# Clinical trial results:
# Phase 2, Randomized, Double Blinded, Study of Nivolumab (BMS-936558) in Combination with Ipilimumab vs Ipilimumab alone in Subjects with Previously Untreated, Unresectable or Metastatic Melanoma (CheckMate 069: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 069)

## Summary

| | |
|---|---|
| EudraCT number | 2013-002018-11 |
| Trial protocol | FR |
| Global end of trial date | 26 February 2021 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 08 March 2022 |
| First version publication date | 08 March 2022 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | CA209-069 |

**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) | |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 23 March 2021 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 26 February 2021 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To compare the ORR, as determined by investigators, of nivolumab combined with ipilimumab to ipilimumab monotherapy in subjects with BRAF wild type (WT) unresectable or metastatic melanoma

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 | 23 August 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | France: 16 |
| Country: Number of subjects enrolled | United States: 126 |
| Worldwide total number of subjects | 142 |
| EEA total number of subjects | 16 |

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) | 68 |
| From 65 to 84 years | 71 |
| 85 years and over | 3 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

142 participants were randomized, and 140 participants received treatment.

### Period 1

| | |
|---|---|
| Period 1 title | Pre-Treatment Period |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Nivolumab + Ipilimumab |

Arm description:

Participants received 1 mg/kg of nivolumab + 3 mg/kg of ipilimumab solution intravenously every 3 weeks for 4 doses (4 cycles), then 3 mg/kg of nivolumab intravenously every 2 weeks until documented disease progression, toxicity, withdrawal of consent, or study completion.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | BMS-986165 |
| Investigational medicinal product code | |
| Other name | Nivolumab |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1 mg/kg Q3W for 4 cycles, then 3 mg/kg Q2W

| | |
|---|---|
| Investigational medicinal product name | Placebo matching BMS-986165 |
| Investigational medicinal product code | |
| Other name | 0.9% Sodium Chloride |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

matching nivolumab (BMS-986165)

| | |
|---|---|
| Investigational medicinal product name | Ipilimumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

3 mg/kg Q3W for 4 cycles

| | |
|---|---|
| **Arm title** | Ipilimumab |

Arm description:

Participants received placebo-matching nivolumab + 3 mg/kg of ipilimumab solution intravenously every 3 weeks for 4 doses (4 cycles), then placebo-matching nivolumab solution intravenously every 2 weeks until documented disease progression, toxicity, withdrawal of consent, or study completion.

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

| | |
|---|---|
| Investigational medicinal product name | Ipilimumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

3 mg/kg Q3W for 4 cycles

| **Number of subjects in period 1** | Nivolumab + Ipilimumab | Ipilimumab |
|---|---|---|
| Started | 95 | 47 |
| Completed | 94 | 46 |
| Not completed | 1 | 1 |
| Adverse event unrelated to study drug | - | 1 |
| Participants no longer meeting study criteria | 1 | - |

## Period 2

| | |
|---|---|
| Period 2 title | Treatment Period |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor |

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Nivolumab + Ipilimumab |

Arm description:

Participants received 1 mg/kg of nivolumab + 3 mg/kg of ipilimumab solution intravenously every 3 weeks for 4 doses (4 cycles), then 3 mg/kg of nivolumab intravenously every 2 weeks until documented disease progression, toxicity, withdrawal of consent, or study completion.

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

Dosage and administration details:

3 mg/kg Q3W for 4 cycles

| | |
|---|---|
| Investigational medicinal product name | BMS-936558 |
| Investigational medicinal product code | |
| Other name | Nivolumab |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1 mg/kg Q3W for 4 cycles, then 3 mg/kg Q2W

| **Arm title** | Ipilimumab |
|---|---|

Arm description:

Participants received placebo-matching nivolumab + 3 mg/kg of ipilimumab solution intravenously every 3 weeks for 4 doses (4 cycles), then placebo-matching nivolumab solution intravenously every 2 weeks until documented disease progression, toxicity, withdrawal of consent, or study completion.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Placebo matching BMS-986165 |
| Investigational medicinal product code | |
| Other name | 0.9% Sodium Chloride |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

matching nivolumab (BMS-986165)

| | |
|---|---|
| Investigational medicinal product name | Ipilimumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

3 mg/kg Q3W for 4 cycles

| **Number of subjects in period 2** | Nivolumab + Ipilimumab | Ipilimumab |
|---|---|---|
| Started | 94 | 46 |
| Completed | 0 | 0 |
| Not completed | 94 | 46 |
| Adverse event, serious fatal | - | 1 |
| Consent withdrawn by subject | 1 | 1 |
| Disease progression | 17 | 20 |
| Not Reported | 1 | 1 |
| Study drug toxicity | 48 | 10 |
| Participant request to discontinue | 12 | 4 |
| Maximum Clinical Benefit | 6 | 2 |
| Adverse event unrelated to study drug | 6 | 3 |
| Other reasons | 3 | 4 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Nivolumab + Ipilimumab |
| Reporting group description: | |
| Participants received 1 mg/kg of nivolumab + 3 mg/kg of ipilimumab solution intravenously every 3 weeks for 4 doses (4 cycles), then 3 mg/kg of nivolumab intravenously every 2 weeks until documented disease progression, toxicity, withdrawal of consent, or study completion. | |
| Reporting group title | Ipilimumab |
| Reporting group description: | |
| Participants received placebo-matching nivolumab + 3 mg/kg of ipilimumab solution intravenously every 3 weeks for 4 doses (4 cycles), then placebo-matching nivolumab solution intravenously every 2 weeks until documented disease progression, toxicity, withdrawal of consent, or study completion. | |

| Reporting group values | Nivolumab + Ipilimumab | Ipilimumab | Total |
|---|---|---|---|
| Number of subjects | 95 | 47 | 142 |
| Age Categorical<br>Units: Participants | | | |
| Younger than 65 years | 48 | 20 | 68 |
| 65 years and older to younger than 75 years | 35 | 22 | 57 |
| 75 years and older | 12 | 5 | 17 |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 63.3 | 64.5 | |
| standard deviation | ± 11.0 | ± 10.2 | - |
| Sex: Female, Male<br>Units: | | | |
| Female | 32 | 15 | 47 |
| Male | 63 | 32 | 95 |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 1 | 0 | 1 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 0 |
| White | 92 | 47 | 139 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 2 | 0 | 2 |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 1 | 0 | 1 |
| Not Hispanic or Latino | 82 | 43 | 125 |
| Unknown or Not Reported | 12 | 4 | 16 |

## End points

### End points reporting groups

| Reporting group title | Nivolumab + Ipilimumab |
|---|---|
| Reporting group description: | |
| Participants received 1 mg/kg of nivolumab + 3 mg/kg of ipilimumab solution intravenously every 3 weeks for 4 doses (4 cycles), then 3 mg/kg of nivolumab intravenously every 2 weeks until documented disease progression, toxicity, withdrawal of consent, or study completion. | |
| Reporting group title | Ipilimumab |
| Reporting group description: | |
| Participants received placebo-matching nivolumab + 3 mg/kg of ipilimumab solution intravenously every 3 weeks for 4 doses (4 cycles), then placebo-matching nivolumab solution intravenously every 2 weeks until documented disease progression, toxicity, withdrawal of consent, or study completion. | |
| Reporting group title | Nivolumab + Ipilimumab |
| Reporting group description: | |
| Participants received 1 mg/kg of nivolumab + 3 mg/kg of ipilimumab solution intravenously every 3 weeks for 4 doses (4 cycles), then 3 mg/kg of nivolumab intravenously every 2 weeks until documented disease progression, toxicity, withdrawal of consent, or study completion. | |
| Reporting group title | Ipilimumab |
| Reporting group description: | |
| Participants received placebo-matching nivolumab + 3 mg/kg of ipilimumab solution intravenously every 3 weeks for 4 doses (4 cycles), then placebo-matching nivolumab solution intravenously every 2 weeks until documented disease progression, toxicity, withdrawal of consent, or study completion. | |

### Primary: Objective Response Rate (ORR) - BRAF wild-type (WT) participants

| End point title | Objective Response Rate (ORR) - BRAF wild-type (WT) participants |
|---|---|
| End point description: | |
| Objective Response Rate is defined as the percentage of participants with a best overall response of Complete Response (CR) or Partial Response (PR), assessed by the investigator by using RECIST 1.1 criteria.<br>CR=all target and nontarget lesions have disappeared. Lymph nodes selected must have returned to normal size (<10 mm).<br>PR=at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. | |
| End point type | Primary |
| End point timeframe: | |
| From 12 weeks after Randomization, assessed every 6 weeks up to Week 49 of study treatment and then every 12 weeks until disease progression (up to approximately 76 months) | |

| End point values | Nivolumab + Ipilimumab | Ipilimumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 73 | 37 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 60.3 (48.1 to 71.5) | 10.8 (3.0 to 25.4) | | |

**Statistical analyses**

| **Statistical analysis title** | ORR - BRAF WT 1 |
|---|---|
| Comparison groups | Nivolumab + Ipilimumab v Ipilimumab |
| Number of subjects included in analysis | 110 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Newcombe's method |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 49.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 31.4 |
| upper limit | 61.8 |

| **Statistical analysis title** | ORR - BRAF WT 2 |
|---|---|
| Comparison groups | Nivolumab + Ipilimumab v Ipilimumab |
| Number of subjects included in analysis | 110 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Fisher exact |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 12.52 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.79 |
| upper limit | 52.55 |

**Secondary: Progression-Free Survival (PFS) - BRAF wild-type (WT) participants**

| End point title | Progression-Free Survival (PFS) - BRAF wild-type (WT) participants |
|---|---|

End point description:

PFS is defined as the time between the date of randomization and the first date of documented progression, as assessed by the investigator, or death due to any cause, whichever occurs first. Participants who died without a reported progression were considered to have progressed on the date of their death. Participants who did not progress or died were censored on the date of their last evaluable tumor assessment.
PFS values are based on Kaplan-Meier Estimates.

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

End point timeframe:

From randomization to progression or death (up to approximately 88 months)

| End point values | Nivolumab + Ipilimumab | Ipilimumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 73 | 37 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 58.41 (7.23 to 99999) | 4.30 (2.76 to 5.32) | | |

**Statistical analyses**

| Statistical analysis title | PFS - BRAF WT |
|---|---|
| Comparison groups | Nivolumab + Ipilimumab v Ipilimumab |
| Number of subjects included in analysis | 110 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Unstratified Cox proportional hazard |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.36 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.21 |
| upper limit | 0.59 |

**Secondary: Objective Response Rate (ORR) - BRAF mutant participants**

| End point title | Objective Response Rate (ORR) - BRAF mutant participants |
|---|---|

End point description:

Objective Response Rate is defined as the percentage of participants with a best overall response of Complete Response (CR) or Partial Response (PR), assessed by the investigator by using RECIST 1.1 criteria.
CR=all target and nontarget lesions have disappeared. Lymph nodes selected must have returned to normal size (<10 mm).
PR=at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD.

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

End point timeframe:

From 12 weeks after Randomization, assessed every 6 weeks up to Week 49 of study treatment and then every 12 weeks until disease progression (up to approximately 76 months)

| End point values | Nivolumab + Ipilimumab | Ipilimumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 | 10 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 54.5 (32.2 to 75.6) | 10.0 (0.3 to 44.5) | | |

**Statistical analyses**

| **Statistical analysis title** | ORR - BRAF Mutant 1 |
|---|---|
| Comparison groups | Nivolumab + Ipilimumab v Ipilimumab |
| Number of subjects included in analysis | 32 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Newcombe's method |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 44.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 8.2 |
| upper limit | 64.8 |

| **Statistical analysis title** | ORR - BRAF Mutant 2 |
|---|---|
| Comparison groups | Nivolumab + Ipilimumab v Ipilimumab |
| Number of subjects included in analysis | 32 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Fisher exact |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 10.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.07 |
| upper limit | 511.89 |

| **Secondary: Progression-Free Survival (PFS) - BRAF mutant participants** | |
|---|---|
| End point title | Progression-Free Survival (PFS) - BRAF mutant participants |

End point description:

PFS is defined as the time between the date of randomization and the first date of documented progression, as assessed by the investigator, or death due to any cause, whichever occurs first. Participants who died without a reported progression were considered to have progressed on the date of their death. Participants who did not progress or died were censored on the date of their last evaluable tumor assessment.
PFS values are based on Kaplan-Meier Estimates.

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

End point timeframe:

From randomization to progression or death (up to approximately 88 months)

| End point values | Nivolumab + Ipilimumab | Ipilimumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 | 10 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 8.61 (2.79 to 99999) | 2.73 (0.99 to 5.42) | | |

**Statistical analyses**

| Statistical analysis title | PFS - BRAF Mutant |
|---|---|
| Comparison groups | Nivolumab + Ipilimumab v Ipilimumab |
| Number of subjects included in analysis | 32 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Unstratified Cox proportional hazard |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.36 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.14 |
| upper limit | 0.97 |

## Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer (EORTC) Overall Quality of Life (QOL) C30 Score

| End point title | Change From Baseline in European Organization for Research and Treatment of Cancer (EORTC) Overall Quality of Life (QOL) C30 Score |
|---|---|

End point description:

The EORTC QLQ-C30 version 3 is a questionnaire developed to assess the QOL of cancer patients. The questionnaire is a 30-item tool, and it comprises 6 functional subscales (physical functioning, role functioning, cognitive functioning, emotional functioning, social functioning and global quality of life) as well as 9 symptom subscales (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).
Scores for each subscale range from 0 to 100. For the 6 functional subscales, a higher score represents a better level of functioning/health status. For the 9 symptom subscales, a lower score represents a better outcome (low level of symptomatology).
Scores for the 15 subscales are presented individually.

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

End point timeframe:

From Baseline (prior to start of study treatment) to Week 25 after first dose

| End point values | Nivolumab + Ipilimumab | Ipilimumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 | 13 | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Physical Functioning | 2.12 (± 17.625) | 1.03 (± 9.367) | | |
| Role Functioning | -1.52 (± 22.950) | 5.13 (± 21.926) | | |
| Emotional Functioning | 8.33 (± 10.603) | 10.26 (± 17.063) | | |
| Cognitive Functioning | -1.52 (± 15.352) | -2.56 (± 11.479) | | |
| Social Functioning | 2.27 (± 22.593) | 0.00 (± 16.667) | | |
| Global Health Status | 3.79 (± 11.422) | -0.64 (± 29.357) | | |
| Fatigue | -3.54 (± 21.520) | -0.85 (± 17.836) | | |
| Nausea and Vomiting | -3.03 (± 12.211) | -2.56 (± 6.259) | | |
| Pain | -2.27 (± 12.905) | -8.97 (± 21.099) | | |
| Dyspnea | -9.09 (± 23.417) | -7.69 (± 27.735) | | |
| Insomnia | -12.12 (± 31.782) | -12.82 (± 16.879) | | |
| Appetite Loss | -13.64 (± 30.271) | -2.56 (± 16.452) | | |
| Constipation | -3.03 (± 20.339) | 0.00 (± 13.608) | | |
| Diarrhea | -3.03 (± 14.213) | 5.13 (± 12.518) | | |
| Financial Difficulties | -3.03 (± 22.792) | -2.78 (± 22.285) | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All-cause mortality was assessed from date of first dose to study completion.
Serious Adverse events and other adverse events were assessed from date of first dose to 100 days following date of last dose.

Adverse event reporting additional description:

All treated participants

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 23.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Ipilimumab |

Reporting group description:

Participants received placebo-matching nivolumab + 3 mg/kg of ipilimumab solution intravenously every 3 weeks for 4 doses (4 cycles), then placebo-matching nivolumab solution intravenously every 2 weeks until documented disease progression, toxicity, withdrawal of consent, or study completion.

| | |
|---|---|
| Reporting group title | Nivolumab + Ipilimumab |

Reporting group description:

Participants received 1 mg/kg of nivolumab + 3 mg/kg of ipilimumab solution intravenously every 3 weeks for 4 doses (4 cycles), then 3 mg/kg of nivolumab intravenously every 2 weeks until documented disease progression, toxicity, withdrawal of consent, or study completion.

| Serious adverse events | Ipilimumab | Nivolumab + Ipilimumab | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 27 / 46 (58.70%) | 69 / 94 (73.40%) | |
| number of deaths (all causes) | 29 | 44 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 8 / 46 (17.39%) | 10 / 94 (10.64%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 10 | |
| deaths causally related to treatment / all | 0 / 8 | 0 / 9 | |
| Metastatic malignant melanoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 3 / 94 (3.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolism | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 94 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 94 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 0 / 94 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Chills | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 94 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Generalised oedema | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 94 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 2 / 94 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 94 (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 / 46 (8.70%) | 6 / 94 (6.38%) | |
| occurrences causally related to treatment / all | 2 / 4 | 4 / 9 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchial obstruction | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 94 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 3 / 94 (3.19%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hypoxia | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 0 / 94 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Pleuritic pain | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 7 / 94 (7.45%) | |
| occurrences causally related to treatment / all | 2 / 2 | 7 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 3 / 94 (3.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Investigations | | | |
| Amylase increased | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 2 / 94 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 3 / 94 (3.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| 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 creatinine increased | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 2 / 94 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lipase increased | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 2 / 94 (2.13%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 2 / 94 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 94 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 2 / 94 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 2 / 94 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Ventricular arrhythmia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolic stroke | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Guillain-Barre syndrome | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 94 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningoradiculitis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 0 / 94 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord compression | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 94 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 94 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tremor | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| 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 | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemolysis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukocytosis | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 94 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 2 / 94 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain lower | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 94 (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 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Autoimmune colitis | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 3 / 94 (3.19%) | |
| occurrences causally related to treatment / all | 2 / 2 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 13 / 94 (13.83%) | |
| occurrences causally related to treatment / all | 3 / 3 | 16 / 16 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 2 / 94 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 5 / 46 (10.87%) | 10 / 94 (10.64%) | |
| occurrences causally related to treatment / all | 5 / 6 | 10 / 11 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Diarrhoea haemorrhagic | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 94 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine perforation | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune-mediated enterocolitis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal pain | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| 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 / 46 (4.35%) | 0 / 94 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 2 / 94 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 2 / 94 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |

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|---|---|---|---|
| subjects affected / exposed | 2 / 46 (4.35%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatocellular injury | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| 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 / 46 (0.00%) | 3 / 94 (3.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 94 (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 | 1 / 46 (2.17%) | 0 / 94 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 46 (0.00%) | 3 / 94 (3.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adrenocortical insufficiency acute | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Autoimmune thyroiditis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorder | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| 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 | 1 / 46 (2.17%) | 0 / 94 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypophysitis | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 2 / 94 (2.13%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypopituitarism | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 94 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthralgia | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 94 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myalgia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 94 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abscess | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| 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 / 46 (2.17%) | 0 / 94 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterococcal bacteraemia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epididymitis | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Necrotising fasciitis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Periorbital cellulitis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 3 / 94 (3.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 4 / 94 (4.26%) | |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 2 / 94 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 46 (2.17%) | 2 / 94 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 2 / 94 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 2 / 94 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| 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 / 46 (2.17%) | 0 / 94 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 94 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 2 / 94 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Type 1 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 94 (1.06%) | |
| 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** | Ipilimumab | Nivolumab + Ipilimumab | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed | 45 / 46 (97.83%) | 90 / 94 (95.74%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 4 / 46 (8.70%) | 12 / 94 (12.77%) | |
| occurrences (all) | 4 | 16 | |
| Hot flush | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 1 / 94 (1.06%) | |
| occurrences (all) | 3 | 1 | |
| Flushing | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 5 / 94 (5.32%) | |
| occurrences (all) | 1 | 5 | |
| Hypotension | | | |
| subjects affected / exposed | 5 / 46 (10.87%) | 11 / 94 (11.70%) | |
| occurrences (all) | 5 | 13 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 11 / 46 (23.91%) | 17 / 94 (18.09%) | |
| occurrences (all) | 15 | 31 | |
| Chills | | | |
| subjects affected / exposed | 8 / 46 (17.39%) | 21 / 94 (22.34%) | |
| occurrences (all) | 11 | 25 | |
| Fatigue | | | |
| subjects affected / exposed | 34 / 46 (73.91%) | 57 / 94 (60.64%) | |
| occurrences (all) | 47 | 86 | |
| Influenza like illness | | | |
| subjects affected / exposed | 6 / 46 (13.04%) | 5 / 94 (5.32%) | |
| occurrences (all) | 7 | 5 | |
| Malaise | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 2 / 94 (2.13%) | |
| occurrences (all) | 3 | 2 | |
| Mucosal inflammation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 5 / 46 (10.87%) | 3 / 94 (3.19%) | |
| occurrences (all) | 5 | 3 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 4 / 46 (8.70%) | 5 / 94 (5.32%) | |
| occurrences (all) | 4 | 9 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 10 / 46 (21.74%) | 26 / 94 (27.66%) | |
| occurrences (all) | 11 | 37 | |
| Pain | | | |
| subjects affected / exposed | 10 / 46 (21.74%) | 14 / 94 (14.89%) | |
| occurrences (all) | 11 | 20 | |
| Peripheral swelling | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 3 / 94 (3.19%) | |
| occurrences (all) | 3 | 4 | |
| Pyrexia | | | |
| subjects affected / exposed | 17 / 46 (36.96%) | 32 / 94 (34.04%) | |
| occurrences (all) | 21 | 51 | |
| Reproductive system and breast disorders | | | |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 0 / 94 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 20 / 46 (43.48%) | 30 / 94 (31.91%) | |
| occurrences (all) | 25 | 43 | |
| Dysphonia | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 7 / 94 (7.45%) | |
| occurrences (all) | 3 | 7 | |
| Dyspnoea | | | |
| subjects affected / exposed | 14 / 46 (30.43%) | 28 / 94 (29.79%) | |
| occurrences (all) | 14 | 32 | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 5 / 94 (5.32%) | |
| occurrences (all) | 3 | 5 | |
| Nasal congestion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 5 / 46 (10.87%) | 9 / 94 (9.57%) | |
| occurrences (all) | 8 | 10 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 5 / 46 (10.87%) | 9 / 94 (9.57%) | |
| occurrences (all) | 5 | 9 | |
| Pleural effusion | | | |
| subjects affected / exposed | 4 / 46 (8.70%) | 5 / 94 (5.32%) | |
| occurrences (all) | 4 | 6 | |
| Productive cough | | | |
| subjects affected / exposed | 4 / 46 (8.70%) | 3 / 94 (3.19%) | |
| occurrences (all) | 4 | 4 | |
| Pneumonitis | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 5 / 94 (5.32%) | |
| occurrences (all) | 2 | 6 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 2 / 94 (2.13%) | |
| occurrences (all) | 3 | 2 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 4 / 46 (8.70%) | 7 / 94 (7.45%) | |
| occurrences (all) | 4 | 7 | |
| Insomnia | | | |
| subjects affected / exposed | 11 / 46 (23.91%) | 20 / 94 (21.28%) | |
| occurrences (all) | 11 | 20 | |
| Depression | | | |
| subjects affected / exposed | 4 / 46 (8.70%) | 4 / 94 (4.26%) | |
| occurrences (all) | 4 | 4 | |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 7 / 46 (15.22%) | 31 / 94 (32.98%) | |
| occurrences (all) | 7 | 48 | |
| Amylase increased | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 14 / 94 (14.89%) | |
| occurrences (all) | 3 | 20 | |
| Alanine aminotransferase increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 7 / 46 (15.22%) | 30 / 94 (31.91%) | |
| occurrences (all) | 8 | 40 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 7 / 46 (15.22%) | 13 / 94 (13.83%) | |
| occurrences (all) | 7 | 16 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 12 / 94 (12.77%) | |
| occurrences (all) | 1 | 16 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 4 / 46 (8.70%) | 10 / 94 (10.64%) | |
| occurrences (all) | 4 | 18 | |
| Blood thyroid stimulating hormone decreased | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 7 / 94 (7.45%) | |
| occurrences (all) | 1 | 7 | |
| Blood thyroid stimulating hormone increased | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 8 / 94 (8.51%) | |
| occurrences (all) | 0 | 9 | |
| Lipase increased | | | |
| subjects affected / exposed | 6 / 46 (13.04%) | 22 / 94 (23.40%) | |
| occurrences (all) | 8 | 37 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 5 / 94 (5.32%) | |
| occurrences (all) | 0 | 8 | |
| Weight decreased | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 16 / 94 (17.02%) | |
| occurrences (all) | 2 | 17 | |
| Weight increased | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 5 / 94 (5.32%) | |
| occurrences (all) | 3 | 8 | |
| Cardiac disorders | | | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 4 / 94 (4.26%) | |
| occurrences (all) | 3 | 4 | |
| Atrial fibrillation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 46 (6.52%) | 6 / 94 (6.38%) | |
| occurrences (all) | 3 | 9 | |
| Tachycardia | | | |
| subjects affected / exposed | 5 / 46 (10.87%) | 5 / 94 (5.32%) | |
| occurrences (all) | 5 | 5 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 11 / 46 (23.91%) | 35 / 94 (37.23%) | |
| occurrences (all) | 14 | 49 | |
| Dysgeusia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 6 / 94 (6.38%) | |
| occurrences (all) | 1 | 6 | |
| Dizziness | | | |
| subjects affected / exposed | 5 / 46 (10.87%) | 17 / 94 (18.09%) | |
| occurrences (all) | 7 | 31 | |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 9 / 94 (9.57%) | |
| occurrences (all) | 0 | 9 | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 4 / 46 (8.70%) | 4 / 94 (4.26%) | |
| occurrences (all) | 6 | 4 | |
| Taste disorder | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 5 / 94 (5.32%) | |
| occurrences (all) | 0 | 5 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 15 / 46 (32.61%) | 24 / 94 (25.53%) | |
| occurrences (all) | 17 | 35 | |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 5 / 94 (5.32%) | |
| occurrences (all) | 1 | 7 | |
| Eye disorders | | | |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 15 / 94 (15.96%) | |
| occurrences (all) | 0 | 17 | |
| Gastrointestinal disorders | | | |

| | | | |
|---|---|---|---|
| Abdominal discomfort | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 4 / 94 (4.26%) | |
| occurrences (all) | 4 | 4 | |
| Abdominal distension | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 9 / 94 (9.57%) | |
| occurrences (all) | 4 | 12 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 9 / 94 (9.57%) | |
| occurrences (all) | 4 | 11 | |
| Abdominal pain | | | |
| subjects affected / exposed | 12 / 46 (26.09%) | 20 / 94 (21.28%) | |
| occurrences (all) | 20 | 25 | |
| Colitis | | | |
| subjects affected / exposed | 4 / 46 (8.70%) | 9 / 94 (9.57%) | |
| occurrences (all) | 4 | 9 | |
| Constipation | | | |
| subjects affected / exposed | 14 / 46 (30.43%) | 32 / 94 (34.04%) | |
| occurrences (all) | 15 | 42 | |
| Diarrhoea | | | |
| subjects affected / exposed | 24 / 46 (52.17%) | 54 / 94 (57.45%) | |
| occurrences (all) | 46 | 112 | |
| Dry mouth | | | |
| subjects affected / exposed | 6 / 46 (13.04%) | 9 / 94 (9.57%) | |
| occurrences (all) | 6 | 9 | |
| Dyspepsia | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 7 / 94 (7.45%) | |
| occurrences (all) | 3 | 7 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 5 / 94 (5.32%) | |
| occurrences (all) | 2 | 5 | |
| Flatulence | | | |
| subjects affected / exposed | 4 / 46 (8.70%) | 4 / 94 (4.26%) | |
| occurrences (all) | 4 | 4 | |
| Nausea | | | |
| subjects affected / exposed | 25 / 46 (54.35%) | 40 / 94 (42.55%) | |
| occurrences (all) | 29 | 64 | |

| | | | |
|---|---|---|---|
| Vomiting | | | |
| subjects affected / exposed | 11 / 46 (23.91%) | 29 / 94 (30.85%) | |
| occurrences (all) | 13 | 44 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 4 / 46 (8.70%) | 1 / 94 (1.06%) | |
| occurrences (all) | 4 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |
| subjects affected / exposed | 5 / 46 (10.87%) | 9 / 94 (9.57%) | |
| occurrences (all) | 5 | 10 | |
| Erythema | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 10 / 94 (10.64%) | |
| occurrences (all) | 1 | 10 | |
| Night sweats | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 8 / 94 (8.51%) | |
| occurrences (all) | 1 | 8 | |
| Rash erythematous | | | |
| subjects affected / exposed | 4 / 46 (8.70%) | 2 / 94 (2.13%) | |
| occurrences (all) | 5 | 2 | |
| Rash | | | |
| subjects affected / exposed | 17 / 46 (36.96%) | 45 / 94 (47.87%) | |
| occurrences (all) | 24 | 73 | |
| Pruritus | | | |
| subjects affected / exposed | 17 / 46 (36.96%) | 47 / 94 (50.00%) | |
| occurrences (all) | 25 | 65 | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 8 / 46 (17.39%) | 16 / 94 (17.02%) | |
| occurrences (all) | 10 | 20 | |
| Rash pruritic | | | |
| subjects affected / exposed | 4 / 46 (8.70%) | 3 / 94 (3.19%) | |
| occurrences (all) | 4 | 3 | |
| Skin hypopigmentation | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 5 / 94 (5.32%) | |
| occurrences (all) | 0 | 5 | |
| Vitiligo | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 46 (8.70%) | 11 / 94 (11.70%) | |
| occurrences (all) | 4 | 11 | |
| Renal and urinary disorders | | | |
| Pollakiuria | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 5 / 94 (5.32%) | |
| occurrences (all) | 1 | 5 | |
| Endocrine disorders | | | |
| Hypophysitis | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 10 / 94 (10.64%) | |
| occurrences (all) | 2 | 10 | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 7 / 94 (7.45%) | |
| occurrences (all) | 3 | 8 | |
| Hypothyroidism | | | |
| subjects affected / exposed | 7 / 46 (15.22%) | 18 / 94 (19.15%) | |
| occurrences (all) | 7 | 18 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 7 / 46 (15.22%) | 19 / 94 (20.21%) | |
| occurrences (all) | 10 | 25 | |
| Arthralgia | | | |
| subjects affected / exposed | 11 / 46 (23.91%) | 26 / 94 (27.66%) | |
| occurrences (all) | 12 | 40 | |
| Muscular weakness | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 12 / 94 (12.77%) | |
| occurrences (all) | 2 | 12 | |
| Muscle spasms | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 6 / 94 (6.38%) | |
| occurrences (all) | 3 | 7 | |
| Myalgia | | | |
| subjects affected / exposed | 13 / 46 (28.26%) | 14 / 94 (14.89%) | |
| occurrences (all) | 13 | 19 | |
| Pain in extremity | | | |
| subjects affected / exposed | 9 / 46 (19.57%) | 10 / 94 (10.64%) | |
| occurrences (all) | 9 | 11 | |
| Infections and infestations | | | |

| | | | |
|---|---|---|---|
| Pneumonia | | | |
| subjects affected / exposed | 5 / 46 (10.87%) | 2 / 94 (2.13%) | |
| occurrences (all) | 5 | 2 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 5 / 46 (10.87%) | 7 / 94 (7.45%) | |
| occurrences (all) | 5 | 8 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 9 / 94 (9.57%) | |
| occurrences (all) | 2 | 9 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 17 / 46 (36.96%) | 26 / 94 (27.66%) | |
| occurrences (all) | 21 | 28 | |
| Dehydration | | | |
| subjects affected / exposed | 4 / 46 (8.70%) | 22 / 94 (23.40%) | |
| occurrences (all) | 6 | 28 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 13 / 94 (13.83%) | |
| occurrences (all) | 3 | 16 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 8 / 94 (8.51%) | |
| occurrences (all) | 4 | 12 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 6 / 46 (13.04%) | 11 / 94 (11.70%) | |
| occurrences (all) | 6 | 14 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 5 / 94 (5.32%) | |
| occurrences (all) | 2 | 9 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 5 / 46 (10.87%) | 15 / 94 (15.96%) | |
| occurrences (all) | 6 | 22 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 11 / 94 (11.70%) | |
| occurrences (all) | 3 | 13 | |
| Hyponatraemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed<br>occurrences (all) | 6 / 46 (13.04%)<br>7 | 22 / 94 (23.40%)<br>38 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 08 July 2013 | Updated Study Design and Statistical Analysis Design |
| 07 October 2013 | Updated Clinical Lab evaluations section |
| 17 December 2014 | Provided instructions for unblinding participants |
| 30 August 2016 | Updated frequency of assessments |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported