------------------------|----------------------------|
| Subject analysis set title | Intent-to-treat population |
|----------------------------|----------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

Intent-to-treat (ITT) population included all participants who were randomized, regardless of whether they received any study medication or completed the full course of treatment.

| | |
|----------------------------|-------------------|
| Subject analysis set title | Safety population |
|----------------------------|-------------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Safety population included all randomized participants who received any study treatment (at least one full or partial dose of either study medication or chemotherapy).

Primary: Progression-free Survival as Determined by the Investigator Using Response Evaluation Criteria in Solid Tumors

| | |
|-----------------|--|
| End point title | Progression-free Survival as Determined by the Investigator Using Response Evaluation Criteria in Solid Tumors |
|-----------------|--|

End point description:

Progression-free Survival (PFS) was defined as time from randomization to first documented disease progression (PD). It was determined by investigator using Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 or death due to any cause, whichever occurred first. For target lesions, PD was defined as at least 20% increase in sum of the longest diameter of target lesions, taking as reference the smallest sum of the longest diameter recorded since treatment started or appearance of one or more new lesions. For non-target lesions, PD was defined as the appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. ITT population was considered for this end point.

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

End point timeframe:

From first participant in (15 December 2005) till PFS analysis cut-off (31 July 2008) (Up to 2 years, 7 months)

| End point values | Bevacizumab + Taxane or Anthracycline | Placebo + Taxane or Anthracycline | Bevacizumab + Capecitabine | Placebo + Capecitabine |
|----------------------------------|---------------------------------------|-----------------------------------|----------------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 415 | 207 | 409 | 206 |
| Units: Months | | | | |
| median (confidence interval 95%) | 9.2 (8.6 to 10.1) | 8 (6.7 to 8.4) | 8.6 (8.1 to 9.5) | 5.7 (4.3 to 6.2) |

Statistical analyses

| Statistical analysis title | T/Anth+Placebo VS T/Anth+BV |
|---|---|
| Comparison groups | Bevacizumab + Taxane or Anthracycline v Placebo + Taxane or Anthracycline |
| Number of subjects included in analysis | 622 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.644 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.522 |
| upper limit | 0.795 |

| Statistical analysis title | Cap+Placebo VS Cap+BV |
|---|---|
| Comparison groups | Bevacizumab + Capecitabine v Placebo + Capecitabine |
| Number of subjects included in analysis | 615 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0002 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.688 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.564 |
| upper limit | 0.84 |

Secondary: Objective Response Rate as Assessed by Investigator Using RECIST

| | |
|-----------------|--|
| End point title | Objective Response Rate as Assessed by Investigator Using RECIST |
|-----------------|--|

End point description:

An objective response was defined as a complete response or a partial response determined on two consecutive occasions ≥ 4 weeks apart as determined by the investigator using RECIST 1.0. Objective response rate (ORR) was defined as the percentage of participants who had an objective response. For target lesions, a complete response was defined as the disappearance of all target lesions and 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. For non-target lesions, a complete response was defined as the disappearance of all non-target lesions and a partial response was defined as the persistence of one or more non-target lesions. Analysis population consisted of randomized participants (ITT population) who had measurable disease at baseline.

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

End point timeframe:

From first participant in (15 December 2005) till ORR analysis cut-off (31 July 2008) (Up to 2 years, 7 months)

| End point values | Bevacizumab + Taxane or Anthracycline | Placebo + Taxane or Anthracycline | Bevacizumab + Capecitabine | Placebo + Capecitabine |
|-----------------------------------|---------------------------------------|-----------------------------------|----------------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 345 ^[1] | 177 ^[2] | 325 ^[3] | 161 ^[4] |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 51.3 (45.9 to 56.7) | 37.9 (30.7 to 45.2) | 35.4 (30.2 to 40.6) | 23.6 (17.6 to 30.7) |

Notes:

[1] - Only participants with measurable disease at baseline were included in the analysis.

[2] - Only participants with measurable disease at baseline were included in the analysis.

[3] - Only participants with measurable disease at baseline were included in the analysis.

[4] - Only participants with measurable disease at baseline were included in the analysis.

Statistical analyses

| Statistical analysis title | T/Anth+Placebo vs T/Anth+BV |
|---|---|
| Comparison groups | Placebo + Taxane or Anthracycline v Bevacizumab + Taxane or Anthracycline |
| Number of subjects included in analysis | 522 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0054 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Percentage difference in ORR |
| Point estimate | 13.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.6 |
| upper limit | 22.3 |

| Statistical analysis title | Cap+Placebo VS Cap+BV |
|-----------------------------------|---|
| Comparison groups | Bevacizumab + Capecitabine v Placebo + Capecitabine |

| | |
|---|------------------------------|
| Number of subjects included in analysis | 486 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0097 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Percentage difference in ORR |
| Point estimate | 11.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.4 |
| upper limit | 20.2 |

Secondary: Duration of Objective Response as Determined by the Investigator Using RECIST

| | |
|-----------------|---|
| End point title | Duration of Objective Response as Determined by the Investigator Using RECIST |
|-----------------|---|

End point description:

Duration of objective response was defined as the time from the first tumor assessment that led to a determination of an objective response to the time of disease progression or death due to any cause, whichever occurred first. Analysis population consisted of randomized participants (ITT population) who had measurable disease at baseline and achieved an objective response.

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

End point timeframe:

From first participant in (15 December 2005) till objective response analysis cut-off (31 July 2008) (Up to 2 years, 7 months)

| End point values | Bevacizumab + Taxane or Anthracycline | Placebo + Taxane or Anthracycline | Bevacizumab + Capecitabine | Placebo + Capecitabine |
|----------------------------------|---------------------------------------|-----------------------------------|----------------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 177 ^[5] | 67 ^[6] | 115 ^[7] | 38 ^[8] |
| Units: Months | | | | |
| median (confidence interval 95%) | 8.3 (7.2 to 10.7) | 7.1 (6.2 to 8.8) | 9.2 (8.5 to 10.4) | 7.2 (5.1 to 9.3) |

Notes:

[5] - Only participants with measurable disease at baseline and who had objective response were included.

[6] - Only participants with measurable disease at baseline and who had objective response were included.

[7] - Only participants with measurable disease at baseline and who had objective response were included.

[8] - Only participants with measurable disease at baseline and who had objective response were included.

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | T/Anth+Placebo VS T/Anth+BV |
| Comparison groups | Bevacizumab + Taxane or Anthracycline v Placebo + Taxane or Anthracycline |

| | |
|---|-------------------|
| Number of subjects included in analysis | 244 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0064 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.627 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.447 |
| upper limit | 0.88 |

| | |
|---|---|
| Statistical analysis title | Cap+Placebo VS Cap+BV |
| Comparison groups | Bevacizumab + Capecitabine v Placebo + Capecitabine |
| Number of subjects included in analysis | 153 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0326 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.612 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.388 |
| upper limit | 0.964 |

Secondary: Overall Survival

| | |
|--|------------------|
| End point title | Overall Survival |
| End point description: | |
| <p>Overall survival was defined as the time from randomization until death from any cause. ITT population was considered for this end point. The median value and value of upper limit of confidence interval for Placebo + Taxane or Anthracycline was 'not reached' and 'not estimable', respectively. However, the EudraCT portal does not accept blank field or have free text option for the explanation; therefore, we have presented an arbitrary value (99999) for the same.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| <p>From first participant in (15 December 2005) till overall survival analysis cut-off (24 February 2009) (Up to 3 years, 2 months)</p> | |

| End point values | Bevacizumab + Taxane or Anthracycline | Placebo + Taxane or Anthracycline | Bevacizumab + Capecitabine | Placebo + Capecitabine |
|----------------------------------|---------------------------------------|-----------------------------------|----------------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 415 | 207 | 409 | 206 |
| Units: Months | | | | |
| median (confidence interval 95%) | 27.5 (25.6 to 31.4) | 99999 (23.6 to 99999) | 25.7 (22 to 28.4) | 22.8 (20.5 to 28.4) |

Statistical analyses

| Statistical analysis title | T/Anth+Placebo VS T/Anth+BV |
|---|---|
| Comparison groups | Bevacizumab + Taxane or Anthracycline v Placebo + Taxane or Anthracycline |
| Number of subjects included in analysis | 622 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.44 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.86 |
| upper limit | 1.43 |

| Statistical analysis title | Cap+Placebo VS Cap+BV |
|---|---|
| Comparison groups | Bevacizumab + Capecitabine v Placebo + Capecitabine |
| Number of subjects included in analysis | 615 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.33 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.88 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.69 |
| upper limit | 1.13 |

Secondary: One-year Survival Rate

| | |
|-----------------|------------------------|
| End point title | One-year Survival Rate |
|-----------------|------------------------|

End point description:

One-year survival rate was defined as the percentage of participants who were alive one-year after randomization. The percentage of participants alive at one-year was determined using Kaplan-Meier analyses and the 95% confidence intervals were computed using the Greenwood's formula. ITT population was considered for this end point.

End point type Secondary

End point timeframe:

One year after randomization for each participant

| End point values | Bevacizumab + Taxane or Anthracycline | Placebo + Taxane or Anthracycline | Bevacizumab + Capecitabine | Placebo + Capecitabine |
|-----------------------------------|---------------------------------------|-----------------------------------|----------------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 415 | 207 | 409 | 206 |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 80.7 (76.8 to 84.5) | 83.2 (78.1 to 88.4) | 81 (77.1 to 84.8) | 74.8 (68.7 to 80.8) |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | T/Anth+Placebo vs T/Anth+BV |
| Comparison groups | Bevacizumab + Taxane or Anthracycline v Placebo + Taxane or Anthracycline |
| Number of subjects included in analysis | 622 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.436 |
| Method | Normal approximation |
| Parameter estimate | % difference in one-year survival rate |
| Point estimate | -2.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9 |
| upper limit | 3.9 |

| | |
|---|---|
| Statistical analysis title | Cap+Placebo VS Cap+BV |
| Comparison groups | Bevacizumab + Capecitabine v Placebo + Capecitabine |
| Number of subjects included in analysis | 615 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.092 |
| Method | Normal approximation |
| Parameter estimate | % difference in one-year survival rate |
| Point estimate | 6.2 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | 13.4 |

Secondary: PFS as Determined by the Independent Review Committee Using RECIST

| | |
|-----------------|--|
| End point title | PFS as Determined by the Independent Review Committee Using RECIST |
|-----------------|--|

End point description:

PFS was defined as time from randomization to first documented PD. It was determined by independent review committee using RECIST 1.0 or death due to any cause, whichever occurred first. For target lesions, PD was defined as at least 20% increase in sum of the longest diameter of target lesions, taking as reference the smallest sum of the longest diameter recorded since treatment started or appearance of one or more new lesions. For non-target lesions, PD was defined as the appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. ITT population was considered for this end point.

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

End point timeframe:

From first participant in (15 December 2005) till PFS analysis cut-off (31 July 2008) (Up to 2 years, 7 months)

| End point values | Bevacizumab + Taxane or Anthracycline | Placebo + Taxane or Anthracycline | Bevacizumab + Capecitabine | Placebo + Capecitabine |
|----------------------------------|---------------------------------------|-----------------------------------|----------------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 415 | 207 | 409 | 206 |
| Units: Months | | | | |
| median (confidence interval 95%) | 10.7 (9.9 to 12.1) | 8.3 (8 to 9.9) | 9.8 (8.4 to 10.4) | 6.2 (4.7 to 7.8) |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | T/Anth+Placebo VS T/Anth+BV |
| Comparison groups | Bevacizumab + Taxane or Anthracycline v Placebo + Taxane or Anthracycline |
| Number of subjects included in analysis | 622 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.04 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.77 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.601 |
| upper limit | 0.988 |

| | |
|---|---|
| Statistical analysis title | Cap+Placebo VS Cap+BV |
| Comparison groups | Bevacizumab + Capecitabine v Placebo + Capecitabine |
| Number of subjects included in analysis | 615 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0011 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.681 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.54 |
| upper limit | 0.858 |

Secondary: Number of Participants With Serious Adverse Events after final overall survival analysis (24 February 2009) till end of study (8 January 2015)

| | |
|-----------------|--|
| End point title | Number of Participants With Serious Adverse Events after final overall survival analysis (24 February 2009) till end of study (8 January 2015) |
|-----------------|--|

End point description:

A serious adverse event (SAE) is any untoward medical occurrence that at any dose results in death, is life threatening, requires hospitalization or prolongation of hospitalization or results in disability/incapacity, and congenital anomaly/birth defect. The SAEs presented here were collected from 24 February 2009 to 8 January 2015. Safety population was considered for this end point.

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

End point timeframe:

Post final overall survival analysis (24 February 2009) till end of study (8 January 2015) (Approximately 6 years)

| | | | | |
|-----------------------------|----------------------|--|--|--|
| End point values | Safety population | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 1220 | | | |
| Units: Number | 21 | | | |

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 3 years, 2 months (First participant enrolment [15 December 2005] to data cut-off date [24 February 2009])

Adverse event reporting additional description:

Adverse event is reported for safety population which included all randomized participants who received any study treatment, defined as at least one full or partial dose of either study drug or chemotherapy.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 12.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------------------------|
| Reporting group title | Bevacizumab + Taxane or Anthracycline |
|-----------------------|---------------------------------------|

Reporting group description:

Participants received bevacizumab 15 mg/kg IV on Day 1 of every 21-day cycle + either a taxane or anthracycline (minimum 6 cycles and maximum 8 cycles of anthracycline)-based standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Placebo + Taxane or Anthracycline |
|-----------------------|-----------------------------------|

Reporting group description:

Participants received bevacizumab matching placebo IV on Day 1 of every 21-day cycle + either a taxane or anthracycline (minimum 6 cycles and maximum 8 cycles of anthracycline)-based standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.

| | |
|-----------------------|----------------------------|
| Reporting group title | Bevacizumab + Capecitabine |
|-----------------------|----------------------------|

Reporting group description:

Participants received bevacizumab 15 mg/kg IV on Day 1 of every 21-day cycle + capecitabine standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.

| | |
|-----------------------|------------------------|
| Reporting group title | Placebo + Capecitabine |
|-----------------------|------------------------|

Reporting group description:

Participants received bevacizumab matching placebo IV on Day 1 of every 21-day cycle + capecitabine standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.

| Serious adverse events | Bevacizumab + Taxane or Anthracycline | Placebo + Taxane or Anthracycline | Bevacizumab + Capecitabine |
|---|---------------------------------------|-----------------------------------|----------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 146 / 413 (35.35%) | 57 / 202 (28.22%) | 132 / 404 (32.67%) |
| number of deaths (all causes) | 18 | 9 | 15 |
| number of deaths resulting from adverse events | 6 | 4 | 1 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Bladder neoplasm | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast cancer | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Breast cancer metastatic | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 413 (0.48%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Metastases to meninges | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour ulceration | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Metastatic neoplasm | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric cancer | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant pleural effusion | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ovarian cancer | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 413 (0.48%) | 1 / 202 (0.50%) | 3 / 404 (0.74%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 5 / 413 (1.21%) | 0 / 202 (0.00%) | 2 / 404 (0.50%) |
| occurrences causally related to treatment / all | 6 / 6 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 1 / 202 (0.50%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Jugular vein thrombosis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombosis | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Varicose vein | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Venous thrombosis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Venous thrombosis limb | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Chest pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 3 / 413 (0.73%) | 1 / 202 (0.50%) | 2 / 404 (0.50%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 413 (0.48%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Malaise | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mucosal inflammation | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 6 / 404 (1.49%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 3 / 413 (0.73%) | 2 / 202 (0.99%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 4 / 413 (0.97%) | 1 / 202 (0.50%) | 7 / 404 (1.73%) |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 1 | 0 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden death | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Immune system disorders | | | |
| Hypersensitivity | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Reproductive system and breast disorders | | | |
| Metrorrhagia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Uterine haemorrhage | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 1 / 202 (0.50%) | 0 / 404 (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 |
| Asthma | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Chronic obstructive pulmonary disease | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cough | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Diaphragmatic hernia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 5 / 413 (1.21%) | 2 / 202 (0.99%) | 6 / 404 (1.49%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 3 | 1 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Dyspnoea exertional | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Epistaxis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 413 (0.48%) | 1 / 202 (0.50%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemothorax | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxia | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung infiltration | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 413 (0.48%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 5 / 413 (1.21%) | 3 / 202 (1.49%) | 5 / 404 (1.24%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 4 | 0 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Pleuritic pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Pneumothorax | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 413 (0.48%) | 1 / 202 (0.50%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |

| | | | |
|--|-----------------|-----------------|-----------------|
| Pulmonary embolism alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 3 / 413 (0.73%) | 3 / 202 (1.49%) | 8 / 404 (1.98%) |
| occurrences causally related to treatment / all | 3 / 3 | 2 / 3 | 6 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| Pulmonary haemorrhage alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Respiratory arrest alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Respiratory failure alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 413 (0.48%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| Tracheomalacia alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Psychiatric disorders | | | |
| Anxiety alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Completed suicide alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Confusional state | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 413 (0.48%) | 0 / 202 (0.00%) | 3 / 404 (0.74%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depression | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 1 / 202 (0.50%) | 0 / 404 (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 |
| Mental status changes | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 1 / 202 (0.50%) | 3 / 404 (0.74%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Blood potassium increased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 1 / 202 (0.50%) | 0 / 404 (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 |
| Haemoglobin decreased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 1 / 202 (0.50%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rotavirus test positive | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical condition abnormal | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Cervical vertebral fracture | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Concussion | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug toxicity | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Femoral neck fracture alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Fibula fracture alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Head injury alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 3 / 404 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Overdose alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Procedural pain alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 1 / 202 (0.50%) | 0 / 404 (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 |
| Radiation oesophagitis alternative assessment type: Non-systematic | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 413 (0.00%) | 1 / 202 (0.50%) | 0 / 404 (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 |
| Spinal compression fracture alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper limb fracture alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound dehiscence alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial tachycardia | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 2 / 413 (0.48%) | 1 / 202 (0.50%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 2 / 202 (0.99%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| Cardiogenic shock | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Cardiomyopathy | | | |
| subjects affected / exposed | 2 / 413 (0.48%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intracardiac thrombus | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 413 (0.00%) | 1 / 202 (0.50%) | 0 / 404 (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 |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Left ventricular failure | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 6 / 404 (1.49%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 3 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 1 / 202 (0.50%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericarditis | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Restrictive cardiomyopathy | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Sinus arrest | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus tachycardia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Ventricular dysfunction | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac valve disease | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Ataxia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 1 / 202 (0.50%) | 0 / 404 (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 |
| Carotid sinus syndrome | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral ischaemia | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coma hepatic | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Convulsion | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 1 / 202 (0.50%) | 0 / 404 (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 |
| Facial palsy | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 1 / 202 (0.50%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 3 / 413 (0.73%) | 1 / 202 (0.50%) | 2 / 404 (0.50%) |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lethargy | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|-----------------|-----------------|-----------------|
| Nervous system disorder alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 413 (0.48%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Neuralgia alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral motor neuropathy alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 sensory neuropathy alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 413 (0.48%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Reversible posterior leukoencephalopathy syndrome alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sciatica alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Somnolence alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 413 (0.00%) | 1 / 202 (0.50%) | 0 / 404 (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 |
| Syncope | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 3 / 413 (0.73%) | 1 / 202 (0.50%) | 3 / 404 (0.74%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysphasia | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 1 / 202 (0.50%) | 0 / 404 (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 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 1 / 202 (0.50%) | 0 / 404 (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 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 413 (0.73%) | 0 / 202 (0.00%) | 3 / 404 (0.74%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile bone marrow aplasia | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |

| | | | |
|---|------------------|------------------|-----------------|
| subjects affected / exposed | 26 / 413 (6.30%) | 11 / 202 (5.45%) | 3 / 404 (0.74%) |
| occurrences causally related to treatment / all | 2 / 29 | 0 / 11 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 10 / 413 (2.42%) | 5 / 202 (2.48%) | 3 / 404 (0.74%) |
| occurrences causally related to treatment / all | 2 / 15 | 0 / 5 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Eye disorders | | | |
| Blindness | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Macular hole | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 4 / 413 (0.97%) | 1 / 202 (0.50%) | 4 / 404 (0.99%) |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 1 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Colitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 2 / 404 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 8 / 413 (1.94%) | 0 / 202 (0.00%) | 6 / 404 (1.49%) |
| occurrences causally related to treatment / all | 2 / 8 | 0 / 0 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenal ulcer | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Duodenal ulcer haemorrhage | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Faecaloma | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis erosive | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal perforation | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 5 / 413 (1.21%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 4 / 5 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Gastrointestinal toxicity | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhoids | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileal ulcer perforation | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Ileus | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 2 / 404 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Intestinal perforation | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 1 / 202 (0.50%) | 0 / 404 (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 |
| Jejunitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 413 (0.48%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Nausea | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 6 / 413 (1.45%) | 1 / 202 (0.50%) | 2 / 404 (0.50%) |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophagitis | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Pancreatitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Small intestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 2 / 413 (0.48%) | 0 / 202 (0.00%) | 2 / 404 (0.50%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stomatitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Upper gastrointestinal haemorrhage | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Vomiting | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 6 / 413 (1.45%) | 3 / 202 (1.49%) | 4 / 404 (0.99%) |
| occurrences causally related to treatment / all | 2 / 7 | 0 / 3 | 1 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 413 (0.48%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis acute | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 1 / 202 (0.50%) | 0 / 404 (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 |
| Cholelithiasis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic cirrhosis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic failure | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 2 / 404 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Hepatic function abnormal | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatorenal failure | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Hyperbilirubinaemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Jaundice cholestatic | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Skin and subcutaneous tissue disorders | | | |
| Decubitus ulcer | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain of skin | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Palmar–plantar erythrodysesthesia syndrome | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin ulcer | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Renal and urinary disorders | | | |
| Calculus ureteric | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Nephrotic syndrome | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure acute | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 3 / 413 (0.73%) | 1 / 202 (0.50%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ureteric obstruction | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Urinary retention | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Endocrine disorders | | | |
| Hypercalcaemia of malignancy | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Back pain | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 413 (0.24%) | 1 / 202 (0.50%) | 5 / 404 (1.24%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 1 / 202 (0.50%) | 0 / 404 (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 |
| Neck pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteonecrosis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal deformity | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Abdominal abscess | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Abscess intestinal | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 413 (0.00%) | 1 / 202 (0.50%) | 0 / 404 (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 |
| Abscess jaw | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis bacterial | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 1 / 202 (0.50%) | 0 / 404 (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 |
| Bacteraemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacterial sepsis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 1 / 202 (0.50%) | 0 / 404 (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 |
| Breast cellulitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 1 / 202 (0.50%) | 0 / 404 (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 |
| Bronchitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 1 / 202 (0.50%) | 2 / 404 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Bronchopneumonia alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchopulmonary aspergillosis alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Catheter related infection alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 3 / 404 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 7 / 413 (1.69%) | 1 / 202 (0.50%) | 2 / 404 (0.50%) |
| occurrences causally related to treatment / all | 1 / 8 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Central line infection alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridial infection alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Cystitis alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 413 (0.00%) | 1 / 202 (0.50%) | 0 / 404 (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 |
| Diverticulitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 2 / 404 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Gastroenteritis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 2 / 404 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes oesophagitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 4 / 413 (0.97%) | 1 / 202 (0.50%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Klebsiella bacteraemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|-----------------|-----------------|-----------------|
| Lobar pneumonia alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Lower respiratory tract infection alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nasopharyngitis alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Neutropenic sepsis alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 2 / 202 (0.99%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Osteomyelitis alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngitis alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 413 (0.73%) | 5 / 202 (2.48%) | 6 / 404 (1.49%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 5 | 0 / 6 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Salpingo-oophoritis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Sepsis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 6 / 413 (1.45%) | 1 / 202 (0.50%) | 3 / 404 (0.74%) |
| occurrences causally related to treatment / all | 2 / 7 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 1 / 2 | 0 / 1 | 0 / 1 |
| Sinusitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Staphylococcal bacteraemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Sweat gland infection | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Urinary tract infection | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 2 / 202 (0.99%) | 2 / 404 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|-----------------|-----------------|-----------------|
| Wound infection alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 0 / 404 (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 |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 7 / 413 (1.69%) | 1 / 202 (0.50%) | 5 / 404 (1.24%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 1 | 0 / 7 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Fluid overload alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypercalcaemia alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 0 / 404 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 413 (0.00%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 413 (0.48%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anorexia | | | |
| subjects affected / exposed | 1 / 413 (0.24%) | 0 / 202 (0.00%) | 1 / 404 (0.25%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Placebo + Capecitabine | | |
|--|------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 64 / 201 (31.84%) | | |
| number of deaths (all causes) | 11 | | |
| number of deaths resulting from adverse events | 2 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Bladder neoplasm | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Breast cancer | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Breast cancer metastatic | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metastases to meninges | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 201 (1.00%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Tumour pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tumour ulceration | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metastatic neoplasm | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastric cancer | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malignant pleural effusion | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ovarian cancer | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 201 (1.00%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypertension | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypotension | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Jugular vein thrombosis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombosis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Varicose vein | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Venous thrombosis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Venous thrombosis limb | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 201 (1.00%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chest pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 3 / 201 (1.49%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fatigue | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General physical health deterioration | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malaise | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mucosal inflammation | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 201 (1.00%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sudden death | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Metrorrhagia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Uterine haemorrhage | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Asthma | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chronic obstructive pulmonary disease | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cough | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diaphragmatic hernia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnoea | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 201 (1.00%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnoea exertional | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epistaxis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemothorax | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Hypoxia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Lung infiltration alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pleural effusion alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 5 / 201 (2.49%) | | | |
| occurrences causally related to treatment / all | 1 / 5 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Pleuritic pain alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia aspiration alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Pneumonitis alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumothorax alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pulmonary embolism alternative assessment type: Non-systematic | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 5 / 201 (2.49%) | | |
| occurrences causally related to treatment / all | 3 / 5 | | |
| deaths causally related to treatment / all | 2 / 2 | | |
| Pulmonary haemorrhage | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory arrest | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory failure | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tracheomalacia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Completed suicide | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Confusional state | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Depression | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mental status changes | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Blood potassium increased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemoglobin decreased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rotavirus test positive | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General physical condition abnormal | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cervical vertebral fracture | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Concussion | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Drug toxicity | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fall | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Femoral neck fracture alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fibula fracture alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Head injury alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hip fracture alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Overdose alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Procedural pain alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Radiation oesophagitis alternative assessment type: Non-systematic | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal compression fracture | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper limb fracture | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wound dehiscence | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial tachycardia | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiogenic shock | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiomyopathy | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intracardiac thrombus | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Left ventricular failure | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pericardial effusion | | | |
| subjects affected / exposed | 2 / 201 (1.00%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Restrictive cardiomyopathy | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sinus arrest | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sinus tachycardia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ventricular dysfunction | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac valve disease | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Ataxia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Carotid sinus syndrome | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral ischaemia | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Cerebrovascular accident | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coma hepatic | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Convulsion | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Facial palsy | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Headache | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lethargy | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Nervous system disorder alternative assessment type: Non-systematic subjects affected / exposed | 0 / 201 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neuralgia alternative assessment type: Non-systematic subjects affected / exposed | 0 / 201 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peripheral motor neuropathy alternative assessment type: Non-systematic subjects affected / exposed | 0 / 201 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peripheral sensory neuropathy alternative assessment type: Non-systematic subjects affected / exposed | 0 / 201 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Reversible posterior leukoencephalopathy syndrome alternative assessment type: Non-systematic subjects affected / exposed | 0 / 201 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sciatica alternative assessment type: Non-systematic subjects affected / exposed | 0 / 201 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Somnolence alternative assessment type: Non-systematic | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient ischaemic attack | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dysphasia | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile bone marrow aplasia | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile neutropenia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 3 / 201 (1.49%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenia | | | |
| subjects affected / exposed | 2 / 201 (1.00%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Blindness | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Macular hole | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 201 (1.00%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain upper | | | |
| alternative assessment type: Non-systematic | | | |

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|---|-----------------|--|--|
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ascites | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Constipation | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 201 (1.00%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Duodenal ulcer | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Duodenal ulcer haemorrhage | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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|---|-----------------|--|--|--|
| Faecaloma | | | | |
| alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastritis erosive | | | | |
| alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal haemorrhage | | | | |
| alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal perforation | | | | |
| alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal toxicity | | | | |
| alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Haemorrhoids | | | | |
| alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ileal ulcer perforation | | | | |
| alternative assessment type: Non-systematic | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ileus | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal obstruction | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal perforation | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Jejunitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Small intestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Stomatitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper gastrointestinal haemorrhage | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 3 / 201 (1.49%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholecystitis acute | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholelithiasis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic cirrhosis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic failure | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic function abnormal | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatorenal failure | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperbilirubinaemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Jaundice cholestatic | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Decubitus ulcer | | | |
| alternative assessment type: Non-systematic | | | |

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|---|-----------------|--|--|
| subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pain of skin | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Palmar–plantar erythrodysaesthesia syndrome | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin ulcer | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Calculus ureteric | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nephrotic syndrome | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure | | | |
| alternative assessment type: Non-systematic | | | |

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|--|-----------------|--|--|
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure acute | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ureteric obstruction | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary retention | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Hypercalcaemia of malignancy | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Back pain | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 201 (1.00%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bone pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neck pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteonecrosis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal deformity | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Abdominal abscess | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abscess intestinal | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abscess jaw | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arthritis bacterial | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bacteraemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bacterial sepsis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Breast cellulitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|--|-----------------|--|--|--|
| Bronchopneumonia alternative assessment type: Non-systematic subjects affected / exposed | 0 / 201 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bronchopulmonary aspergillosis alternative assessment type: Non-systematic subjects affected / exposed | 0 / 201 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Catheter related infection alternative assessment type: Non-systematic subjects affected / exposed | 0 / 201 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cellulitis alternative assessment type: Non-systematic subjects affected / exposed | 2 / 201 (1.00%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Central line infection alternative assessment type: Non-systematic subjects affected / exposed | 0 / 201 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Clostridial infection alternative assessment type: Non-systematic subjects affected / exposed | 0 / 201 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cystitis alternative assessment type: Non-systematic | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diverticulitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Erysipelas | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 201 (1.00%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Herpes oesophagitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infection | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Klebsiella bacteraemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|--|-----------------|--|--|--|
| Lobar pneumonia alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lower respiratory tract infection alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nasopharyngitis alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neutropenic sepsis alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Osteomyelitis alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pharyngitis alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia alternative assessment type: Non-systematic | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 4 / 201 (1.99%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Salpingo-oophoritis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sinusitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Staphylococcal bacteraemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sweat gland infection | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Wound infection alternative assessment type: Non-systematic subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper respiratory tract infection subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urosepsis subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders Dehydration alternative assessment type: Non-systematic subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fluid overload alternative assessment type: Non-systematic subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypercalcaemia alternative assessment type: Non-systematic subjects affected / exposed | 1 / 201 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperglycaemia alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoglycaemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anorexia | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Bevacizumab + Taxane or Anthracycline | Placebo + Taxane or Anthracycline | Bevacizumab + Capecitabine |
|--|---------------------------------------|-----------------------------------|----------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 96 / 413 (23.24%) | 28 / 202 (13.86%) | 80 / 404 (19.80%) |
| Vascular disorders | | | |
| Hypertension | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 43 / 413 (10.41%) | 8 / 202 (3.96%) | 51 / 404 (12.62%) |
| occurrences (all) | 122 | 14 | 149 |
| Cardiac disorders | | | |
| Left ventricular dysfunction | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 19 / 413 (4.60%) | 8 / 202 (3.96%) | 3 / 404 (0.74%) |
| occurrences (all) | 53 | 17 | 6 |
| Nervous system disorders | | | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 21 / 413 (5.08%) | 10 / 202 (4.95%) | 18 / 404 (4.46%) |
| occurrences (all) | 49 | 26 | 37 |
| Blood and lymphatic system disorders | | | |

| | | | |
|---|-------------------------|-----------------------|------------------------|
| Neutropenia subjects affected / exposed occurrences (all) | 25 / 413 (6.05%) 137 | 6 / 202 (2.97%) 13 | 18 / 404 (4.46%) 59 |
|---|-------------------------|-----------------------|------------------------|

| | | | |
|--|---------------------------|--|--|
| Non-serious adverse events | Placebo + Capecitabine | | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 20 / 201 (9.95%) | | |
| Vascular disorders Hypertension alternative assessment type: Non- systematic subjects affected / exposed occurrences (all) | 8 / 201 (3.98%) 11 | | |
| Cardiac disorders Left ventricular dysfunction alternative assessment type: Non- systematic subjects affected / exposed occurrences (all) | 2 / 201 (1.00%) 7 | | |
| Nervous system disorders Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 5 / 201 (2.49%) 7 | | |
| Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all) | 5 / 201 (2.49%) 12 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 01 February 2006 | <p>Study AVF3694g was amended to provide more clarity and rigorous guidelines for study therapy in both the blinded treatment and post-progression phases. Safety information was also updated to be consistent with current standard bevacizumab dose modification guidelines. Protocol-specified selected adverse events and special reporting for nonserious cardiac adverse events were further defined. For this study, all intracranial hemorrhages were reported as serious and were therefore subject to serious adverse event reporting requirements. Safety monitoring of left ventricular function during initial screening was added for subjects with prior exposure to anthracycline-based therapy, rather than only for subjects entering the anthracycline cohort. All Grade ≥ 2 left ventricular systolic dysfunction events were reported immediately to the Sponsor to allow for a timely and thorough review of cardiotoxicity events by the Data Monitoring Committee.</p> |
| 22 November 2006 | <p>Study AVF3694g was amended to better fit the practice patterns of oncologists treating first-line metastatic breast cancer with chemotherapy. Major changes to the protocol are described below:</p> <ul style="list-style-type: none"> • Secondary objectives and outcome measures were amended to include 1-year survival. • Modifications were made to the exclusion criteria, including allowing subjects who had unknown HER2 status and for whom the determination of HER2 status was not possible and disallowing subjects who had received radiotherapy within 2 weeks prior to Day 0. • Subjects with a history of anaphylactic reaction to monoclonal antibody therapy not controlled with treatment premedication were excluded from receiving bevacizumab. • Optional unblinding was allowed when a subject had documented progressive disease and if such information was instrumental in determining the next course of treatment. • For subjects who received prior anthracycline therapy or who were to be enrolled to the anthracycline cohort, an echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan was required (may be performed within 12 weeks prior to Day 0 if no cardiotoxic treatments or events occur within that period). Subjects who were to be enrolled into the anthracycline cohort should have had left ventricular ejection fraction (LVEF) $\geq 50\%$. Subjects who had received prior anthracycline therapy and were to be enrolled into the taxane or capecitabine cohort could not have New York Heart Association (NYHA) Grade II or higher CHF. • Subjects who had alkaline phosphatase $> 2 \times$ the upper limit of normal (ULN; $> 7 \times$ ULN in subjects with known bone involvement) were excluded from study entry. |
| 20 February 2007 | <p>Study AVF3694g was amended to detect, statistically, the clinical benefit of the addition of bevacizumab to capecitabine therapy compared with capecitabine alone for first-line metastatic breast cancer participants. This study design allowed detection of the clinical benefit of the addition of bevacizumab to taxane therapy and anthracycline-based therapy in a parallel analysis.</p> |
| 24 July 2007 | <p>Study AVF3694g was amended to provide more information in support of the primary endpoint of progression free survival (PFS) and secondary endpoint of overall survival. An Independent Review Committee (IRC) assessment was added to meet study design guidelines and provide a sensitivity analysis for the investigator assessment-based primary endpoint. Additional subsequent anti-cancer therapy during the survival follow-up phase for all subjects were captured to provide information on therapies that may contribute to overall survival of participants after they had discontinued from the blinded phase of the study. The definition of PFS was updated, to be well characterized and accepted by the regulatory and research communities.</p> |

| | |
|---------------|---|
| 27 March 2008 | Study AVF3694g was amended to provide bevacizumab in an optional extended treatment phase to all subjects receiving study treatment when the study analysis was complete if the primary efficacy analysis showed significant improvement with bevacizumab without a detrimental effect on subject safety. The maximum duration of treatment with bevacizumab (blinded treatment phase plus optional open-label post-progression phase and/or extended treatment phase) was increased to 48 months; this allowed subjects who were benefiting from bevacizumab treatment to continue to receive it. |
| 12 May 2011 | <p>Study AVF3694g was amended to remove the maximum duration of treatment with bevacizumab (blinded treatment phase plus optional open-label post-progression phase and/or extended treatment phase) to all participants receiving study treatment when the study analysis was complete, if the primary efficacy analysis shows significant improvement with bevacizumab without a detrimental effect on subject safety. This was allow participants who are benefiting from bevacizumab treatment to continue to receive it. Other significant changes to the protocol has been described below:</p> <ul style="list-style-type: none"> • Study treatment information and the study assessment schedule have been updated to reflect the amended duration of treatment of the optional extended treatment phase. • Only serious adverse event data was continue to be collected and reported as currently required by the protocol. Participants who were no longer receiving bevacizumab through the study have completed the study, and no further data need to be recorded. • Bevacizumab safety information was updated. • The sample Informed Consent Form was revised to reflect the changes to the protocol and the updated risk section. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported