



Clinical trial results: versus Pemetrexed with Cisplatin or Carboplatin as First Line Therapy in unresectable Pleural Mesothelioma. CheckMate 743: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 743

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2016-001859-43 |
| Trial protocol | GR NL BE DE FR PL GB IT |
| Global end of trial date | 28 April 2023 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 10 May 2024 |
| First version publication date | 10 May 2024 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | CA209-743 |
|-----------------------|-----------|

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 | Chaussée de la Hulpe 185, Brussels, Belgium, 1170 |
| Public contact | EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, 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 | 14 June 2023 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 April 2023 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Investigate efficacy of nivolumab combined with ipilimumab to pemetrexed plus cisplatin or carboplatin regimen as first line treatment in subjects with unresectable malignant pleural mesothelioma.

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 | 29 November 2016 |
| 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 | Australia: 33 |
| Country: Number of subjects enrolled | Belgium: 19 |
| Country: Number of subjects enrolled | Brazil: 5 |
| Country: Number of subjects enrolled | Chile: 9 |
| Country: Number of subjects enrolled | China: 5 |
| Country: Number of subjects enrolled | Colombia: 16 |
| Country: Number of subjects enrolled | France: 102 |
| Country: Number of subjects enrolled | Germany: 41 |
| Country: Number of subjects enrolled | Greece: 11 |
| Country: Number of subjects enrolled | Italy: 61 |
| Country: Number of subjects enrolled | Japan: 60 |
| Country: Number of subjects enrolled | Mexico: 39 |
| Country: Number of subjects enrolled | Netherlands: 31 |
| Country: Number of subjects enrolled | Poland: 22 |
| Country: Number of subjects enrolled | Romania: 6 |
| Country: Number of subjects enrolled | Russian Federation: 12 |
| Country: Number of subjects enrolled | South Africa: 13 |
| Country: Number of subjects enrolled | Switzerland: 9 |
| Country: Number of subjects enrolled | Türkiye: 14 |
| Country: Number of subjects enrolled | United Kingdom: 38 |

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United States: 59 |
| Worldwide total number of subjects | 605 |
| EEA total number of subjects | 293 |

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) | 167 |
| From 65 to 84 years | 432 |
| 85 years and over | 6 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

605 participants randomized and 584 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 | Treatment A |

Arm description:

Nivolumab 3 mg/kg IV Q2W + Ipilimumab 1 mg/kg IV Q6W

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

Dosage and administration details:

3 mg/kg Q2W

| | |
|--|---------------------|
| Investigational medicinal product name | Ipilimumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection, Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1 mg/kg Q6W

| | |
|------------------|-------------|
| Arm title | Treatment B |
|------------------|-------------|

Arm description:

Pemetrexed 500 mg/m² + Cisplatin 75 mg/m² or Carboplatin 5 AUC up to 6 cycles

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

Dosage and administration details:

as a 10-minute dose of 500 mg/m² on Day 1 of a q 21 day cycle

| | |
|--|--|
| Investigational medicinal product name | Carboplatin Area Under the Curve (AUC) 5 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Day 1 of every 21 days per cycle for 6 cycles.

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

Dosage and administration details:

75 mg/m²

| Number of subjects in period 1 | Treatment A | Treatment B |
|--|-------------|-------------|
| Started | 303 | 302 |
| Completed | 300 | 284 |
| Not completed | 3 | 18 |
| Participant withdrew consent | 1 | 11 |
| Not reported | - | 1 |
| Participant no longer meets study criteria | 2 | 3 |
| Participant request to discontinue study treatment | - | 3 |

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 | Treatment A |

Arm description:

Nivolumab 3 mg/kg IV Q2W + Ipilimumab 1 mg/kg IV Q6W

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

Dosage and administration details:

1 mg/kg Q6W

| | |
|--|---------------------|
| Investigational medicinal product name | Nivolumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection, Infusion |

| | |
|--------------------------|-----------------|
| Routes of administration | Intravenous use |
|--------------------------|-----------------|

Dosage and administration details:

3 mg/kg Q2W

| | |
|------------------|-------------|
| Arm title | Treatment B |
|------------------|-------------|

Arm description:

Pemetrexed 500 mg/m² + Cisplatin 75 mg/m² or Carboplatin 5 AUC up to 6 cycles

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|--|------------|
| Investigational medicinal product name | Pemetrexed |
|--|------------|

| | |
|--|--|
| Investigational medicinal product code | |
|--|--|

| | |
|------------|--|
| Other name | |
|------------|--|

| | |
|----------------------|----------|
| Pharmaceutical forms | Infusion |
|----------------------|----------|

| | |
|--------------------------|-----------------|
| Routes of administration | Intravenous use |
|--------------------------|-----------------|

Dosage and administration details:

as a 10-minute dose of 500 mg/m² on Day 1 of a q 21 day cycle

| | |
|--|--|
| Investigational medicinal product name | Carboplatin Area Under the Curve (AUC) 5 |
|--|--|

| | |
|--|--|
| Investigational medicinal product code | |
|--|--|

| | |
|------------|--|
| Other name | |
|------------|--|

| | |
|----------------------|----------|
| Pharmaceutical forms | Infusion |
|----------------------|----------|

| | |
|--------------------------|-----------------|
| Routes of administration | Intravenous use |
|--------------------------|-----------------|

Dosage and administration details:

Day 1 of every 21 days per cycle for 6 cycles.

| | |
|--|-----------|
| Investigational medicinal product name | Cisplatin |
|--|-----------|

| | |
|--|--|
| Investigational medicinal product code | |
|--|--|

| | |
|------------|--|
| Other name | |
|------------|--|

| | |
|----------------------|----------|
| Pharmaceutical forms | Infusion |
|----------------------|----------|

| | |
|--------------------------|-----------------|
| Routes of administration | Intravenous use |
|--------------------------|-----------------|

Dosage and administration details:

75 mg/m²

| Number of subjects in period 2 | Treatment A | Treatment B |
|--|-------------|-------------|
| Started | 300 | 284 |
| Completed | 0 | 189 |
| Not completed | 300 | 95 |
| Administrative reason by Sponsor | 2 | - |
| Participant withdrew consent | 6 | 3 |
| Not reported | 7 | - |
| Maximum Clinical Benefit | 11 | 2 |
| Participant no longer meets study criteria | 4 | - |
| Adverse Event unrelated to Study Drug | 11 | 9 |
| Poor/Non-compliance | 1 | - |
| Other reasons | 12 | 2 |
| Study Drug Toxicity | 60 | 24 |

| | | |
|--|-----|----|
| Lost to follow-up | - | 2 |
| Disease Progression | 182 | 43 |
| Participant request to discontinue study treatment | 4 | 10 |

Baseline characteristics

Reporting groups

| | |
|---|-------------|
| Reporting group title | Treatment A |
| Reporting group description: Nivolumab 3 mg/kg IV Q2W + Ipilimumab 1 mg/kg IV Q6W | |
| Reporting group title | Treatment B |
| Reporting group description: Pemetrexed 500 mg/m ² + Cisplatin 75 mg/m ² or Carboplatin 5 AUC up to 6 cycles | |

| Reporting group values | Treatment A | Treatment B | Total |
|------------------------------------|-------------|-------------|-------|
| Number of subjects | 303 | 302 | 605 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|---------------|---------------|-----|
| Age Continuous Units: years arithmetic mean standard deviation | 68.7 ± 8.5 | 67.8 ± 9.7 | - |
| Sex: Female, Male Units: Participants | | | |
| Female | 69 | 69 | 138 |
| Male | 234 | 233 | 467 |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 2 | 4 | 6 |
| Asian | 26 | 39 | 65 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 0 |
| White | 266 | 250 | 516 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 9 | 9 | 18 |
| Ethnicity (NIH/OMB) Units: Subjects | | | |
| Hispanic or Latino | 19 | 19 | 38 |
| Not Hispanic or Latino | 122 | 136 | 258 |
| Unknown or Not Reported | 162 | 147 | 309 |

End points

End points reporting groups

| | |
|---|-------------|
| Reporting group title | Treatment A |
| Reporting group description: | |
| Nivolumab 3 mg/kg IV Q2W + Ipilimumab 1 mg/kg IV Q6W | |
| Reporting group title | Treatment B |
| Reporting group description: | |
| Pemetrexed 500 mg/m ² + Cisplatin 75 mg/m ² or Carboplatin 5 AUC up to 6 cycles | |
| Reporting group title | Treatment A |
| Reporting group description: | |
| Nivolumab 3 mg/kg IV Q2W + Ipilimumab 1 mg/kg IV Q6W | |
| Reporting group title | Treatment B |
| Reporting group description: | |
| Pemetrexed 500 mg/m ² + Cisplatin 75 mg/m ² or Carboplatin 5 AUC up to 6 cycles | |

Primary: Overall Survival (OS)

| | |
|--|-----------------------|
| End point title | Overall Survival (OS) |
| End point description: | |
| Overall Survival was defined as the time from randomization to the date of death due to any cause. A participant who has not died was censored at last known date alive. | |
| End point type | Primary |
| End point timeframe: | |
| From randomization to the date of death (Up to 40 Months) | |

| End point values | Treatment A | Treatment B | | |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 303 | 302 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 18.07 (16.82 to 21.45) | 14.09 (12.45 to 16.23) | | |

Statistical analyses

| | |
|---|---------------------------|
| Statistical analysis title | OS Hazard Ratio (HR) |
| Comparison groups | Treatment A v Treatment B |
| Number of subjects included in analysis | 605 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.002 ^[1] |
| Method | Stratified Log Rank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.74 |

| | |
|---------------------|---------------|
| Confidence interval | |
| level | Other: 96.6 % |
| sides | 2-sided |
| lower limit | 0.6 |
| upper limit | 0.91 |

Notes:

[1] - Boundary for statistical significance was a p-value < 0.0345

Secondary: Objective Response Rate (ORR)

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

End point description:

Objective Response Rate is defined as the percentage of randomized participants who achieve a best overall response of complete response (CR) or partial response (PR) per Blinded Independent Central Review (BICR) assessments. Per adapted m-RECIST for pleural mesothelioma, each single tumor measurement must be at least 10 mm in length to qualify as measurable disease and contribute to the sum that defines the pleural uni-variate measure. Per RECIST 1.1 for solid tumors, confirmation of response required:

CR=Disappearance of all target lesions;

PR=At least a 30% decrease in the sum of the Total Tumor Measurement;

Progressive disease (PD)=At least a 20% increase in the sum of the Total Tumor Measurement.

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

End point timeframe:

From randomization date to the date of objectively documented progression or the date of subsequent anti-cancer therapy, whichever occurs first (Up to 76 months)

| End point values | Treatment A | Treatment B | | |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 303 | 302 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 39.3 (33.7 to 45.0) | 44.4 (38.7 to 50.2) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

| | |
|-----------------|----------------------------|
| End point title | Disease Control Rate (DCR) |
|-----------------|----------------------------|

End point description:

Disease Control Rate is defined as the percentage of all randomized participants whose Best Overall Response was complete response (CR), partial response (PR), stable disease (SD) or Non-CR/Non-PD as assessed by Blinded Independent Central Review (BICR). Per adapted m-RECIST for pleural mesothelioma, each single tumor measurement must be at least 10 mm in length to qualify as measurable disease and contribute to the sum that defines the pleural uni-variate measure. Per RECIST 1.1 for solid tumors, confirmation of response required:

CR=Disappearance of all target lesions;

PR=At least a 30% decrease in the sum of the Total Tumor Measurement;

Progressive disease (PD)=At least a 20% increase in the sum of the Total Tumor Measurement;

SD=Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD;

Non-CR/Non-PD: Persistence of one or more non-target lesion(s).

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

End point timeframe:

From randomization date to the date of objectively documented progression or the date of subsequent anti-cancer therapy, whichever occurs first (Up to 76 months)

| End point values | Treatment A | Treatment B | | |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 303 | 302 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 76.6 (71.4 to 81.2) | 85.8 (81.3 to 89.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title | Progression Free Survival (PFS)

End point description:

Progression Free Survival is defined as the time between the date of randomization and the date of first documented tumor progression per Blinded Independent Central Review (BICR) assessments (using adapted m-RECIST and RECIST 1.1), or death due to any cause, whichever occurs first. Participants who received subsequent anticancer therapy prior to documented progression were censored at the date of the last evaluable tumor assessment conducted on or prior to the date of initiation of the subsequent anticancer therapy.

Progressive disease (PD)=At least a 20% increase in the sum of the Total Tumor Measurement.

End point type | Secondary

End point timeframe:

From randomization date to the date of first documented tumor progression or death due to any cause, whichever occurs first. (up to 76 months)

| End point values | Treatment A | Treatment B | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 303 | 302 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 6.77 (5.59 to 7.36) | 7.23 (6.93 to 8.05) | | |

Statistical analyses

Statistical analysis title | PFS Hazard Ratio (HR)

Comparison groups | Treatment A v Treatment B

| | |
|---|-------------------|
| Number of subjects included in analysis | 605 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.93 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.77 |
| upper limit | 1.13 |

Secondary: Overall Survival (OS) According to PD-L1 Expression Level

| | |
|---|---|
| End point title | Overall Survival (OS) According to PD-L1 Expression Level |
| End point description: | |
| <p>PD-L1 Expression is defined as the percent of tumor cells membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 immunohistochemistry (IHC) assay. This is referred to as quantifiable PD-L1 expression and efficacy is determined by overall survival (OS) analysis. OS was defined as the time from randomization to the date of death due to any cause. A participant who has not died was censored at last known date alive.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| From randomization date to the date of death (Up to 76 Months) | |

| End point values | Treatment A | Treatment B | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 289 | 297 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| <1% PD-L1 | 17.3 (10.1 to 23.9) | 16.6 (13.4 to 20.8) | | |
| ≥1% PD-L1 | 18.0 (16.8 to 21.5) | 13.3 (11.6 to 15.4) | | |

Statistical analyses

| | |
|-----------------------------------|---------------------------|
| Statistical analysis title | OS Hazard Ratio (HR) |
| Statistical analysis description: | |
| <1% PD-L1 | |
| Comparison groups | Treatment A v Treatment B |

| | |
|---|-------------------|
| Number of subjects included in analysis | 586 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.64 |
| upper limit | 1.32 |

| | |
|--|---------------------------|
| Statistical analysis title | OS Hazard Ratio (HR) |
| Statistical analysis description: ≥1% PD-L1 | |
| Comparison groups | Treatment A v Treatment B |
| Number of subjects included in analysis | 586 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.72 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.59 |
| upper limit | 0.88 |

Secondary: Progression Free Survival (PFS) According to PD-L1 Expression Level

| | |
|-----------------|---|
| End point title | Progression Free Survival (PFS) According to PD-L1 Expression Level |
|-----------------|---|

End point description:

PD-L1 Expression is defined as the percent of tumor cells membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 immunohistochemistry (IHC) assay. This is referred to as quantifiable PD-L1 expression and efficacy is determined by progression free survival (PFS) analysis. PFS is defined as the time between the date of randomization and the date of first documented tumor progression per Blinded Independent Central Review (BICR) assessments (using adapted m-RECIST and RECIST 1.1), or death due to any cause, whichever occurs first. Participants who received subsequent anticancer therapy prior to documented progression were censored at the date of the last evaluable tumor assessment conducted on or prior to the date of initiation of the subsequent anticancer therapy. Progressive disease (PD)=At least a 20% increase in the sum of the Total Tumor Measurement.

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

End point timeframe:

From randomization date to the date of first documented tumor progression or death due to any cause, whichever occurs first. (up to 76 months)

| End point values | Treatment A | Treatment B | | |
|----------------------------------|------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 289 | 297 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| <1% PD-L1 | 4.1 (2.7 to 5.6) | 8.3 (7.0 to 11.1) | | |
| ≥1% PD-L1 | 7.0 (5.8 to 8.5) | 7.1 (6.2 to 7.6) | | |

Statistical analyses

| Statistical analysis title | PFS Hazard Ratio (HR) |
|--|---------------------------|
| Statistical analysis description: ≥1% PD-L1 | |
| Comparison groups | Treatment A v Treatment B |
| Number of subjects included in analysis | 586 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.77 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.61 |
| upper limit | 0.96 |

| Statistical analysis title | PFS Hazard Ratio (HR) |
|---|---------------------------|
| Statistical analysis description: < 1% PD-L1 | |
| Comparison groups | Treatment A v Treatment B |
| Number of subjects included in analysis | 586 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.79 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.22 |
| upper limit | 2.63 |

Secondary: Objective Response Rate (ORR) According to PD-L1 Expression Level

| End point title | Objective Response Rate (ORR) According to PD-L1 Expression Level |
|------------------------|---|
|------------------------|---|

End point description:

PD-L1 Expression is defined as the percent of tumor cells membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 immunohistochemistry (IHC) assay. This is referred to as quantifiable PD-L1 expression and efficacy is determined by objective response rate (ORR) analysis. ORR is defined as the percentage of participants who achieve a best overall response of complete response (CR) or partial response (PR) per Blinded Independent Central Review (BICR) assessments. Per adapted m-RECIST for pleural mesothelioma, each single tumor measurement must be at least 10 mm in length to qualify as measurable disease and contribute to the sum that defines the pleural univariate measure.

per RECIST 1.1 for solid tumors, confirmation of response required:

CR=Disappearance of all target lesions;

PR=At least a 30% decrease in the sum of the Total Tumor Measurement;

Progressive disease (PD)=At least a 20% increase in the sum of the Total Tumor Measurement.

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

End point timeframe:

From randomization date to the date of objectively documented progression or the date of subsequent anti-cancer therapy, whichever occurs first (Up to 76 months)

| End point values | Treatment A | Treatment B | | |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 289 | 297 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | | | | |
| <1% PD-L1 | 21.1 (11.4 to 33.9) | 41.0 (30.0 to 52.7) | | |
| ≥1% PD-L1 | 43.1 (36.6 to 49.7) | 45.7 (38.9 to 52.5) | | |

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Overall Survival was defined as the time from randomization to the date of death due to any cause. A participant who has not died was censored at last known date alive.

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

End point timeframe:

From randomization date to the date of death (Up to 76 Months)

| End point values | Treatment A | Treatment B | | |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 303 | 302 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 18.07 (16.82 to 20.99) | 14.09 (12.45 to 16.33) | | |

Statistical analyses

| | |
|---|---------------------------|
| Statistical analysis title | OS Hazard Ratio (HR) |
| Comparison groups | Treatment A v Treatment B |
| Number of subjects included in analysis | 605 |
| Analysis specification | Post-hoc |
| Analysis type | |
| P-value | = 0.0008 |
| Method | Stratified Log Rank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.74 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.62 |
| upper limit | 0.88 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Subjects were assessed for deaths (all-causes) from their first dose to their study completion (up to approximately 76 months.) SAEs and NSAEs were assessed from first dose to 100 days post the last dose of study therapy (up to approximately 29 months).

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 26.0 |
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Reporting groups

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| Reporting group title | Treatment B |
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Reporting group description:

Pemetrexed 500 mg/m² + Cisplatin 75 mg/m² or Carboplatin 5 AUC up to 6 cycles

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|-----------------------|-------------|
| Reporting group title | Treatment A |
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Reporting group description:

Nivolumab 3 mg/kg IV Q2W + Ipilimumab 1 mg/kg IV Q6W

| Serious adverse events | Treatment B | Treatment A | |
|---|--------------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 106 / 284 (37.32%) | 188 / 300 (62.67%) | |
| number of deaths (all causes) | 259 | 251 | |
| number of deaths resulting from adverse events | 49 | 58 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 2 / 284 (0.70%) | 0 / 300 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Breast neoplasm | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant melanoma in situ | | | |

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|---|-------------------|-------------------|--|
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small cell lung cancer | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mesothelioma malignant | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mesothelioma | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (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 | 42 / 284 (14.79%) | 51 / 300 (17.00%) | |
| occurrences causally related to treatment / all | 0 / 45 | 0 / 52 | |
| deaths causally related to treatment / all | 0 / 40 | 0 / 44 | |
| Vascular disorders | | | |
| Superior vena cava syndrome | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Embolism | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Giant cell arteritis | | | |

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|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (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 | | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 284 (0.70%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest pain | | | |
| subjects affected / exposed | 4 / 284 (1.41%) | 4 / 300 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 2 / 300 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Hyperpyrexia | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 2 / 300 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperthermia | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Illness | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Malaise | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 1 / 284 (0.35%) | 2 / 300 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 4 / 300 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Performance status decreased | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (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 | 4 / 284 (1.41%) | 16 / 300 (5.33%) | |
| occurrences causally related to treatment / all | 1 / 4 | 3 / 16 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |

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|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infusion related hypersensitivity reaction | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Contrast media allergy | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| 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 / 284 (2.82%) | 9 / 300 (3.00%) | |
| occurrences causally related to treatment / all | 0 / 9 | 1 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoxia | | | |
| subjects affected / exposed | 2 / 284 (0.70%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 3 / 300 (1.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Pleural effusion | | | |
| subjects affected / exposed | 3 / 284 (1.06%) | 9 / 300 (3.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 14 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

| | | | |
|---|-----------------|-----------------|--|
| Pleurisy | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 3 / 300 (1.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleuritic pain | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| 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 / 284 (0.00%) | 9 / 300 (3.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 7 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Pneumothorax | | | |
| subjects affected / exposed | 2 / 284 (0.70%) | 2 / 300 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Productive cough | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 3 / 284 (1.06%) | 6 / 300 (2.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 2 / 300 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory distress | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (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 | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 3 / 300 (1.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Aspiration | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Mental status changes | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depression | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Completed suicide | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Investigations | | | |
| General physical condition abnormal | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (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 | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| 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 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Fracture | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Head injury | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Heat exhaustion | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infusion related reaction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 284 (0.00%) | 6 / 300 (2.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 5 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular access complication | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic valve disease | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (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 / 284 (0.35%) | 3 / 300 (1.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial thrombosis | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 2 / 300 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 2 / 300 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiomyopathy | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 284 (0.35%) | 2 / 300 (0.67%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Myocarditis | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleuropericarditis | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Migraine | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Limbic encephalitis | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 2 / 300 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cognitive disorder | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 2 / 300 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cauda equina syndrome | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myasthenia gravis | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myelitis transverse | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuralgia | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neurological symptom | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Presyncope | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 2 / 300 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| 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 / 284 (0.00%) | 3 / 300 (1.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myasthenic syndrome | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 9 / 284 (3.17%) | 5 / 300 (1.67%) | |
| occurrences causally related to treatment / all | 11 / 16 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Myelosuppression | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Haematotoxicity | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 3 / 284 (1.06%) | 0 / 300 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenic purpura | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 3 / 284 (1.06%) | 0 / 300 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Opsoclonus myoclonus | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Duodenal ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal hernia | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 284 (0.70%) | 5 / 300 (1.67%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal fissure | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 9 / 300 (3.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 10 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 5 / 300 (1.67%) | |
| occurrences causally related to treatment / all | 1 / 1 | 4 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 284 (0.00%) | 2 / 300 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Gastritis | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis erosive | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal motility disorder | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune-mediated enterocolitis | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 284 (0.35%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Overflow diarrhoea | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 3 / 300 (1.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Retroperitoneal haematoma | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subileus | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Superior mesenteric artery dissection | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 284 (0.70%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enteritis | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 3 / 300 (1.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Autoimmune hepatitis | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Biliary obstruction | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 3 / 300 (1.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 2 / 300 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 5 / 300 (1.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 5 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune-mediated hepatitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 284 (0.00%) | 5 / 300 (1.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Cutaneous vasculitis | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erythema multiforme | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 2 / 300 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subcutaneous emphysema | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal haemorrhage | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| 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 / 284 (0.35%) | 2 / 300 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrolithiasis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 284 (0.70%) | 7 / 300 (2.33%) | |
| occurrences causally related to treatment / all | 0 / 2 | 5 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 2 / 300 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Adrenocorticotrophic hormone deficiency | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia of malignancy | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hypophysitis | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypopituitarism | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 284 (0.00%) | 4 / 300 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inappropriate antidiuretic hormone secretion | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 3 / 300 (1.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myositis | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 2 / 300 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Back pain | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthralgia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 284 (0.00%) | 3 / 300 (1.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 2 / 300 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abscess intestinal | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthritis bacterial | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Candida sepsis | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| 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 / 284 (0.35%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Empyema | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 284 (0.35%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Klebsiella urinary tract infection | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Otitis externa fungal | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural infection | | | |

| | | |
|---|-----------------|------------------|
| subjects affected / exposed | 1 / 284 (0.35%) | 2 / 300 (0.67%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Pleurisy bacterial | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Pneumocystis jirovecii pneumonia | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) |
| 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 / 284 (2.11%) | 14 / 300 (4.67%) |
| occurrences causally related to treatment / all | 1 / 7 | 0 / 14 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 |
| Pneumonia aspiration | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 1 / 300 (0.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 |
| Respiratory tract infection | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 1 / 300 (0.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Sepsis | | |
| subjects affected / exposed | 2 / 284 (0.70%) | 3 / 300 (1.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 |
| Septic shock | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 1 / 300 (0.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 |
| Skin infection | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 284 (0.00%) | 2 / 300 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 2 / 300 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |

| | | |
|---|-----------------|-----------------|
| subjects affected / exposed | 1 / 284 (0.35%) | 4 / 300 (1.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Hyperglycaemic hyperosmolar nonketotic syndrome | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Hyperkalaemia | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 |
| Hypokalaemia | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 1 / 300 (0.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Hypomagnesaemia | | |
| subjects affected / exposed | 1 / 284 (0.35%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Hyponatraemia | | |
| subjects affected / exposed | 2 / 284 (0.70%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Cachexia | | |
| subjects affected / exposed | 0 / 284 (0.00%) | 1 / 300 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Treatment B | Treatment A | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 264 / 284 (92.96%) | 277 / 300 (92.33%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 8 / 284 (2.82%) | 16 / 300 (5.33%) | |
| occurrences (all) | 8 | 20 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 14 / 284 (4.93%) | 50 / 300 (16.67%) | |
| occurrences (all) | 19 | 79 | |
| Pain | | | |
| subjects affected / exposed | 11 / 284 (3.87%) | 20 / 300 (6.67%) | |
| occurrences (all) | 14 | 21 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 19 / 284 (6.69%) | 47 / 300 (15.67%) | |
| occurrences (all) | 19 | 49 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 16 / 284 (5.63%) | 39 / 300 (13.00%) | |
| occurrences (all) | 16 | 47 | |
| Malaise | | | |
| subjects affected / exposed | 17 / 284 (5.99%) | 8 / 300 (2.67%) | |
| occurrences (all) | 20 | 9 | |
| Fatigue | | | |
| subjects affected / exposed | 78 / 284 (27.46%) | 90 / 300 (30.00%) | |
| occurrences (all) | 96 | 110 | |
| Chest pain | | | |
| subjects affected / exposed | 21 / 284 (7.39%) | 22 / 300 (7.33%) | |
| occurrences (all) | 23 | 23 | |
| Asthenia | | | |
| subjects affected / exposed | 58 / 284 (20.42%) | 52 / 300 (17.33%) | |
| occurrences (all) | 63 | 74 | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|-------------------------|-------------------------|--|
| Cough subjects affected / exposed occurrences (all) | 25 / 284 (8.80%) 25 | 65 / 300 (21.67%) 79 | |
| Hiccups subjects affected / exposed occurrences (all) | 17 / 284 (5.99%) 28 | 2 / 300 (0.67%) 2 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 41 / 284 (14.44%) 42 | 77 / 300 (25.67%) 92 | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 16 / 284 (5.63%) 17 | 27 / 300 (9.00%) 29 | |
| Investigations Weight decreased subjects affected / exposed occurrences (all) | 24 / 284 (8.45%) 25 | 17 / 300 (5.67%) 17 | |
| Lipase increased subjects affected / exposed occurrences (all) | 4 / 284 (1.41%) 4 | 27 / 300 (9.00%) 42 | |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 19 / 284 (6.69%) 20 | 26 / 300 (8.67%) 49 | |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 3 / 284 (1.06%) 3 | 18 / 300 (6.00%) 22 | |
| Amylase increased subjects affected / exposed occurrences (all) | 4 / 284 (1.41%) 4 | 24 / 300 (8.00%) 36 | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 4 / 284 (1.41%) 4 | 22 / 300 (7.33%) 36 | |
| Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all) | 2 / 284 (0.70%) 2 | 22 / 300 (7.33%) 26 | |

| | | | |
|--------------------------------------|--------------------|-------------------|--|
| Nervous system disorders | | | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 15 / 284 (5.28%) | 3 / 300 (1.00%) | |
| occurrences (all) | 15 | 3 | |
| Headache | | | |
| subjects affected / exposed | 12 / 284 (4.23%) | 24 / 300 (8.00%) | |
| occurrences (all) | 12 | 28 | |
| Dysgeusia | | | |
| subjects affected / exposed | 22 / 284 (7.75%) | 15 / 300 (5.00%) | |
| occurrences (all) | 23 | 16 | |
| Dizziness | | | |
| subjects affected / exposed | 10 / 284 (3.52%) | 16 / 300 (5.33%) | |
| occurrences (all) | 11 | 16 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 118 / 284 (41.55%) | 41 / 300 (13.67%) | |
| occurrences (all) | 136 | 56 | |
| Leukopenia | | | |
| subjects affected / exposed | 25 / 284 (8.80%) | 0 / 300 (0.00%) | |
| occurrences (all) | 31 | 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 79 / 284 (27.82%) | 5 / 300 (1.67%) | |
| occurrences (all) | 137 | 5 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 32 / 284 (11.27%) | 5 / 300 (1.67%) | |
| occurrences (all) | 54 | 6 | |
| Eye disorders | | | |
| Lacrimation increased | | | |
| subjects affected / exposed | 19 / 284 (6.69%) | 1 / 300 (0.33%) | |
| occurrences (all) | 19 | 1 | |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 55 / 284 (19.37%) | 47 / 300 (15.67%) | |
| occurrences (all) | 78 | 56 | |
| Nausea | | | |
| subjects affected / exposed | 124 / 284 (43.66%) | 76 / 300 (25.33%) | |
| occurrences (all) | 200 | 95 | |

| | | | |
|---|--------------------------|--------------------------|--|
| Diarrhoea subjects affected / exposed occurrences (all) | 34 / 284 (11.97%) 45 | 96 / 300 (32.00%) 152 | |
| Abdominal pain subjects affected / exposed occurrences (all) | 13 / 284 (4.58%) 15 | 30 / 300 (10.00%) 30 | |
| Constipation subjects affected / exposed occurrences (all) | 86 / 284 (30.28%) 104 | 57 / 300 (19.00%) 73 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash maculo-papular subjects affected / exposed occurrences (all) | 5 / 284 (1.76%) 5 | 18 / 300 (6.00%) 21 | |
| Rash subjects affected / exposed occurrences (all) | 21 / 284 (7.39%) 23 | 60 / 300 (20.00%) 76 | |
| Pruritus subjects affected / exposed occurrences (all) | 5 / 284 (1.76%) 5 | 62 / 300 (20.67%) 70 | |
| Dry skin subjects affected / exposed occurrences (all) | 7 / 284 (2.46%) 7 | 16 / 300 (5.33%) 16 | |
| Endocrine disorders | | | |
| Hypothyroidism subjects affected / exposed occurrences (all) | 3 / 284 (1.06%) 3 | 37 / 300 (12.33%) 38 | |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity subjects affected / exposed occurrences (all) | 9 / 284 (3.17%) 9 | 18 / 300 (6.00%) 19 | |
| Myalgia subjects affected / exposed occurrences (all) | 7 / 284 (2.46%) 7 | 24 / 300 (8.00%) 27 | |
| Back pain subjects affected / exposed occurrences (all) | 13 / 284 (4.58%) 14 | 21 / 300 (7.00%) 23 | |

| | | | |
|---|--|---|--|
| Arthralgia subjects affected / exposed occurrences (all) | 9 / 284 (3.17%) 10 | 49 / 300 (16.33%) 55 | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 8 / 284 (2.82%) 8 | 21 / 300 (7.00%) 32 | |
| Metabolism and nutrition disorders Hyponatraemia subjects affected / exposed occurrences (all) Hypoalbuminaemia subjects affected / exposed occurrences (all) Decreased appetite subjects affected / exposed occurrences (all) | 11 / 284 (3.87%) 11 11 / 284 (3.87%) 13 75 / 284 (26.41%) 109 | 19 / 300 (6.33%) 23 19 / 300 (6.33%) 24 72 / 300 (24.00%) 78 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 13 October 2017 | inclusion and exclusion criteria updated |
| 25 April 2019 | Endpoints updated |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported