



Clinical trial results:

A Phase II Safety Trial of Nivolumab in Patients with Metastatic Renal Cell Carcinoma Who Have Progressed During or After Prior Systemic Anti-Angiogenic Regimen.

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-004117-24 |
| Trial protocol | FR |
| Global end of trial date | 30 June 2021 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 21 May 2025 |
| First version publication date | 21 May 2025 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | GETUG-AFU26 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03013335 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | UNICANCER |
| Sponsor organisation address | 101 rue de Tolbiac, Paris, France, |
| Public contact | Nourredine AIT RAHMOUNE, UNICANCER, +33 0171936704, n.ait-rahmoune@unicancer.fr |
| Scientific contact | Nourredine AIT RAHMOUNE, UNICANCER, +33 0171936704, n.ait-rahmoune@unicancer.fr |

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 April 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 30 June 2021 |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 June 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the incidence of high-grade (i.e. Grade 3-4 and Grade 5 of CTCAE v4.0) adverse reactions of interest in patients with metastatic RCC who have progressed during or after receiving at least one prior systemic anti-angiogenic treatment and who are eligible for nivolumab monotherapy.

Protection of trial subjects:

This study was conducted in compliance with the protocol and in accordance with the French national regulatory requirements and the Declaration of Helsinki (1964) and subsequent amendments, ICH Good Clinical Practice (GCP) Guidelines (CPMP/ICH/135/95), the European Directive (2001/20/CE) and the applicable local regulatory requirements and laws.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 01 December 2015 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 5 Years |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | France: 720 |
| Worldwide total number of subjects | 720 |
| EEA total number of subjects | 720 |

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) | 353 |

| | |
|---------------------|-----|
| From 65 to 84 years | 360 |
| 85 years and over | 7 |

Subject disposition

Recruitment

Recruitment details:

From 01-Feb-2016 to 27-Jul-2017, 729 patients were enrolled in the NIVOREN study across 26 centers in France.

The 720 patients who received at least 1 dose of nivolumab were included and analyzed.

Pre-assignment

Screening details:

Patients were included in the study with mRCC with clear cell component; at least one prior systemic anti-angiogenic treatment; ECOG ≤ 2 . Patients will be treated with nivolumab every 2 weeks until disease progression without clinical benefit, unacceptable toxicity, or withdrawal of informed consent, follow-up is planned to last up to 5 years.

Period 1

| | |
|------------------------------|----------------------------------|
| Period 1 title | Overall periode (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

NA

Arms

| | |
|-----------|-----------|
| Arm title | NIVOLUMAB |
|-----------|-----------|

Arm description:

Only one arm in this trial

Treatment: Nivolumab

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

Dosage and administration details:

The dose and schedule of nivolumab in this study was 3 mg/kg every 2 weeks. Infusion of nivolumab were performed in 30 minutes (± 5 minutes).

Nivolumab was administered until death, disease progression, unacceptable toxicity or withdrawal of the informed consent.

| Number of subjects in period 1 | NIVOLUMAB |
|--|-----------|
| Started | 720 |
| Completed | 0 |
| Not completed | 720 |
| Physician decision | 22 |
| Patient decision | 23 |
| End of study/ Progressive disease | 495 |
| Response observed by physician/patient/other (Comp | 24 |
| Death | 41 |

| | |
|------------------------|-----|
| Other | 1 |
| Toxicity/adverse event | 114 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------------|
| Reporting group title | Overall periode |
|-----------------------|-----------------|

Reporting group description: -

| Reporting group values | Overall periode | Total | |
|--|-----------------|-------|--|
| Number of subjects | 720 | 720 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 353 | 353 | |
| From 65-84 years | 360 | 360 | |
| 85 years and over | 7 | 7 | |
| Age continuous | | | |
| Units: years | | | |
| median | 64 | | |
| full range (min-max) | 22 to 90 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 164 | 164 | |
| Male | 556 | 556 | |
| ECOG | | | |
| Units: Subjects | | | |
| Missing data | 36 | 36 | |
| ECOG 0 | 229 | 229 | |
| ECOG 1 | 352 | 352 | |
| ECOG 2 | 100 | 100 | |
| ECOG 3 | 3 | 3 | |
| Menopausal status | | | |
| Units: Subjects | | | |
| Missing data | 2 | 2 | |
| Non-menopause | 17 | 17 | |
| Pre-menopause | 4 | 4 | |
| Menopause | 131 | 131 | |
| Unknown | 10 | 10 | |
| Non applicable | 556 | 556 | |
| Hemoglobin ≤LLN | | | |
| Units: Subjects | | | |
| NO | 324 | 324 | |
| YES | 396 | 396 | |
| Calcium (corrected) ≥ULN | | | |

| | | | |
|---|-----|-----|--|
| Units: Subjects | | | |
| Missing data | 2 | 2 | |
| No | 553 | 553 | |
| Yes | 165 | 165 | |
| Neutrophils \geq ULN | | | |
| Units: Subjects | | | |
| No | 645 | 645 | |
| Yes | 75 | 75 | |
| Platelets >ULN | | | |
| Units: Subjects | | | |
| No | 623 | 623 | |
| Yes | 97 | 97 | |
| IMDC prognostic/ Score | | | |
| Units: Subjects | | | |
| Missing data | 2 | 2 | |
| Score = 0 | 132 | 132 | |
| Score =1 | 234 | 234 | |
| Score =2 | 171 | 171 | |
| Score =3 | 94 | 94 | |
| Score =4 | 54 | 54 | |
| Score =5 | 25 | 25 | |
| Score =6 | 8 | 8 | |
| IMDC Prognostic | | | |
| Units: Subjects | | | |
| Missing data | 2 | 2 | |
| Favorable | 132 | 132 | |
| Intermediate | 405 | 405 | |
| Poor | 181 | 181 | |
| Favorable/intermediate versus poor IMDC prognostic | | | |
| Units: Subjects | | | |
| Missing data | 2 | 2 | |
| Favorable/intermediate prognostic | 537 | 537 | |
| Poor prognostic | 181 | 181 | |

End points

End points reporting groups

| | |
|------------------------------|-----------|
| Reporting group title | NIVOLUMAB |
| Reporting group description: | |
| Only one arm in this trial | |
| Treatment: Nivolumab | |

Primary: Incidence of Grade 3, 4, or 5 ADR

| | |
|--|--|
| End point title | Incidence of Grade 3, 4, or 5 ADR ^[1] |
| End point description: | |
| The primary endpoint of this study was the incidence for high-grade (Grade 3-4 and Grade 5) adverse reactions of interest [i.e. adverse event related to the study treatment (TRAE)]. The adverse reactions of interest were skin, endocrinopathy, gastrointestinal, hepatic, renal, pulmonary, and hypersensitivity adverse events. Due to the frequency of TRAEs observed during the study, safety analyses were done on all TRAEs of grade 3 or more observed by the investigator during the study. | |
| End point type | Primary |
| End point timeframe: | |
| 5 years | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The primary endpoint of this study was the incidence for high-grade (Grade 3-4 and Grade 5) adverse reactions of interest (i.e. adverse event related to the study treatment). The forms AE from the CRF was used and correspond to the adverse event related to the study treatment judged from investigator. The number of patients with at least one AE of grade ≥ 3 related to nivolumab were presented with count, % and 95% confidence interval. Only one arm in this study ,there were no statistical analyses

| End point values | NIVOLUMAB | | | |
|--|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 720 | | | |
| Units: percent of patients | | | | |
| number (not applicable) | | | | |
| Patient with at least 1 ADR \geq grade 3 | 19.9 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

| | |
|--|-----------------------|
| End point title | Overall survival (OS) |
| End point description: | |
| OS is defined as the time from first dosing date to the date of death. A patient who has not died will be censored at last known date alive. OS will be followed continuously while patients are on the treatment and every 3 months via in-person or phone contact after patients discontinue the study drug. | |
| End point type | Secondary |
| End point timeframe: | |
| 5 years | |

| | | | | |
|----------------------------------|---------------------|--|--|--|
| End point values | NIVOLUMAB | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 720 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 55.9 (54.4 to 57.3) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate (ORR)

| | |
|--|-------------------------------|
| End point title | Objective response rate (ORR) |
| End point description: | |
| Objective response rate (ORR) is defined as the number and percentage of patients with a Best Overall Response (BOR) of confirmed complete response (CR) or partial response (PR). Best overall response (BOR) is defined as the best response designation, recorded between the date of first dose and the date of the initial objectively documented tumor progression per RECIST v1.1 or the date of subsequent therapy, whichever occurs first. For Patients without documented progression or subsequent therapy, all available response designations will contribute to the BOR determination. | |
| End point type | Secondary |
| End point timeframe: | |
| 5 years | |

| | | | | |
|----------------------------------|---------------------|--|--|--|
| End point values | NIVOLUMAB | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 720 | | | |
| Units: percent | | | | |
| median (confidence interval 95%) | 21.3 (18.3 to 24.5) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From inclusion until 30 days after end of treatment (up to 5 years).

Adverse event reporting additional description:

For non serious adverse events only treatment-related adverse events (TRAEs) were available.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 24.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | NIVOLUMAB |
|-----------------------|-----------|

Reporting group description:

Of the 729 patients included in the study, 720 patients received at least one dose of nivolumab and were evaluable for the safety analysis. Nine patients did not received the study treatment and were excluded of the safety analysis.

| Serious adverse events | NIVOLUMAB | | |
|---|--------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 330 / 720 (45.83%) | | |
| number of deaths (all causes) | 518 | | |
| number of deaths resulting from adverse events | 8 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute myeloblastic leukemia | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 4 / 720 (0.56%) | | |
| occurrences causally related to treatment / all | 1 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bone metastases | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Brain metastases | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 4 / 720 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Breast cancer | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cancer pain | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal metastasis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lentigo maligna melanoma | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lobular breast carcinoma (in situ) | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lymphangitis carcinomatosa | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 4 / 720 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 4 | | |
| Metastases to pituitary gland | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metastatic pain | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myeloid leukaemia | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myeloma | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neoplasm progression | | | |
| subjects affected / exposed | 10 / 720 (1.39%) | | |
| occurrences causally related to treatment / all | 0 / 10 | | |
| deaths causally related to treatment / all | 0 / 7 | | |
| Osteolytic bone metastases | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatic cancer | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Prostate cancer | | | |
| subjects affected / exposed | 3 / 720 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinocellular carcinom | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Squamous cell carcinoma of the cervix | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Superficial basal cell carcinoma | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tumor compression | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tumor progression | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Aortic thrombosis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral hemorrhage | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Ischemic stroke | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Pregnancy | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Anasarca | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Asthenia | | | |
| subjects affected / exposed | 4 / 720 (0.56%) | | |
| occurrences causally related to treatment / all | 2 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chest pain | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chronic pain | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Death | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Disease progression | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |

| | | | | |
|---|------------------|--|--|--|
| Drug side effect | | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Face edema | | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Face oedema | | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fatigue | | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fever | | | | |
| subjects affected / exposed | 7 / 720 (0.97%) | | | |
| occurrences causally related to treatment / all | 2 / 7 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fever malignant | | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| General physical health deterioration | | | | |
| subjects affected / exposed | 32 / 720 (4.44%) | | | |
| occurrences causally related to treatment / all | 2 / 33 | | | |
| deaths causally related to treatment / all | 0 / 14 | | | |
| Hyperthermia | | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pain | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 5 / 720 (0.69%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thoracic pain | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Unknown cause of death | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Immune system disorders | | | |
| Allergic reaction | | | |
| subjects affected / exposed | 4 / 720 (0.56%) | | |
| occurrences causally related to treatment / all | 4 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Benign prostatic hypertrophy | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Asthmatoid bronchitis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atelectasis | | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchial hemorrhage | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchial obstruction | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chronic obstructive pulmonary disease exacerbation | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Distress respiratory | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Dyspnea | | | |
| subjects affected / exposed | 11 / 720 (1.53%) | | |
| occurrences causally related to treatment / all | 1 / 11 | | |
| deaths causally related to treatment / all | 0 / 3 | | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Interstitial pneumonitis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia interstitial | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonitis allergic | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumopathy | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Toxic pneumonitis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Clinomania | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Confusion | | | |
| subjects affected / exposed | 4 / 720 (0.56%) | | |
| occurrences causally related to treatment / all | 1 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Depressive symptom | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychomotor retardation | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Suicide | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Investigations | | | |
| Lost weight | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Arm fracture | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral edema | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Drug overdose | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fall | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Femur fracture | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Humerus fracture | | | |
| subjects affected / exposed | 3 / 720 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pathological fracture | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Radiation proctitis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Scalp injury NOS | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Trauma | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wrist fracture | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |

| | | | | |
|---|-----------------|--|--|--|
| Acute coronary syndrome | | | | |
| subjects affected / exposed | 3 / 720 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atrial fibrillation | | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atrial flutter | | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atrioventricular block | | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bradycardia | | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac failure | | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 1 / 1 | | | |
| Cardiomyopathy | | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Decompensation cardiac | | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Heart failure | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocarditis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pericardial tamponade | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pericarditis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pleuropericarditis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sinus bradycardia | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thoracic pain | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cervical myelopathy | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Encephalopathy | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epileptic seizure | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Generalized tonic-clonic seizure | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hemiparesis (right) | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ischemic stroke | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myasthenia gravis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neurologic disorder NOS | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Paresthesia lower limb | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Quadripareisis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sciatica | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Seizure | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Seizures | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal cord compression | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 7 / 720 (0.97%) | | |
| occurrences causally related to treatment / all | 0 / 7 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Blood and lymphatic system disorders | | | |
| Acute anemia | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anemia | | | |
| subjects affected / exposed | 7 / 720 (0.97%) | | |
| occurrences causally related to treatment / all | 3 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Macrophage activation syndrome | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Ear and labyrinth disorders | | | |
| Vestibular disorder | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Posterior uveitis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Uveitis | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Visual impairment | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 5 / 720 (0.69%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute hemorrhagic ulcerative colitis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute pancreatitis | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ascites | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Autoimmune colitis | | | |
| subjects affected / exposed | 3 / 720 (0.42%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bleeding gastrointestinal | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bleeding rectal | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| C.difficile diarrhoea | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colitis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colon perforation | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colonic obstruction | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Diarrhea | | | |
| subjects affected / exposed | 8 / 720 (1.11%) | | |
| occurrences causally related to treatment / all | 8 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Duodenal stenosis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastric hemorrhage | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastric ulcer hemorrhage | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal bleeding | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hemorrhage gastric | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hemorrhage of digestive tract | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Inguinal hernia | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lip oedema | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Melena | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis acute | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peritonitis biliary | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rectal bleeding | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rectal hemorrhage | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Small bowel obstruction | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Stomach hemorrhage | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Subocclusive syndrom | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper gastrointestinal bleeding | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Acute cholecystitis | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholangitis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic cytolysis | | | |
| subjects affected / exposed | 5 / 720 (0.69%) | | |
| occurrences causally related to treatment / all | 5 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatitis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Icterus | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Liver cholestasis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Obstruction of bile duct | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Portal hypertension | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Bullous dermatitis | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dermatosis bullous | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lupus syndrome | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Maculo-papular rash | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Papular rash | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |

| | | | |
|---|-----------------|--|--|
| Acute prerenal failure | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute renal failure | | | |
| subjects affected / exposed | 9 / 720 (1.25%) | | |
| occurrences causally related to treatment / all | 2 / 10 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute renal insufficiency | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hematuria | | | |
| subjects affected / exposed | 3 / 720 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Proteinuria | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure | | | |
| subjects affected / exposed | 5 / 720 (0.69%) | | |
| occurrences causally related to treatment / all | 6 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 6 / 720 (0.83%) | | |
| occurrences causally related to treatment / all | 5 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Autoimmune thyroiditis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Decompensated diabetes | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Goiter | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypophysitis | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Inappropriate antidiuretic hormone secretion | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arthralgia multiple | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bone pain | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Costal pain | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Inflammatory arthritis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Leg pain | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lumbalgia | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lumbar pain | | | |
| subjects affected / exposed | 3 / 720 (0.42%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteolytic lesion | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain in leg | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain sacroiliac | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Polyarthritis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Polymyalgia rheumatica | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sacroiliac fracture | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal pain | | | |
| subjects affected / exposed | 3 / 720 (0.42%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vertebral pain | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Abscess periodontal | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute appendicitis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aspergillosis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bacterial infection | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchial infection | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchiolitis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Catheter infection | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Catheter related infection | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Enterococcus faecalis infection | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epiduritis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Foot infection | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemophilus influenza infection | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatitis E | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infection NOS | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infection urinary tract | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infectious pneumonitis | | | |
| subjects affected / exposed | 7 / 720 (0.97%) | | |
| occurrences causally related to treatment / all | 1 / 7 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Lung infection | | | |
| subjects affected / exposed | 5 / 720 (0.69%) | | |
| occurrences causally related to treatment / all | 2 / 5 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Parvovirus B19 infection | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peritonitis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumocystis pneumonia | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Prostatic abscess | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 3 / 720 (0.42%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis syndrome | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Septic cholangitis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Septic encephalopathy | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Septic shock | | | |
| subjects affected / exposed | 3 / 720 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Septicemia | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Staphylococcus epidermidis infection | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical site infection | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary infection | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Anorexia | | | |
| subjects affected / exposed | 4 / 720 (0.56%) | | |
| occurrences causally related to treatment / all | 1 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetic metabolic decompensation | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypercalcemia | | | |
| subjects affected / exposed | 26 / 720 (3.61%) | | |
| occurrences causally related to treatment / all | 1 / 29 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperglycemia | | | |
| subjects affected / exposed | 5 / 720 (0.69%) | | |
| occurrences causally related to treatment / all | 3 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperkalemia | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyponatremia | | | |
| subjects affected / exposed | 5 / 720 (0.69%) | | |
| occurrences causally related to treatment / all | 4 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |

Frequency threshold for reporting non-serious adverse events: 1 %

| Non-serious adverse events | NIVOLUMAB | | |
|--|--------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 676 / 720 (93.89%) | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences (all) | 8 | | |
| Seborrheic keratosis | | | |

| | | | |
|--|----------------------|--|--|
| subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 2 | | |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 3 / 720 (0.42%) | | |
| occurrences (all) | 3 | | |
| Hot flush | | | |
| subjects affected / exposed | 4 / 720 (0.56%) | | |
| occurrences (all) | 6 | | |
| Hypertension | | | |
| subjects affected / exposed | 8 / 720 (1.11%) | | |
| occurrences (all) | 14 | | |
| Hypotension | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences (all) | 2 | | |
| Varicose vein | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 1 | | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion missed | | | |
| subjects affected / exposed | 3 / 720 (0.42%) | | |
| occurrences (all) | 6 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 185 / 720 (25.69%) | | |
| occurrences (all) | 929 | | |
| Chest discomfort | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences (all) | 2 | | |
| Chest pain | | | |
| subjects affected / exposed | 3 / 720 (0.42%) | | |
| occurrences (all) | 4 | | |
| Chills | | | |
| subjects affected / exposed | 9 / 720 (1.25%) | | |
| occurrences (all) | 12 | | |
| Exercise tolerance decreased | | | |

| | | | |
|---------------------------------------|------------------|--|--|
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 1 | | |
| Face edema | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 2 | | |
| Fatigue | | | |
| subjects affected / exposed | 52 / 720 (7.22%) | | |
| occurrences (all) | 234 | | |
| Feeling cold | | | |
| subjects affected / exposed | 3 / 720 (0.42%) | | |
| occurrences (all) | 3 | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 3 / 720 (0.42%) | | |
| occurrences (all) | 4 | | |
| Generalized edema | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 2 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 5 / 720 (0.69%) | | |
| occurrences (all) | 5 | | |
| Malaise | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 2 | | |
| Mucosal dryness | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences (all) | 2 | | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 15 / 720 (2.08%) | | |
| occurrences (all) | 48 | | |
| Edema | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 1 | | |
| Edema peripheral | | | |
| subjects affected / exposed | 11 / 720 (1.53%) | | |
| occurrences (all) | 29 | | |
| Pain | | | |

| | | | |
|--|-------------------------|--|--|
| subjects affected / exposed occurrences (all) | 6 / 720 (0.83%) 8 | | |
| Pyrexia subjects affected / exposed occurrences (all) | 15 / 720 (2.08%) 24 | | |
| Sense of oppression subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 1 | | |
| Xerosis subjects affected / exposed occurrences (all) | 36 / 720 (5.00%) 259 | | |
| Immune system disorders | | | |
| Hypersensitivity subjects affected / exposed occurrences (all) | 6 / 720 (0.83%) 8 | | |
| Sarcoidosis subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 4 | | |
| Reproductive system and breast disorders | | | |
| Balanoposthitis subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 4 | | |
| Erectile dysfunction subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 13 | | |
| Genital erythema subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 2 | | |
| Genital rash subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 4 | | |
| Heavy menstrual bleeding subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 1 | | |
| Penile edema | | | |

| | | | |
|--|------------------------|--|--|
| subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 2 | | |
| Pruritus genital subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 5 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 14 / 720 (1.94%) 40 | | |
| Dysphonia subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 6 | | |
| Dyspnea subjects affected / exposed occurrences (all) | 25 / 720 (3.47%) 47 | | |
| Dyspnea exertional subjects affected / exposed occurrences (all) | 6 / 720 (0.83%) 20 | | |
| Epistaxis subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 12 | | |
| Hiccups subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 2 | | |
| Hypersensitivity pneumonitis subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 3 | | |
| Hypoxia subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 1 | | |
| Immune-mediated lung disease subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 3 | | |
| Interstitial lung disease | | | |

| | | | |
|--|-----------------------|--|--|
| subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 4 | | |
| Lung disorder subjects affected / exposed occurrences (all) | 9 / 720 (1.25%) 15 | | |
| Organizing pneumonia subjects affected / exposed occurrences (all) | 4 / 720 (0.56%) 14 | | |
| Oropharyngeal discomfort subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 19 | | |
| Pharyngeal paresthesia subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 1 | | |
| Pulmonary embolism subjects affected / exposed occurrences (all) | 3 / 720 (0.42%) 6 | | |
| Pulmonary interstitial emphysema syndrome subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 5 | | |
| Sneezing subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 4 | | |
| Psychiatric disorders | | | |
| Affective disorder subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 1 | | |
| Anxiety subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 1 | | |
| Confusional state subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 3 | | |
| Insomnia | | | |

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|--|------------------------|--|--|
| subjects affected / exposed occurrences (all) | 3 / 720 (0.42%) 5 | | |
| Psychomotor retardation subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 3 | | |
| Sleep disorder subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 2 | | |
| Investigations | | | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 11 / 720 (1.53%) 36 | | |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 9 / 720 (1.25%) 26 | | |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 7 / 720 (0.97%) 17 | | |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 2 | | |
| Blood creatinine subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 1 | | |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 19 | | |
| Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all) | 3 / 720 (0.42%) 13 | | |
| Blood potassium increased subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 2 | | |
| Blood thyroid stimulating hormone decreased | | | |

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|---|-----------------|--|--|
| subjects affected / exposed | 3 / 720 (0.42%) | | |
| occurrences (all) | 11 | | |
| Blood thyroid stimulating hormone increased | | | |
| subjects affected / exposed | 6 / 720 (0.83%) | | |
| occurrences (all) | 28 | | |
| Blood urea increased | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 6 | | |
| Creatinine renal clearance decreased | | | |
| subjects affected / exposed | 4 / 720 (0.56%) | | |
| occurrences (all) | 8 | | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 9 / 720 (1.25%) | | |
| occurrences (all) | 28 | | |
| Lipase increased | | | |
| subjects affected / exposed | 4 / 720 (0.56%) | | |
| occurrences (all) | 16 | | |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences (all) | 4 | | |
| Lymphocyte count increased | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 1 | | |
| Neutrophil count increased | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 1 | | |
| Thyroid hormones decreased | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 3 | | |
| Thyroid hormones increased | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 12 | | |
| Thyroxine free increased | | | |

| | | | |
|--|-----------------------|--|--|
| subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 1 | | |
| Transaminases increased subjects affected / exposed occurrences (all) | 3 / 720 (0.42%) 5 | | |
| Tri-iodothyronine free increased subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 1 | | |
| Weight decreased subjects affected / exposed occurrences (all) | 6 / 720 (0.83%) 8 | | |
| Weight increased subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 64 | | |
| White blood cell count increased subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 4 | | |
| Diabetes mellitus inadequate control subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 25 | | |
| Gout subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 1 | | |
| Hypercalcemia subjects affected / exposed occurrences (all) | 3 / 720 (0.42%) 11 | | |
| Hypercholesterolemia subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 1 | | |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 1 | | |
| Lip injury | | | |

| | | | |
|--|-----------------------|--|--|
| subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 1 | | |
| Muscle rupture subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 1 | | |
| Cardiac disorders | | | |
| atrial fibrillation subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 2 | | |
| Atrioventricular block subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 2 | | |
| Cardiac arrest subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 1 | | |
| Cardiac failure subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 1 | | |
| Cyanosis subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 6 | | |
| Myocarditis subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 2 | | |
| Pleuropericarditis subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 3 | | |
| Tachycardia subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 1 | | |
| Nervous system disorders | | | |
| Anosmia subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 10 | | |
| Burning sensation | | | |

| | | | |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 1 | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 1 | | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences (all) | 2 | | |
| Dysarthria | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 1 | | |
| Dysgeusia | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences (all) | 8 | | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 2 | | |
| Headache | | | |
| subjects affected / exposed | 10 / 720 (1.39%) | | |
| occurrences (all) | 29 | | |
| Hypoesthesia | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 2 | | |
| Ischemic stroke | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 1 | | |
| Migraine | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 2 | | |
| Motor dysfunction | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences (all) | 18 | | |
| Myasthenia gravis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 3 | | |
| Nervous system disorder | | | |

| | | | |
|---|------------------------|--|--|
| subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 1 | | |
| Neuralgia subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 2 | | |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 10 | | |
| Paresthesia subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 6 | | |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 10 | | |
| Sciatica subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 1 | | |
| Seizure subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 4 | | |
| Sensorimotor disorder subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 8 | | |
| Somnolence subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 1 | | |
| Tremor subjects affected / exposed occurrences (all) | 3 / 720 (0.42%) 3 | | |
| Blood and lymphatic system disorders | | | |
| Anemia subjects affected / exposed occurrences (all) | 22 / 720 (3.06%) 87 | | |
| Autoimmune hemolytic anemia subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 2 | | |

| | | | |
|-----------------------------|------------------|--|--|
| Eosinophilia | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences (all) | 15 | | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 1 | | |
| Lymphopenia | | | |
| subjects affected / exposed | 12 / 720 (1.67%) | | |
| occurrences (all) | 36 | | |
| Neutropenia | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences (all) | 17 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences (all) | 40 | | |
| Ear and labyrinth disorders | | | |
| Tinnitus | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 2 | | |
| Vertigo | | | |
| subjects affected / exposed | 4 / 720 (0.56%) | | |
| occurrences (all) | 7 | | |
| Vertigo positional | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 2 | | |
| Eye disorders | | | |
| Abnormal sensation in eye | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 1 | | |
| Blepharitis | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences (all) | 4 | | |
| Diplopia | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 7 | | |
| Dry eye | | | |

| | | | |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 8 / 720 (1.11%) | | |
| occurrences (all) | 27 | | |
| Episcleritis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 3 | | |
| Eyelid edema | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 7 | | |
| Eyelids pruritus | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 2 | | |
| Keratitis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 2 | | |
| Ocular hyperemia | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 2 | | |
| Uveitis | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences (all) | 8 | | |
| Vision blurred | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences (all) | 2 | | |
| Xerophthalmia | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences (all) | 55 | | |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 3 / 720 (0.42%) | | |
| occurrences (all) | 5 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 10 / 720 (1.39%) | | |
| occurrences (all) | 32 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 8 / 720 (1.11%) | | |
| occurrences (all) | 22 | | |

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|-----------------------------|-------------------|--|--|
| Aphthous ulcer | | | |
| subjects affected / exposed | 4 / 720 (0.56%) | | |
| occurrences (all) | 10 | | |
| Aptyalism | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 4 | | |
| Autoimmune colitis | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences (all) | 3 | | |
| Colitis | | | |
| subjects affected / exposed | 4 / 720 (0.56%) | | |
| occurrences (all) | 7 | | |
| Constipation | | | |
| subjects affected / exposed | 25 / 720 (3.47%) | | |
| occurrences (all) | 56 | | |
| Diarrhea | | | |
| subjects affected / exposed | 76 / 720 (10.56%) | | |
| occurrences (all) | 209 | | |
| Dry mouth | | | |
| subjects affected / exposed | 14 / 720 (1.94%) | | |
| occurrences (all) | 110 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences (all) | 2 | | |
| Frequent bowel movements | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 2 | | |
| Gastric disorder | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal hemorrhage | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 1 | | |
| Hemorrhoids | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 2 | | |

| | | | |
|-----------------------------|------------------|--|--|
| Large intestine polyp | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 1 | | |
| Mouth hemorrhage | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 3 | | |
| Nausea | | | |
| subjects affected / exposed | 35 / 720 (4.86%) | | |
| occurrences (all) | 60 | | |
| Oral discomfort | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 2 | | |
| Oral lichen planus | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 5 | | |
| Rectal hemorrhage | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 5 | | |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 2 | | |
| Vomiting | | | |
| subjects affected / exposed | 17 / 720 (2.36%) | | |
| occurrences (all) | 32 | | |
| Hepatobiliary disorders | | | |
| Autoimmune hepatitis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 2 | | |
| Cholangitis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 2 | | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 1 | | |
| Cholestasis | | | |

| | | | |
|--|------------------------|--|--|
| subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 7 | | |
| Hepatic cytolysis subjects affected / exposed occurrences (all) | 7 / 720 (0.97%) 16 | | |
| Hepatitis subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 1 | | |
| Portal hypertension subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 2 | | |
| Skin and subcutaneous tissue disorders | | | |
| Acne subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 10 | | |
| Alopecia subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 5 | | |
| Dermatitis acneiform subjects affected / exposed occurrences (all) | 4 / 720 (0.56%) 9 | | |
| Dermatitis bullous subjects affected / exposed occurrences (all) | 4 / 720 (0.56%) 17 | | |
| Dermatitis diaper subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 1 | | |
| Dry skin subjects affected / exposed occurrences (all) | 13 / 720 (1.81%) 35 | | |
| Dyshidrotic eczema subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 3 | | |
| Eczema subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 19 | | |

| | | | |
|--|------------------|--|--|
| Erythema | | | |
| subjects affected / exposed | 11 / 720 (1.53%) | | |
| occurrences (all) | 25 | | |
| Erythrosis | | | |
| subjects affected / exposed | 3 / 720 (0.42%) | | |
| occurrences (all) | 7 | | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 3 / 720 (0.42%) | | |
| occurrences (all) | 4 | | |
| Hyperkeratosis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 3 | | |
| Lichen planus | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 1 | | |
| Macule | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 1 | | |
| Nail disorder | | | |
| subjects affected / exposed | 3 / 720 (0.42%) | | |
| occurrences (all) | 29 | | |
| Nail toxicity | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 3 | | |
| Night sweats | | | |
| subjects affected / exposed | 4 / 720 (0.56%) | | |
| occurrences (all) | 11 | | |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences (all) | 2 | | |
| Pemphigoid | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 1 | | |
| Photosensitivity reaction | | | |

| | | | |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 3 / 720 (0.42%) | | |
| occurrences (all) | 4 | | |
| Plantar erythema | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 1 | | |
| Prurigo | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 4 | | |
| Pruritus | | | |
| subjects affected / exposed | 66 / 720 (9.17%) | | |
| occurrences (all) | 450 | | |
| Psoriasis | | | |
| subjects affected / exposed | 6 / 720 (0.83%) | | |
| occurrences (all) | 52 | | |
| Purpura | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 4 | | |
| Rash | | | |
| subjects affected / exposed | 43 / 720 (5.97%) | | |
| occurrences (all) | 167 | | |
| Rash erythematous | | | |
| subjects affected / exposed | 7 / 720 (0.97%) | | |
| occurrences (all) | 17 | | |
| Rash macular | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 4 | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 11 / 720 (1.53%) | | |
| occurrences (all) | 17 | | |
| Rash papular | | | |
| subjects affected / exposed | 5 / 720 (0.69%) | | |
| occurrences (all) | 37 | | |
| Rash pruritic | | | |
| subjects affected / exposed | 3 / 720 (0.42%) | | |
| occurrences (all) | 4 | | |
| Skin exfoliation | | | |

| | | | |
|--|------------------------|--|--|
| subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 2 | | |
| Skin lesion subjects affected / exposed occurrences (all) | 7 / 720 (0.97%) 26 | | |
| Skin reaction subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 2 | | |
| Skin toxicity subjects affected / exposed occurrences (all) | 4 / 720 (0.56%) 4 | | |
| Telangiectasia subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 4 | | |
| Toxic skin eruption subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 7 | | |
| Vitiligo subjects affected / exposed occurrences (all) | 5 / 720 (0.69%) 47 | | |
| Xeroderma subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 1 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury subjects affected / exposed occurrences (all) | 5 / 720 (0.69%) 7 | | |
| Chronic kidney disease subjects affected / exposed occurrences (all) | 3 / 720 (0.42%) 14 | | |
| Proteinuria subjects affected / exposed occurrences (all) | 4 / 720 (0.56%) 16 | | |
| Renal failure subjects affected / exposed occurrences (all) | 10 / 720 (1.39%) 27 | | |

| | | | |
|--|-------------------------|--|--|
| Renal impairment subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 2 | | |
| Endocrine disorders | | | |
| Adrenal insufficiency subjects affected / exposed occurrences (all) | 8 / 720 (1.11%) 109 | | |
| Adrenocortical insufficiency acute subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 3 | | |
| Autoimmune thyroiditis subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 9 | | |
| Hyperthyroidism subjects affected / exposed occurrences (all) | 12 / 720 (1.67%) 39 | | |
| Hypophysitis subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 1 | | |
| Hypothyroidism subjects affected / exposed occurrences (all) | 26 / 720 (3.61%) 163 | | |
| Thyroid disorder subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 15 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 61 / 720 (8.47%) 251 | | |
| Arthritis subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 8 | | |
| Back pain subjects affected / exposed occurrences (all) | 12 / 720 (1.67%) 31 | | |
| Bone pain | | | |

| | | | |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 2 | | |
| Flank pain | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 1 | | |
| Muscle contracture | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 1 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 7 / 720 (0.97%) | | |
| occurrences (all) | 16 | | |
| Muscular weakness | | | |
| subjects affected / exposed | 4 / 720 (0.56%) | | |
| occurrences (all) | 22 | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 2 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 10 | | |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences (all) | 2 | | |
| Myalgia | | | |
| subjects affected / exposed | 28 / 720 (3.89%) | | |
| occurrences (all) | 82 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 6 / 720 (0.83%) | | |
| occurrences (all) | 19 | | |
| Pain in jaw | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 2 | | |
| Plantar fasciitis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 1 | | |
| Polyarthrititis | | | |

| | | | |
|--|-----------------------|--|--|
| subjects affected / exposed occurrences (all) | 4 / 720 (0.56%) 19 | | |
| Polymyalgia rheumatica subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 2 | | |
| Rheumatoid arthritis subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 9 | | |
| Sjogren's syndrome subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 2 | | |
| Spinal pain subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 4 | | |
| Systemic lupus erythematosus subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 1 | | |
| Tendon disorder subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 2 | | |
| Infections and infestations | | | |
| Acute sinusitis subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 1 | | |
| Bronchitis subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 2 | | |
| Bronchopulmonary aspergillosis subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 1 | | |
| Chorioretinitis subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 19 | | |
| Dermatitis infected subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 1 | | |

| | | | |
|----------------------------------|-----------------|--|--|
| Ecthyma | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 1 | | |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 2 | | |
| Folliculitis | | | |
| subjects affected / exposed | 4 / 720 (0.56%) | | |
| occurrences (all) | 26 | | |
| Genital infection | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 2 | | |
| Herpes simplex | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 3 | | |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 1 | | |
| Infection | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 2 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 1 | | |
| Onychomycosis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 5 | | |
| Oral candidiasis | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences (all) | 3 | | |
| Oral herpes | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 3 | | |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 1 | | |

| | | | |
|------------------------------------|------------------|--|--|
| Pneumonia | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 1 | | |
| Prostatic abscess | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 1 | | |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 1 | | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 2 | | |
| Skin infection | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences (all) | 7 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 1 | | |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 1 / 720 (0.14%) | | |
| occurrences (all) | 2 | | |
| Metabolism and nutrition disorders | | | |
| Cell death | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences (all) | 3 | | |
| Decreased appetite | | | |
| subjects affected / exposed | 34 / 720 (4.72%) | | |
| occurrences (all) | 90 | | |
| Dehydration | | | |
| subjects affected / exposed | 3 / 720 (0.42%) | | |
| occurrences (all) | 6 | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 2 / 720 (0.28%) | | |
| occurrences (all) | 53 | | |
| Hyperglycemia | | | |

| | | | |
|--|-----------------------|--|--|
| subjects affected / exposed occurrences (all) | 7 / 720 (0.97%) 74 | | |
| Hyperkaliemia subjects affected / exposed occurrences (all) | 9 / 720 (1.25%) 22 | | |
| Hyperuricemia subjects affected / exposed occurrences (all) | 2 / 720 (0.28%) 2 | | |
| Hypochloremia subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 1 | | |
| Hypokalemia subjects affected / exposed occurrences (all) | 3 / 720 (0.42%) 5 | | |
| Hypomagnesaemia subjects affected / exposed occurrences (all) | 1 / 720 (0.14%) 8 | | |
| Hyponatremia subjects affected / exposed occurrences (all) | 7 / 720 (0.97%) 10 | | |
| Hypophosphatemia subjects affected / exposed occurrences (all) | 5 / 720 (0.69%) 18 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 10 March 2016 | - Modification of the investigators list |
| 25 April 2016 | - Modification of the document of reference for the tumor evaluation - Modification of inclusion and non-inclusion criteria - Modification of the study design scheme - Addition of optional ancillary study - Modification of the flowchart - Correction of typographic errors within the protocol and the synopsis - Modification of the informed consent form - Addition of the co-coordinating investigator - Addition of the statistician's contact information - Modification of the project leader - Modification of the investigators list |
| 10 June 2016 | - Modification of the sample size - Redaction of a patient information letter to explain the rational for the new sample size - Modification of the investigators list |
| 05 July 2016 | - Modification of the inclusion criteria - Clarification of the statistical analysis plan - Modification of mode of declaration SAE related to disease progression - Modification of the informed consent form - Modification of the investigators list |
| 28 October 2016 | - Modification of the sample size - Harmonization of the protocol and inform consent form for treatment after disease progression - Declaration of new center involved in the ancillary study - Modification of the investigators list |
| 26 January 2017 | - Extension of the recruitment period - Modification of the investigators list |
| 11 May 2017 | - Modification of the investigators list |
| 03 May 2018 | - Update of the safety section (protocol and inform consent form) based on the new version of the investigator brochure - New version of investigator brochure - Modification of the investigators list |
| 15 July 2019 | - Modification of the informed consent form to inform patient that their personal data will be collected and processed in accordance with the new national data protection legislation: Regulation (EU) 2016/679 (General Data Protection Regulation). - Update of the safety section (inform consent form) based on the new version of the investigator brochure - New version of investigator brochure - Modification of the investigators list |
| 06 November 2020 | - Update of the safety section (inform consent form) based on the new version of the investigator brochure - Addition of a new ancillary study including collection of data for bone metastases - New version of investigator brochure - Modification of the investigators list |

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| 11 May 2021 | <ul style="list-style-type: none">- The follow up period was reduced for a new end of study planned on June 2021- New version of investigator brochure- Modification of the investigators list |
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported