



Clinical trial results:

A Randomized, Double-Blind, Phase 3 Study Evaluating The Efficacy And Safety Of ABP 215 Compared With Bevacizumab In Subjects With Advanced Non-Small Cell Lung Cancer

Summary

| | |
|--------------------------|----------------------------|
| EudraCT number | 2013-000738-36 |
| Trial protocol | HU CZ DE IT ES NL GR BG PL |
| Global end of trial date | 23 July 2015 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 28 July 2016 |
| First version publication date | 28 July 2016 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 20120265 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01966003 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 23 July 2015 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 23 July 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective for this study was to compare the efficacy of ABP 215 with bevacizumab.

Protection of trial subjects:

This study was conducted in accordance with the Note for Guidance on GCP (ICH Harmonised Tripartite Guideline E6 (R1); FDA CFR (21 CFR § 50, 56, 312)), Declaration of Helsinki, and all applicable regulatory requirements.

This study was conducted in compliance with Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines - including Title 21 Part 56 of the US Code of Federal Regulations (CFR) relating to IRBs/IECs and GCP as described in the US Food and Drug Administration (FDA) CFR (21 CFR § 50, 56, 312) - in accordance with applicable ICH regulations regarding clinical safety data management (E2A, E2B(R3)), European Community directives 2001/20, 2001/83, 2003/94 and 2005/28 as enacted into local law, and with ICH guidelines regarding scientific integrity (E4, E8, E9, and E10). In addition this study adhered to all local regulatory requirements and requirements for data protection. The investigator explained the benefits and risks of participation in the study to each subject or the subject's legally acceptable representative and obtained written informed consent. Written informed consent was required to be obtained prior to the subject entering the study and before initiation of any study-related procedure (including administration of investigational product [IP]).

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 11 November 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Russian Federation: 113 |
| Country: Number of subjects enrolled | Hungary: 78 |
| Country: Number of subjects enrolled | Romania: 78 |
| Country: Number of subjects enrolled | Poland: 54 |
| Country: Number of subjects enrolled | Greece: 26 |
| Country: Number of subjects enrolled | Bulgaria: 15 |
| Country: Number of subjects enrolled | Czech Republic: 11 |
| Country: Number of subjects enrolled | Spain: 44 |
| Country: Number of subjects enrolled | Italy: 25 |
| Country: Number of subjects enrolled | Netherlands: 9 |
| Country: Number of subjects enrolled | United States: 45 |

| | |
|--------------------------------------|---------------|
| Country: Number of subjects enrolled | Mexico: 9 |
| Country: Number of subjects enrolled | Canada: 3 |
| Country: Number of subjects enrolled | Australia: 50 |
| Country: Number of subjects enrolled | Taiwan: 5 |
| Country: Number of subjects enrolled | Hong Kong: 1 |
| Country: Number of subjects enrolled | Germany: 76 |
| Worldwide total number of subjects | 642 |
| EEA total number of subjects | 416 |

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) | 390 |
| From 65 to 84 years | 252 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 101 sites (14 sites in the US, 11 in Russia, 10 in Australia, 9 in Germany, 8 in Poland, 7 in Hungary, 7 in Romania, 6 in Italy, 6 in Spain, 5 in Bulgaria, 5 in Greece, 3 in the Czech Republic, 3 in Mexico, 3 in Taiwan, 2 in the Netherlands, 1 in Canada, and 1 in Hong Kong).

Pre-assignment

Screening details:

Eligible participants were randomized in a 1:1 ratio to receive ABP 215 or bevacizumab. Subjects were stratified by geographic region (Eastern Europe vs Western Europe vs Asia Pacific/Other vs North America), Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1), and sex.

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 | ABP 215 |

Arm description:

Participants received 15 mg/kg ABP 215 administered as an intravenous (IV) infusion every 3 weeks (Q3W) for 6 cycles and carboplatin and paclitaxel chemotherapy Q3W for at least 4 and not more than 6 cycles.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | ABP 215 |
| Investigational medicinal product code | ABP 215 |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Administered 15 mg/kg Q3W by IV infusion

| | |
|--|-----------------------|
| Investigational medicinal product name | Carboplatin |
| Investigational medicinal product code | |
| Other name | Paraplatin |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Administered at an area under the concentration-time curve (AUC) 6 by IV infusion Q3W

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

Dosage and administration details:

Administered 200 mg/m² IV Q3W

| | |
|------------------|-------------|
| Arm title | Bevacizumab |
|------------------|-------------|

Arm description:

Participants received bevacizumab 15 mg/kg administered as an intravenous (IV) infusion every 3 weeks (Q3W) for 6 cycles and carboplatin and paclitaxel chemotherapy Q3W for at least 4 and not more

than 6 cycles.

| | |
|--|-----------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Bevacizumab |
| Investigational medicinal product code | |
| Other name | Avastin® |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

15 mg/kg Q3W by IV infusion

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

Dosage and administration details:

Administered 200 mg/m² IV Q3W

| | |
|--|-----------------------|
| Investigational medicinal product name | Carboplatin |
| Investigational medicinal product code | |
| Other name | Paraplatin |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Administered at an area under the concentration-time curve (AUC) 6 by IV infusion Q3W

| Number of subjects in period 1 | ABP 215 | Bevacizumab |
|--|----------------|--------------------|
| Started | 328 | 314 |
| Received Study Drug | 324 | 309 |
| Completed | 58 | 44 |
| Not completed | 270 | 270 |
| Consent withdrawn by subject | 29 | 19 |
| Physician decision | 12 | 13 |
| Plan to receive commercial bevacizumab | 44 | 67 |
| Death | 43 | 36 |
| Other | 1 | 1 |
| Plan to receive non-study anticancer therapy | 131 | 127 |
| Lost to follow-up | 4 | 3 |
| Protocol deviation | 6 | 4 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | ABP 215 |
|-----------------------|---------|

Reporting group description:

Participants received 15 mg/kg ABP 215 administered as an intravenous (IV) infusion every 3 weeks (Q3W) for 6 cycles and carboplatin and paclitaxel chemotherapy Q3W for at least 4 and not more than 6 cycles.

| | |
|-----------------------|-------------|
| Reporting group title | Bevacizumab |
|-----------------------|-------------|

Reporting group description:

Participants received bevacizumab 15 mg/kg administered as an intravenous (IV) infusion every 3 weeks (Q3W) for 6 cycles and carboplatin and paclitaxel chemotherapy Q3W for at least 4 and not more than 6 cycles.

| Reporting group values | ABP 215 | Bevacizumab | Total |
|---|----------------|----------------|-------|
| Number of subjects | 328 | 314 | 642 |
| Age Categorical Units: Subjects | | | |
| < 65 years | 199 | 191 | 390 |
| ≥ 65 years | 129 | 123 | 252 |
| Age Continuous Units: years arithmetic mean standard deviation | 61.6 ± 9.09 | 61.6 ± 8.88 | - |
| Gender Categorical Units: Subjects | | | |
| Female | 132 | 126 | 258 |
| Male | 196 | 188 | 384 |
| Geographic Region Units: Subjects | | | |
| Eastern Europe | 189 | 186 | 375 |
| Western Europe | 78 | 76 | 154 |
| North America | 31 | 26 | 57 |
| Asia Pacific/Other | 30 | 26 | 56 |
| Eastern Cooperative Oncology Group (ECOG) Performance Status Units: Subjects | | | |
| Grade 0 | 127 | 117 | 244 |
| Grade 1 | 201 | 197 | 398 |

End points

End points reporting groups

| | |
|---|-------------|
| Reporting group title | ABP 215 |
| Reporting group description: Participants received 15 mg/kg ABP 215 administered as an intravenous (IV) infusion every 3 weeks (Q3W) for 6 cycles and carboplatin and paclitaxel chemotherapy Q3W for at least 4 and not more than 6 cycles. | |
| Reporting group title | Bevacizumab |
| Reporting group description: Participants received bevacizumab 15 mg/kg administered as an intravenous (IV) infusion every 3 weeks (Q3W) for 6 cycles and carboplatin and paclitaxel chemotherapy Q3W for at least 4 and not more than 6 cycles. | |

Primary: Percentage of Participants with an Objective Response

| | |
|--|---|
| End point title | Percentage of Participants with an Objective Response |
| End point description: Tumor assessments were performed by central, independent, blinded radiologists according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 using computed tomography (CT) or magnetic resonance imaging (MRI) scans of the chest and abdomen. Objective response is defined as a best overall response of partial response (PR) or complete response (CR) as defined by RECIST v1.1. All participants who did not meet the criteria for CR or PR at the end of the study were considered non-responders. The primary analysis for ORR was based on the intent-to-treat (ITT) population (all randomized subjects). | |
| End point type | Primary |
| End point timeframe: Weeks 7, 13, 19, and approximately every 9 weeks thereafter. The mean (STD) actual follow-up time from randomization was 4.7 (3.04) and 5.0 (3.17) months for ABP 215 and bevacizumab, respectively. | |

| End point values | ABP 215 | Bevacizumab | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 328 | 314 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 39 | 41.7 | | |

Statistical analyses

| | |
|--|----------------------------------|
| Statistical analysis title | Risk Ratio (ABP 215/Bevacizumab) |
| Statistical analysis description: The risk ratio and 90% confidence interval (CI) were estimated using a generalized linear model adjusted for the stratification factors (region, sex, and ECOG performance status). | |
| Comparison groups | ABP 215 v Bevacizumab |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 642 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[1] |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.93 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 1.09 |

Notes:

[1] - Clinical equivalence of the primary endpoint was demonstrated by comparing the 2-sided 90% CI of the risk ratio in ORR between ABP 215 and bevacizumab with an equivalence margin of (0.67, 1.5).

| | |
|-----------------------------------|---|
| Statistical analysis title | Risk Difference (ABP 215 - Bevacizumab) |
|-----------------------------------|---|

Statistical analysis description:

Risk difference and 90% CI were estimated using a generalized linear model adjusted for the randomization stratification factors geographic region, ECOG performance status, and sex.

| | |
|---|-----------------------|
| Comparison groups | ABP 215 v Bevacizumab |
| Number of subjects included in analysis | 642 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Risk difference (RD) |
| Point estimate | -2.9 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -9.26 |
| upper limit | 3.45 |

Secondary: Duration of Response

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

End point description:

Duration of response (DOR) was calculated as the time from the first objective response (PR or CR) to disease progression per RECIST v1.1 based on the central, independent, blinded radiologists' review. DOR was only calculated for participants with a response. For responders not meeting the criterion for progression by the end of the study, DOR was censored at the date of the last evaluable tumor assessment.

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

End point timeframe:

Weeks 7, 13, 19, and approximately every 9 weeks thereafter. The mean (STD) actual follow-up time from randomization was 4.7 (3.04) and 5.0 (3.17) months for ABP 215 and bevacizumab, respectively.

| End point values | ABP 215 | Bevacizumab | | |
|----------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 128 | 131 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 5.8 (4.9 to 7.7) | 5.6 (5.1 to 6.3) | | |

Statistical analyses

| Statistical analysis title | Hazard Ratio for Duration of Response |
|---|---------------------------------------|
| Statistical analysis description: | |
| The hazard ratio for ABP 215 relative to bevacizumab is based on a stratified Cox proportional hazards model. Stratification factors are geographic region, ECOG performance status, and sex. | |
| Comparison groups | ABP 215 v Bevacizumab |
| Number of subjects included in analysis | 259 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.76 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.51 |
| upper limit | 1.14 |

Secondary: Progression-free Survival

| End point title | Progression-free Survival |
|---|---------------------------|
| End point description: | |
| Progression-free survival (PFS) was defined as the time from the randomization date to the date of disease progression using RECIST v1.1 based on the central, independent, blinded radiologists' review, or death. Subjects who were alive and did not meet the criteria for progression by the end of the study were censored at their last evaluable disease assessment date. Subjects with no evaluable tumor assessments after randomization who did not die by the end of the study had their PFS times censored on the randomization date. | |
| End point type | Secondary |
| End point timeframe: | |
| Weeks 7, 13, 19, and approximately every 9 weeks thereafter. The mean (STD) actual follow-up time from randomization was 4.7 (3.04) and 5.0 (3.17) months for ABP 215 and bevacizumab, respectively. | |

| End point values | ABP 215 | Bevacizumab | | |
|----------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 328 | 314 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 6.6 (6.3 to 7.9) | 7.9 (6.6 to 8.2) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Hazard Ratio for Progression-free Survival |
| Statistical analysis description: The hazard ratio for ABP 215 relative to bevacizumab was based on a stratified Cox proportional hazards model. Stratification factors are geographic region, ECOG performance status, and sex. | |
| Comparison groups | ABP 215 v Bevacizumab |
| Number of subjects included in analysis | 642 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.03 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.83 |
| upper limit | 1.29 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

19 weeks

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | ABP 215 |
|-----------------------|---------|

Reporting group description:

Participants received 15 mg/kg ABP 215 administered as an intravenous (IV) infusion every 3 weeks (Q3W) for 6 cycles and carboplatin and paclitaxel chemotherapy Q3W for at least 4 and not more than 6 cycles.

| | |
|-----------------------|-------------|
| Reporting group title | Bevacizumab |
|-----------------------|-------------|

Reporting group description:

Participants received bevacizumab 15 mg/kg administered as an intravenous (IV) infusion every 3 weeks (Q3W) for 6 cycles and carboplatin and paclitaxel chemotherapy Q3W for at least 4 and not more than 6 cycles.

| Serious adverse events | ABP 215 | Bevacizumab | |
|---|-------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 85 / 324 (26.23%) | 71 / 309 (22.98%) | |
| number of deaths (all causes) | 13 | 11 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Metastases to bone | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-----------------|-----------------|--|
| Embolism arterial | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Venous thrombosis | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Prophylaxis | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 2 / 324 (0.62%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 324 (0.62%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| General physical health deterioration | | | |
| subjects affected / exposed | 2 / 324 (0.62%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchial fistula | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 324 (0.93%) | 4 / 309 (1.29%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 2 / 324 (0.62%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoptysis | | | |
| subjects affected / exposed | 3 / 324 (0.93%) | 5 / 309 (1.62%) | |
| occurrences causally related to treatment / all | 0 / 3 | 5 / 6 | |
| deaths causally related to treatment / all | 0 / 2 | 1 / 2 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 2 / 324 (0.62%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary artery thrombosis | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 5 / 324 (1.54%) | 6 / 309 (1.94%) | |
| occurrences causally related to treatment / all | 1 / 5 | 4 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory distress | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 2 / 324 (0.62%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Hallucinations, mixed | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Brain contusion | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Lumbar vertebral fracture subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Road traffic accident subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Toxicity to various agents subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute left ventricular failure subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Acute myocardial infarction subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation subjects affected / exposed | 1 / 324 (0.31%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiopulmonary failure subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Coronary artery disease | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paroxysmal arrhythmia | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Brain oedema | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 2 / 324 (0.62%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depressed level of consciousness | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysarthria | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalopathy | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 324 (0.62%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic cerebral infarction | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Migraine | | | |
| subjects affected / exposed | 2 / 324 (0.62%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord compression | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 2 / 324 (0.62%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 324 (0.93%) | 6 / 309 (1.94%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 11 / 324 (3.40%) | 8 / 309 (2.59%) | |
| occurrences causally related to treatment / all | 0 / 14 | 2 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercoagulation | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Neutropenia | | | |
| subjects affected / exposed | 6 / 324 (1.85%) | 3 / 309 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 2 / 324 (0.62%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal haemorrhage | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 324 (0.93%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea haemorrhagic | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticular perforation | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Faecaloma | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Intestinal perforation | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 324 (0.31%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Large intestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine perforation | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Melaena | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mesenteric artery embolism | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 2 / 324 (0.62%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 2 / 324 (0.62%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 2 / 2 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 324 (0.62%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatitis | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash generalised | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subcutaneous emphysema | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological fracture | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abscess soft tissue | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal abscess | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopulmonary aspergillosis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cytomegalovirus hepatitis | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Empyema | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia bacteraemia | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pilonidal cyst | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 6 / 324 (1.85%) | 5 / 309 (1.62%) | |
| occurrences causally related to treatment / all | 1 / 6 | 1 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pseudomonas infection | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary sepsis | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 2 / 324 (0.62%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 324 (0.31%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Cachexia | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | ABP 215 | Bevacizumab | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 286 / 324 (88.27%) | 276 / 309 (89.32%) | |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 18 / 324 (5.56%) | 16 / 309 (5.18%) | |
| occurrences (all) | 19 | 16 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 51 / 324 (15.74%) | 41 / 309 (13.27%) | |
| occurrences (all) | 66 | 70 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 13 / 324 (4.01%) | 25 / 309 (8.09%) | |
| occurrences (all) | 17 | 33 | |
| Headache | | | |
| subjects affected / exposed | 28 / 324 (8.64%) | 24 / 309 (7.77%) | |
| occurrences (all) | 30 | 32 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 56 / 324 (17.28%) | 38 / 309 (12.30%) | |
| occurrences (all) | 86 | 60 | |
| Paraesthesia | | | |
| subjects affected / exposed | 28 / 324 (8.64%) | 40 / 309 (12.94%) | |
| occurrences (all) | 34 | 50 | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 18 / 324 (5.56%) | 16 / 309 (5.18%) | |
| occurrences (all) | 23 | 34 | |
| Polyneuropathy | | | |
| subjects affected / exposed | 20 / 324 (6.17%) | 22 / 309 (7.12%) | |
| occurrences (all) | 26 | 28 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 65 / 324 (20.06%) | 60 / 309 (19.42%) | |
| occurrences (all) | 111 | 92 | |
| Leukopenia | | | |

| | | | |
|---|--------------------------|--------------------------|--|
| subjects affected / exposed occurrences (all) | 23 / 324 (7.10%) 38 | 23 / 309 (7.44%) 56 | |
| Neutropenia subjects affected / exposed occurrences (all) | 55 / 324 (16.98%) 113 | 60 / 309 (19.42%) 112 | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 47 / 324 (14.51%) 83 | 43 / 309 (13.92%) 79 | |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 49 / 324 (15.12%) 91 | 42 / 309 (13.59%) 62 | |
| Fatigue subjects affected / exposed occurrences (all) | 57 / 324 (17.59%) 70 | 59 / 309 (19.09%) 84 | |
| Pyrexia subjects affected / exposed occurrences (all) | 19 / 324 (5.86%) 22 | 20 / 309 (6.47%) 27 | |
| Gastrointestinal disorders | | | |
| Constipation subjects affected / exposed occurrences (all) | 36 / 324 (11.11%) 39 | 36 / 309 (11.65%) 48 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 39 / 324 (12.04%) 51 | 55 / 309 (17.80%) 79 | |
| Gingival bleeding subjects affected / exposed occurrences (all) | 9 / 324 (2.78%) 9 | 19 / 309 (6.15%) 22 | |
| Nausea subjects affected / exposed occurrences (all) | 82 / 324 (25.31%) 124 | 95 / 309 (30.74%) 159 | |
| Stomatitis subjects affected / exposed occurrences (all) | 15 / 324 (4.63%) 17 | 18 / 309 (5.83%) 26 | |
| Vomiting | | | |

| | | | |
|---|---|---|--|
| subjects affected / exposed occurrences (all) | 37 / 324 (11.42%) 44 | 41 / 309 (13.27%) 54 | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) | 26 / 324 (8.02%) 30 24 / 324 (7.41%) 26 44 / 324 (13.58%) 48 | 21 / 309 (6.80%) 21 24 / 309 (7.77%) 28 39 / 309 (12.62%) 60 | |
| Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) | 140 / 324 (43.21%) 167 | 127 / 309 (41.10%) 159 | |
| Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all) | 26 / 324 (8.02%) 39 | 19 / 309 (6.15%) 25 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Bone pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) | 23 / 324 (7.10%) 25 14 / 324 (4.32%) 15 20 / 324 (6.17%) 24 39 / 324 (12.04%) 78 24 / 324 (7.41%) 28 | 29 / 309 (9.39%) 48 19 / 309 (6.15%) 22 25 / 309 (8.09%) 33 44 / 309 (14.24%) 76 20 / 309 (6.47%) 20 | |

| | | | |
|--|-------------------------|-------------------------|--|
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 54 / 324 (16.67%) 65 | 42 / 309 (13.59%) 52 | |
|--|-------------------------|-------------------------|--|

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|--|
| 22 April 2013 | The primary purposes of Amendment 1 were the following: • Modify the restrictions on chemotherapy pretreatment regimens and treatment regimens for chemotherapy-associated toxicities to accommodate differing international standards • Clarify that the scheduling of tumor assessments should be independent of treatment delays • Add an ADA sample to be collected approximately 6 months after the end of treatment visit for subjects still on study • Clarify that screening radiologic assessment must be MRI or CT and must include both the chest and abdomen • Clarify that abstinence must be true abstinence to be an acceptable method of birth control • Clarify that the study duration was approximately 25 weeks „h Specify that if chemotherapy was delayed due to toxicity, IP should be given according to the original schedule (ie, Q3W) • Clarify that the treatment period ends 21 days after the last dose of study medication or study-specified chemotherapy. |
| 24 March 2014 | The primary purposes of Amendment 2 were the following: • Clarify the entry criteria to o more clearly specify the exclusionary periods for certain medical histories o specify that subjects with low dose anti-coagulation therapy for peripheral port patency were permitted • Revised the primary analysis to be based on the ITT analysis set and updated power calculations. • Clarify the definition of end of the clinical study as 21 days after the last subject on study receives the last dose of IP and/or chemotherapy • Clarify and update the recommended dose adjustments • Update the definition of DOR to reflect that response confirmation is not required and to specify that response and progression were defined by modified RECIST v1.1 • Specify that CT or MRI performed as routine standard of care, prior to the subject signing informed consent, could be used for screening purposes, as long as the assessments were performed within 28 days before randomization, and that baseline assessment (physical examination, vital signs, and clinical laboratory assessments) could be performed 1 day before treatment. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported