# Clinical trial results:
# An Open-label, Randomized, Phase 3 Study of Nivolumab or Chemotherapy in Subjects with Relapsed Small-cell Lung Cancer after Platinum-based First Line Chemotherapy
# (CheckMate 331: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 331)

## Summary

| | |
|---|---|
| EudraCT number | 2015-001097-18 |
| Trial protocol | CZ AT DE BE GB DK HU GR PL ES FR RO IT |
| Global end of trial date | 22 August 2022 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 05 August 2023 |
| First version publication date | 05 August 2023 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | CA209-331 |

**Additional study identifiers**

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

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Bristol-Myers Squibb |
| Sponsor organisation address | Chaussee de la Hulpe 185, Brussels, Belgium, 1170 |
| Public contact | Bristol-Myers Squibb International Corporation, EU Study Start-Up Unit, Clinical.Trials@bms.com |
| Scientific contact | Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.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 | 11 October 2022 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 22 August 2022 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

Compare efficacy of Nivolumab versus chemotherapy in subjects with relapsed small-cell lung cancer (SCLC) after platinum-based, first-line chemotherapy.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 14 September 2015 |
| 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 | Austria: 5 |
| Country: Number of subjects enrolled | Australia: 15 |
| Country: Number of subjects enrolled | Belgium: 18 |
| Country: Number of subjects enrolled | Brazil: 11 |
| Country: Number of subjects enrolled | Chile: 2 |
| Country: Number of subjects enrolled | China: 82 |
| Country: Number of subjects enrolled | Czechia: 4 |
| Country: Number of subjects enrolled | Denmark: 8 |
| Country: Number of subjects enrolled | France: 36 |
| Country: Number of subjects enrolled | Germany: 62 |
| Country: Number of subjects enrolled | Greece: 13 |
| Country: Number of subjects enrolled | Hungary: 4 |
| Country: Number of subjects enrolled | Israel: 7 |
| Country: Number of subjects enrolled | Italy: 24 |
| Country: Number of subjects enrolled | Japan: 46 |
| Country: Number of subjects enrolled | Korea, Democratic People's Republic of: 13 |
| Country: Number of subjects enrolled | Norway: 10 |
| Country: Number of subjects enrolled | Poland: 26 |
| Country: Number of subjects enrolled | Romania: 32 |
| Country: Number of subjects enrolled | Russian Federation: 15 |

| | |
|---|---|
| Country: Number of subjects enrolled | Spain: 57 |
| Country: Number of subjects enrolled | Switzerland: 11 |
| Country: Number of subjects enrolled | United Kingdom: 17 |
| Country: Number of subjects enrolled | United States: 51 |
| Worldwide total number of subjects | 569 |
| EEA total number of subjects | 299 |

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) | 347 |
| From 65 to 84 years | 221 |
| 85 years and over | 1 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

569 randomized and 547 treated

### Period 1

| | |
|---|---|
| Period 1 title | Pre-treatment |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Group A |

Arm description:

Nivolumab 240mg IV on Day 1 of a 14-day cycle

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

Dosage and administration details:

240mg on Day 1 of a 14-day cycle

| | |
|---|---|
| **Arm title** | Group B |

Arm description:

Chemotherapy (Topotecan 1.5 mg/m^2 IV or 2.3 mg/m^2 Oral once daily on Days 1 to 5 of a 21-day cycle / Amrubicin 40 mg/m^2 IV once daily on Days 1 to 3 of a 21-day cycle)

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

Dosage and administration details:

40 mg/m^2 once daily on Days 1 to 3 of a 21-day cycle

| | |
|---|---|
| Investigational medicinal product name | Topotecan |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion, Capsule |
| Routes of administration | Intravenous use, Oral use |

Dosage and administration details:

1.5 mg/m^2 IV OR 2.3 mg/m^2 oral once daily on Days 1 to 5 of a 21-day cycle

| Number of subjects in period 1 | Group A | Group B |
|---|---|---|
| Started | 284 | 285 |
| Completed | 282 | 265 |
| Not completed | 2 | 20 |
| Consent withdrawn by subject | - | 10 |
| subject request to discontinue study treatment | - | 4 |
| Other reasons | 1 | 1 |
| Participant no longer meets Study Criteria | - | 4 |
| Disease Progression | 1 | 1 |

| Period 2 | |
|---|---|
| Period 2 title | Treatment |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

**Arms**

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Group A |

Arm description:

Nivolumab 240mg IV on Day 1 of a 14-day cycle

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

Dosage and administration details:

240mg on Day 1 of a 14-day cycle

| | |
|---|---|
| **Arm title** | Group B |

Arm description:

Chemotherapy (Topotecan 1.5 mg/m^2 IV or 2.3 mg/m^2 Oral once daily on Days 1 to 5 of a 21-day cycle / Amrubicin 40 mg/m^2 IV once daily on Days 1 to 3 of a 21-day cycle)

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

Dosage and administration details:

40 mg/m^2 once daily on Days 1 to 3 of a 21-day cycle

| | |
|---|---|
| Investigational medicinal product name | Topotecan |
| Investigational medicinal product code | |
| Other name | |

| | |
|---|---|
| Pharmaceutical forms | Infusion, Capsule |
| Routes of administration | Intravenous use, Oral use |

Dosage and administration details:

1.5 mg/m^2 IV OR 2.3 mg/m^2 oral once daily on Days 1 to 5 of a 21-day cycle

| **Number of subjects in period 2** | Group A | Group B |
|---|---|---|
| Started | 282 | 265 |
| Completed | 0 | 0 |
| Not completed | 282 | 265 |
| Adverse event, serious fatal | 1 | 1 |
| Consent withdrawn by subject | 2 | 3 |
| Study drug toxicity | 18 | 38 |
| Adverse Event unrelated to Study drug | 14 | 11 |
| Maximum Clinical Benefit | - | 5 |
| subject request to discontinue study treatment | 6 | 34 |
| Other reasons | 6 | 1 |
| Lost to follow-up | 1 | - |
| Disease Progression | 233 | 171 |
| Administrative reason by sponsor | 1 | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Group A |
| Reporting group description: | |
| Nivolumab 240mg IV on Day 1 of a 14-day cycle | |
| Reporting group title | Group B |
| Reporting group description: | |
| Chemotherapy (Topotecan 1.5 mg/m^2 IV or 2.3 mg/m^2 Oral once daily on Days 1 to 5 of a 21-day cycle / Amrubicin 40 mg/m^2 IV once daily on Days 1 to 3 of a 21-day cycle) | |

| Reporting group values | Group A | Group B | Total |
|---|---|---|---|
| Number of subjects | 284 | 285 | 569 |
| Age categorical | | | |
| Units: | | | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 61.5 | 61.6 | |
| standard deviation | ± 9.2 | ± 8.4 | - |
| Sex: Female, Male | | | |
| Units: Participants | | | |
| Female | 110 | 108 | 218 |
| Male | 174 | 177 | 351 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 1 | 1 |
| Asian | 70 | 71 | 141 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 1 | 2 | 3 |
| White | 211 | 211 | 422 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 2 | 0 | 2 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 4 | 6 | 10 |
| Not Hispanic or Latino | 125 | 142 | 267 |
| Unknown or Not Reported | 155 | 137 | 292 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Group A |
| Reporting group description: | |
| Nivolumab 240mg IV on Day 1 of a 14-day cycle | |
| Reporting group title | Group B |
| Reporting group description: | |
| Chemotherapy (Topotecan 1.5 mg/m^2 IV or 2.3 mg/m^2 Oral once daily on Days 1 to 5 of a 21-day cycle / Amrubicin 40 mg/m^2 IV once daily on Days 1 to 3 of a 21-day cycle) | |
| Reporting group title | Group A |
| Reporting group description: | |
| Nivolumab 240mg IV on Day 1 of a 14-day cycle | |
| Reporting group title | Group B |
| Reporting group description: | |
| Chemotherapy (Topotecan 1.5 mg/m^2 IV or 2.3 mg/m^2 Oral once daily on Days 1 to 5 of a 21-day cycle / Amrubicin 40 mg/m^2 IV once daily on Days 1 to 3 of a 21-day cycle) | |

### Primary: Overall Survival (OS)

| | |
|---|---|
| End point title | Overall Survival (OS) |
| End point description: | |
| The time from randomization to the date of death, data was based on Kaplan-Meier Estimates. A participant who has not died will be censored at last known date alive. | |
| End point type | Primary |
| End point timeframe: | |
| OS was followed continuously while participants were on the study drug and every 3 months, minimum follow up for overall survival was 15.8 months | |

| End point values | Group A | Group B | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 284 | 285 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 7.46 (5.65 to 9.20) | 8.38 (7.03 to 10.02) | | |

### Statistical analyses

| Statistical analysis title | Hazard Ratio (HR) |
|---|---|
| Comparison groups | Group A v Group B |

| | |
|---|---|
| Number of subjects included in analysis | 569 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1144 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.72 |
| upper limit | 1.04 |

## Secondary: Objective Response Rate (ORR)

| | |
|---|---|
| End point title | Objective Response Rate (ORR) |

End point description:

ORR is defined as the percentage of randomized participants whose best overall response (BOR) from baseline is either a complete response (CR) or partial response (PR) based on investigator assessment per RECIST 1.1 criteria. For participants without documented progression or subsequent anti-cancer therapy, all available response designations will contribute to the BOR determination. For participants who continue nivolumab beyond progression, the BOR should be determined based on tumor assessments before initial RECIST 1.1 defined progression.
CR= Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to <10 mm.
PR= At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive disease (PD)= At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. The sum must demonstrate an absolute increase of at least 5 mm.

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

End point timeframe:

From randomization to the date of objectively documented progression or the date of subsequent anti-cancer therapy, whichever occurs first (Up to approximately 80 months)

| **End point values** | Group A | Group B | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 284 | 285 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 13.7 (10.0 to 18.3) | 16.8 (12.7 to 21.7) | | |

### Statistical analyses

| **Statistical analysis title** | Estimate of Odds Ratio (OR) |
|---|---|
| Comparison groups | Group A v Group B |

| | |
|---|---|
| Number of subjects included in analysis | 569 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Estimate of Odds Ratio (OR) |
| Point estimate | 0.78 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.49 |
| upper limit | 1.24 |

## Secondary: Progression Free Survival (PFS)

| | |
|---|---|
| End point title | Progression Free Survival (PFS) |

End point description:

PFS is defined as the time from randomization to the date of the first documented tumor progression based on investigator assessment (per RECIST 1.1), or death due to any cause. Participants who die without a reported prior progression will be considered to have progressed on the date of their death. Participants who did not progress or die will be censored on the date of their last evaluable tumor assessment. Participants who did not have any on study tumor assessments and did not die will be censored on the date they were randomized. Participants who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anti-cancer therapy.
Progressive disease (PD)= At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. The sum must demonstrate an absolute increase of at least 5 mm.

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

End point timeframe:

From randomization to the date of first documented tumor progression, or death due to any cause. Tumor response assessed every 6 weeks from first dose until week 30, and every 12 weeks (Up to approximately 80 months)

| **End point values** | Group A | Group B | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 284 | 285 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 1.45 (1.41 to 1.51) | 3.71 (2.96 to 4.24) | | |

### Statistical analyses

| **Statistical analysis title** | Hazard Ratio (HR) |
|---|---|
| Comparison groups | Group A v Group B |

| | |
|---|---|
| Number of subjects included in analysis | 569 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.39 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.16 |
| upper limit | 1.66 |

## Post-hoc: Overall Survival (OS) - Extended Collection

| | |
|---|---|
| End point title | Overall Survival (OS) - Extended Collection |

End point description:

The time from randomization to the date of death, data was based on Kaplan-Meier Estimates. A participant who has not died will be censored at last known date alive.

| | |
|---|---|
| End point type | Post-hoc |

End point timeframe:

OS was followed continuously while participants were on the study drug and every 3 months, minimum follow up for overall survival was 64 months (Up to approximately 80 months)

| **End point values** | Group A | Group B | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 284 | 285 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 7.46 (5.65 to 9.20) | 8.38 (7.03 to 10.02) | | |

### Statistical analyses

| **Statistical analysis title** | Hazard Ratio (HR) |
|---|---|
| Comparison groups | Group A v Group B |
| Number of subjects included in analysis | 569 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.87 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.73 |
| upper limit | 1.04 |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

SAEs and NSAEs are assessed from first dose to 100 days post last dose (Up to approximately 72 months). Participants were assessed for deaths (all causes) from their first dose to study completion (Up to approximately 80 months).

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 25.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Group B |

Reporting group description:

Chemotherapy (Topotecan 1.5 mg/m^2 IV or 2.3 mg/m^2 oral once daily on Days 1 to 5 of a 21-day cycle / Amrubicin 40 mg/m^2 IV once daily on Days 1 to 3 of a 21-day cycle)

| | |
|---|---|
| Reporting group title | Group A |

Reporting group description:

Nivolumab 240mg IV on Day 1 of a 14-day cycle

| Serious adverse events | Group B | Group A | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 171 / 265 (64.53%) | 183 / 282 (64.89%) | |
| number of deaths (all causes) | 246 | 249 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tongue neoplasm | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adenocarcinoma | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cancer pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epiglottic cancer | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 85 / 265 (32.08%) | 108 / 282 (38.30%) | |
| occurrences causally related to treatment / all | 0 / 89 | 0 / 116 | |
| deaths causally related to treatment / all | 0 / 79 | 0 / 96 | |
| Pericardial effusion malignant | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Second primary malignancy | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of lung | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of the tongue | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour invasion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour pain | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Poor venous access | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Superior vena cava syndrome | | | |
| subjects affected / exposed | 2 / 265 (0.75%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Performance status decreased | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 2 / 265 (0.75%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 6 / 265 (2.26%) | 8 / 282 (2.84%) | |
| occurrences causally related to treatment / all | 1 / 8 | 1 / 8 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 4 | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Chest pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Asthenia | | | |
| subjects affected / exposed | 5 / 265 (1.89%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 265 (1.13%) | 4 / 282 (1.42%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malaise | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 2 / 282 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atelectasis | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchial obstruction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 2 / 265 (0.75%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cough | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 8 / 265 (3.02%) | 9 / 282 (3.19%) | |
| occurrences causally related to treatment / all | 1 / 8 | 1 / 9 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoptysis | | | |
| subjects affected / exposed | 3 / 265 (1.13%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infiltration | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophagobronchial fistula | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 265 (0.75%) | 2 / 282 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleurisy | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 10 / 282 (3.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 9 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 4 / 265 (1.51%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory distress | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |

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|---|---|---|---|
| subjects affected / exposed | 2 / 265 (0.75%) | 2 / 282 (0.71%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Mediastinal disorder | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 2 / 265 (0.75%) | 2 / 282 (0.71%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Delirium | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disorientation | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Investigations | | | |
| Amylase increased | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|---|---|---|
| Blood electrolytes abnormal | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| C-reactive protein increased | | | |
| subjects affected / exposed | 2 / 265 (0.75%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 2 / 282 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 10 / 265 (3.77%) | 4 / 282 (1.42%) | |
| occurrences causally related to treatment / all | 12 / 12 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 2 / 265 (0.75%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 4 / 265 (1.51%) | 2 / 282 (0.71%) | |
| occurrences causally related to treatment / all | 3 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Bone contusion | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Contusion | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infusion related reaction | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injection related reaction | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Synovial rupture | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (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 | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac disorders | | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Atrial flutter | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (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 / 265 (0.38%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 2 / 282 (0.71%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac tamponade | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Nervous system disorders | | | |
| Brain oedema | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebellar ataxia | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 2 / 265 (0.75%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hemiparesis | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Lacunar infarction | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neurological symptom | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraneoplastic neurological syndrome | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Seizure | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| 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 / 265 (0.00%) | 1 / 282 (0.35%) | |
| 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 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Toxic encephalopathy | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Blood and lymphatic system disorders** | | | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 3 / 265 (1.13%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |

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|---|---|---|---|
| subjects affected / exposed | 23 / 265 (8.68%) | 7 / 282 (2.48%) | |
| occurrences causally related to treatment / all | 25 / 25 | 0 / 7 | |
| deaths causally related to treatment / all | 3 / 3 | 0 / 1 | |
| Bone marrow failure | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaemia | | | |
| subjects affected / exposed | 14 / 265 (5.28%) | 3 / 282 (1.06%) | |
| occurrences causally related to treatment / all | 13 / 14 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myelosuppression | | | |
| subjects affected / exposed | 10 / 265 (3.77%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 10 / 10 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 11 / 265 (4.15%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 11 / 12 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 8 / 265 (3.02%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 9 / 9 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 15 / 265 (5.66%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 15 / 15 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |

| | | | |
|---|---|---|---|
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal hernia obstructive | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 265 (1.51%) | 4 / 282 (1.42%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 2 / 282 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 2 / 282 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral disorder | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 265 (0.75%) | 2 / 282 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune-mediated enterocolitis | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Duodenal ulcer | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 4 / 282 (1.42%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaundice cholestatic | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraneoplastic pemphigus | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pruritus | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stevens-Johnson syndrome | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Bladder dilatation | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| 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 | 2 / 265 (0.75%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Adrenocorticotropic hormone deficiency | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cushing's syndrome | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Hyperthyroidism | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 2 / 282 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Secondary adrenocortical insufficiency | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inappropriate antidiuretic hormone secretion | | | |
| subjects affected / exposed | 2 / 265 (0.75%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 265 (0.75%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthritis | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoporotic fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 2 / 282 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological fracture | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Bronchitis bacterial | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bullous erysipelas | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic sinusitis | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalitis | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis infectious | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes simplex | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 2 / 282 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infectious pleural effusion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infective exacerbation of chronic obstructive airways disease | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Localised infection | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 4 / 265 (1.51%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ophthalmic herpes zoster | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonsillar abscess | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 9 / 265 (3.40%) | 15 / 282 (5.32%) | |
| occurrences causally related to treatment / all | 1 / 10 | 0 / 17 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 3 | |
| Pneumonia aspiration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural infection | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (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 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 2 / 265 (0.75%) | 3 / 282 (1.06%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 2 / 265 (0.75%) | 2 / 282 (0.71%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 2 / 2 | 0 / 1 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 2 / 282 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular device infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 265 (0.75%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Glucose tolerance impaired | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 2 / 282 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 265 (1.13%) | 5 / 282 (1.77%) | |
| occurrences causally related to treatment / all | 1 / 3 | 2 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Type 1 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 265 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Group B | Group A | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 248 / 265 (93.58%) | 249 / 282 (88.30%) | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 60 / 265 (22.64%) | 65 / 282 (23.05%) | |
| occurrences (all) | 78 | 76 | |
| Fatigue | | | |
| subjects affected / exposed | 78 / 265 (29.43%) | 63 / 282 (22.34%) | |
| occurrences (all) | 95 | 76 | |
| Pyrexia | | | |
| subjects affected / exposed | 37 / 265 (13.96%) | 28 / 282 (9.93%) | |
| occurrences (all) | 37 | 38 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 17 / 265 (6.42%) | 12 / 282 (4.26%) | |
| occurrences (all) | 17 | 12 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 52 / 265 (19.62%) | 63 / 282 (22.34%) | |
| occurrences (all) | 60 | 78 | |
| Dyspnoea | | | |
| subjects affected / exposed | 45 / 265 (16.98%) | 63 / 282 (22.34%) | |
| occurrences (all) | 51 | 80 | |
| Epistaxis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 15 / 265 (5.66%) | 2 / 282 (0.71%) | |
| occurrences (all) | 17 | 2 | |
| Productive cough | | | |
| subjects affected / exposed | 8 / 265 (3.02%) | 20 / 282 (7.09%) | |
| occurrences (all) | 8 | 23 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 17 / 265 (6.42%) | 23 / 282 (8.16%) | |
| occurrences (all) | 25 | 25 | |
| Investigations | | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 9 / 265 (3.40%) | 16 / 282 (5.67%) | |
| occurrences (all) | 10 | 25 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 16 / 265 (6.04%) | 22 / 282 (7.80%) | |
| occurrences (all) | 22 | 28 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 13 / 265 (4.91%) | 22 / 282 (7.80%) | |
| occurrences (all) | 14 | 27 | |
| Amylase increased | | | |
| subjects affected / exposed | 2 / 265 (0.75%) | 15 / 282 (5.32%) | |
| occurrences (all) | 2 | 19 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 11 / 265 (4.15%) | 20 / 282 (7.09%) | |
| occurrences (all) | 14 | 22 | |
| Lipase increased | | | |
| subjects affected / exposed | 4 / 265 (1.51%) | 27 / 282 (9.57%) | |
| occurrences (all) | 6 | 36 | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 14 / 265 (5.28%) | 5 / 282 (1.77%) | |
| occurrences (all) | 18 | 8 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 60 / 265 (22.64%) | 28 / 282 (9.93%) | |
| occurrences (all) | 137 | 44 | |
| Platelet count decreased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 63 / 265 (23.77%) | 20 / 282 (7.09%) | |
| occurrences (all) | 124 | 30 | |
| Weight decreased | | | |
| subjects affected / exposed | 16 / 265 (6.04%) | 26 / 282 (9.22%) | |
| occurrences (all) | 16 | 27 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 46 / 265 (17.36%) | 26 / 282 (9.22%) | |
| occurrences (all) | 123 | 58 | |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction | | | |
| subjects affected / exposed | 16 / 265 (6.04%) | 8 / 282 (2.84%) | |
| occurrences (all) | 22 | 8 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 17 / 265 (6.42%) | 20 / 282 (7.09%) | |
| occurrences (all) | 17 | 21 | |
| Headache | | | |
| subjects affected / exposed | 21 / 265 (7.92%) | 30 / 282 (10.64%) | |
| occurrences (all) | 26 | 35 | |
| Blood and lymphatic system disorders | | | |
| Leukopenia | | | |
| subjects affected / exposed | 41 / 265 (15.47%) | 12 / 282 (4.26%) | |
| occurrences (all) | 114 | 17 | |
| Anaemia | | | |
| subjects affected / exposed | 163 / 265 (61.51%) | 68 / 282 (24.11%) | |
| occurrences (all) | 275 | 95 | |
| Neutropenia | | | |
| subjects affected / exposed | 93 / 265 (35.09%) | 17 / 282 (6.03%) | |
| occurrences (all) | 182 | 25 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 78 / 265 (29.43%) | 19 / 282 (6.74%) | |
| occurrences (all) | 188 | 21 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 14 / 265 (5.28%) | 19 / 282 (6.74%) | |
| occurrences (all) | 16 | 21 | |

| | | | |
|---|---|---|---|
| Abdominal pain upper | | | |
| subjects affected / exposed | 11 / 265 (4.15%) | 16 / 282 (5.67%) | |
| occurrences (all) | 12 | 17 | |
| Stomatitis | | | |
| subjects affected / exposed | 17 / 265 (6.42%) | 12 / 282 (4.26%) | |
| occurrences (all) | 24 | 13 | |
| Nausea | | | |
| subjects affected / exposed | 59 / 265 (22.26%) | 48 / 282 (17.02%) | |
| occurrences (all) | 85 | 61 | |
| Diarrhoea | | | |
| subjects affected / exposed | 44 / 265 (16.60%) | 34 / 282 (12.06%) | |
| occurrences (all) | 56 | 48 | |
| Vomiting | | | |
| subjects affected / exposed | 41 / 265 (15.47%) | 33 / 282 (11.70%) | |
| occurrences (all) | 59 | 48 | |
| Constipation | | | |
| subjects affected / exposed | 49 / 265 (18.49%) | 45 / 282 (15.96%) | |
| occurrences (all) | 59 | 56 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 26 / 265 (9.81%) | 4 / 282 (1.42%) | |
| occurrences (all) | 26 | 4 | |
| Pruritus | | | |
| subjects affected / exposed | 4 / 265 (1.51%) | 27 / 282 (9.57%) | |
| occurrences (all) | 4 | 43 | |
| Rash | | | |
| subjects affected / exposed | 11 / 265 (4.15%) | 21 / 282 (7.45%) | |
| occurrences (all) | 11 | 26 | |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 1 / 265 (0.38%) | 23 / 282 (8.16%) | |
| occurrences (all) | 1 | 23 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 17 / 265 (6.42%) | 27 / 282 (9.57%) | |
| occurrences (all) | 20 | 32 | |

| | | | |
|---|---|---|---|
| Back pain | | | |
| subjects affected / exposed | 25 / 265 (9.43%) | 30 / 282 (10.64%) | |
| occurrences (all) | 27 | 31 | |
| Pain in extremity | | | |
| subjects affected / exposed | 11 / 265 (4.15%) | 16 / 282 (5.67%) | |
| occurrences (all) | 11 | 19 | |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 13 / 265 (4.91%) | 15 / 282 (5.32%) | |
| occurrences (all) | 16 | 21 | |
| Pneumonia | | | |
| subjects affected / exposed | 22 / 265 (8.30%) | 16 / 282 (5.67%) | |
| occurrences (all) | 24 | 18 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 70 / 265 (26.42%) | 79 / 282 (28.01%) | |
| occurrences (all) | 86 | 93 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 8 / 265 (3.02%) | 15 / 282 (5.32%) | |
| occurrences (all) | 10 | 21 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 18 / 265 (6.79%) | 19 / 282 (6.74%) | |
| occurrences (all) | 22 | 27 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 25 / 265 (9.43%) | 24 / 282 (8.51%) | |
| occurrences (all) | 30 | 43 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 15 December 2015 | Study Director and Medical Monitor Updated |
| 07 September 2016 | Analysis timeline and exploratory objectives updated |
| 20 March 2018 | Study personnel updated |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported