# Clinical trial results:
# A Phase 1b/2 Study of Safety and Efficacy of MLN0128 (Dual TORC1/2 Inhibitor) in Combination With Exemestane or Fulvestrant Therapy in Postmenopausal Women With ER+/HER2- Advanced or Metastatic Breast Cancer That Has Progressed on Treatment With Everolimus in Combination With Exemestane or Fulvestrant

## Summary

| | |
|---|---|
| EudraCT number | 2014-001921-34 |
| Trial protocol | BE FR |
| Global end of trial date | 03 July 2018 |

**Results information**

| | |
|---|---|
| Result version number | v2 (current) |
| This version publication date | 08 May 2020 |
| First version publication date | 14 July 2019 |
| Version creation reason | |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | C31001 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02049957 |
| WHO universal trial number (UTN) | U1111-1195-3894 |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Takeda Oncology |
| Sponsor organisation address | 40 Landsdowne Street, Cambridge, United States, 02139 |
| Public contact | Medical Director, Takeda Oncology, +1 8778253327, clinicaltrialregistry@tpna.com |
| Scientific contact | Medical Director, Takeda Oncology, +1 8778253327, clinicaltrialregistry@tpna.com |

Notes:

**Paediatric regulatory details**

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 03 July 2018 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 03 July 2018 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

Phase 1b
- To evaluate the safety and tolerability of MLN0128 in combination with either exemestane or fulvestrant.

Phase 2
- To evaluate the antitumor activity by clinical benefit rate (CBR) at 16 weeks (CBR-16 is defined as the proportion of patients who achieve complete response [CR] or partial response of any duration, or have stable disease [SD] at 16 weeks) of treatment with MLN0128 in combination with either exemestane or fulvestrant.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 13 February 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United States: 95 |
| Country: Number of subjects enrolled | France: 16 |
| Country: Number of subjects enrolled | Belgium: 7 |
| Worldwide total number of subjects | 118 |
| EEA total number of subjects | 23 |

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) | 83 |
| From 65 to 84 years | 35 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Participants took part in the study at 40 investigative sites in Belgium, France and the United States from 13 February 2014 to 03 July 2019.

### Pre-assignment

Screening details:

Postmenopausal women with estrogen receptor positive/human epidermal growth factor receptor-2 negative advanced/metastatic breast cancer who progressed with everolimus (everolimus sensitive-achieved CR/PR of any duration/stable disease for ≥6 months; resistant-without CR/PR/SD < 6 months) were enrolled to receive MLN0128+exemestane/fulvestrant.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Phase 1 (Part 1): Sapanisertib 5 mg + Exemestane |

Arm description:

Sapanisertib 5 mg, unmilled active pharmaceutical ingredient (API) capsule, once daily in a 28-day cycle plus exemestane 25 mg, tablets, once daily in a 28-day cycle (Up to 12 cycles).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Sapanisertib |
| Investigational medicinal product code | |
| Other name | MLN0128 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Sapanisertib capsules

| | |
|---|---|
| Investigational medicinal product name | Exemestane |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Exemestane coated tablets

| | |
|---|---|
| **Arm title** | Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant |

Arm description:

Sapanisertib 5 mg, unmilled API capsule, once daily in a 28-day cycle plus fulvestrant 500 mg, injection, intramuscularly (IM), once on Day 1 of each cycle (Up to 57 cycles).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Sapanisertib |
| Investigational medicinal product code | |
| Other name | MLN0128 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Sapanisertib capsules

| | |
|---|---|
| Investigational medicinal product name | Fulvestrant |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Fulvestrant Intramuscular (IM) injection

| | |
|---|---|
| **Arm title** | Phase 1 (Part 2): Sapanisertib 3 mg + Exemestane |

Arm description:

Sapanisertib 3 mg, milled API capsule, once daily in a 28-day cycle plus exemestane 25 mg, tablets, once daily in a 28-day cycle (Up to 8 cycles).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Sapanisertib |
| Investigational medicinal product code | |
| Other name | MLN0128 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Sapanisertib capsules

| | |
|---|---|
| Investigational medicinal product name | Exemestane |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Exemestane coated tablets

| | |
|---|---|
| **Arm title** | Phase 1 (Part 2): Sapanisertib 3 mg + Fulvestrant |

Arm description:

Sapanisertib 3 mg, milled API capsule, once daily in a 28-day cycle up to 14 cycles plus fulvestrant 500 mg, injection, IM, once on Day 1 of each cycle (Up to 14 cycles).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Sapanisertib |
| Investigational medicinal product code | |
| Other name | MLN0128 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Sapanisertib capsules

| | |
|---|---|
| Investigational medicinal product name | Fulvestrant |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Fulvestrant Intramuscular (IM) injection

| | |
|---|---|
| **Arm title** | Phase 1 (Part 2): Sapanisertib 4 mg + Exemestane |

Arm description:

Sapanisertib 4 mg, milled API capsule, once daily, in a 28-day cycle plus exemestane 25 mg, tablets, once daily in a 28-day cycle (Up to 18 cycles).

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

| | |
|---|---|
| Investigational medicinal product name | Sapanisertib |
| Investigational medicinal product code | |
| Other name | MLN0128 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Sapanisertib capsules

| | |
|---|---|
| Investigational medicinal product name | Exemestane |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Exemestane coated tablets

| | |
|---|---|
| **Arm title** | Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Sensitive) |

Arm description:

Sapanisertib 4 mg, milled API capsule once daily in a 28-day cycle plus exemestane 25 mg, tablets, once daily in a 28-day cycle (Up to 14 cycles) in everolimus sensitive participants.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Sapanisertib |
| Investigational medicinal product code | |
| Other name | MLN0128 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Sapanisertib capsules

| | |
|---|---|
| Investigational medicinal product name | Exemestane |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Exemestane coated tablets

| | |
|---|---|
| **Arm title** | Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Sensitive) |

Arm description:

Sapanisertib 4 mg, milled API capsule once daily in a 28-day cycle plus fulvestrant 500 mg, injection IM, once on Day 1 of each cycle (Up to 17 cycles) in everolimus sensitive participants.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Sapanisertib |
| Investigational medicinal product code | |
| Other name | MLN0128 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Sapanisertib capsules

| | |
|---|---|
| Investigational medicinal product name | Fulvestrant |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Fulvestrant Intramuscular (IM) injection

| **Arm title** | Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Resistant) |
|---|---|

Arm description:

Sapanisertib 4 mg, milled API capsule, once daily, in a 28-day cycle plus exemestane 25 mg, tablets, once daily in a 28-day cycle (Up to 12 cycles) in everolimus resistant participants.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Sapanisertib |
| Investigational medicinal product code | |
| Other name | MLN0128 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Sapanisertib capsules

| | |
|---|---|
| Investigational medicinal product name | Exemestane |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Exemestane coated tablets

| **Arm title** | Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Resistant) |
|---|---|

Arm description:

Sapanisertib 4 mg, milled API capsule, once daily in a 28-day cycle plus fulvestrant 500 mg, injection IM, once on Day 1 of each cycle (Up to 9 cycles) in everolimus resistant participants.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Sapanisertib |
| Investigational medicinal product code | |
| Other name | MLN0128 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Sapanisertib capsules

| | |
|---|---|
| Investigational medicinal product name | Fulvestrant |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Fulvestrant Intramuscular (IM) injection

| **Number of subjects in period 1** | Phase 1 (Part 1): Sapanisertib 5 mg + Exemestane | Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant | Phase 1 (Part 2): Sapanisertib 3 mg + Exemestane |
|---|---|---|---|
| Started | 6 | 6 | 3 |
| Completed | 0 | 0 | 0 |
| Not completed | 6 | 6 | 3 |
| Consent withdrawn by subject | - | - | - |
| Physician decision | - | - | - |
| Adverse event, non-fatal | 1 | 1 | 1 |
| Progressive Disease | 5 | 4 | 2 |
| Study Terminated by Sponsor | - | 1 | - |

| **Number of subjects in period 1** | Phase 1 (Part 2): Sapanisertib 3 mg + Fulvestrant | Phase 1 (Part 2): Sapanisertib 4 mg + Exemestane | Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Sensitive) |
|---|---|---|---|
| Started | 3 | 6 | 43 |
| Completed | 0 | 0 | 0 |
| Not completed | 3 | 6 | 43 |
| Consent withdrawn by subject | 1 | - | 2 |
| Physician decision | - | - | 1 |
| Adverse event, non-fatal | - | - | 5 |
| Progressive Disease | 2 | 6 | 35 |
| Study Terminated by Sponsor | - | - | - |

| **Number of subjects in period 1** | Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Sensitive) | Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Resistant) | Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Resistant) |
|---|---|---|---|
| Started | 8 | 35 | 8 |
| Completed | 0 | 0 | 0 |
| Not completed | 8 | 35 | 8 |
| Consent withdrawn by subject | - | 3 | 1 |
| Physician decision | - | - | - |
| Adverse event, non-fatal | - | 6 | 1 |
| Progressive Disease | 7 | 26 | 6 |
| Study Terminated by Sponsor | 1 | - | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Overall Study |
| Reporting group description: | |
| All enrolled participants | |

| Reporting group values | Overall Study | Total | |
|---|---|---|---|
| Number of subjects | 118 | 118 | |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 83 | 83 | |
| From 65-84 years | 35 | 35 | |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 57.31 | | |
| full range (min-max) | 32 to 83 | - | |
| Sex: Female, Male | | | |
| 9999 = Data for this arm group is available in subject analysis set 'Phase 1 (Part 2): Sapanisertib 3 mg QD+Exemestane/Fulvestrant'. | | | |
| Units: Subjects | | | |
| Female | 118 | 118 | |
| Male | 0 | 0 | |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 4 | 4 | |
| Not Hispanic or Latino | 103 | 103 | |
| Unknown or Not Reported | 11 | 11 | |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| White | 98 | 98 | |
| Not Reported | 6 | 6 | |
| Black or African American | 7 | 7 | |
| Asian | 4 | 4 | |
| Other | 3 | 3 | |
| Region of Enrollment<br>Units: Subjects | | | |
| United States | 95 | 95 | |
| Belgium | 16 | 16 | |
| France | 7 | 7 | |
| Height | | | |
| Number analyzed is the number of participants with data available for height. | | | |
| Units: cm | | | |
| arithmetic mean | 165.02 | | |
| full range (min-max) | 150 to 183 | - | |
| Weight | | | |
| Number analyzed is the number of participants with data available for weight. | | | |
| Units: kg | | | |
| arithmetic mean | 70.37 | | |

| | | | |
|---|---|---|---|
| full range (min-max) | 46.5 to 139 | - | |

## End points

### End points reporting groups

| Reporting group title | Phase 1 (Part 1): Sapanisertib 5 mg + Exemestane |
|---|---|
| Reporting group description: | |
| Sapanisertib 5 mg, unmilled active pharmaceutical ingredient (API) capsule, once daily in a 28-day cycle plus exemestane 25 mg, tablets, once daily in a 28-day cycle (Up to 12 cycles). | |
| Reporting group title | Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant |
| Reporting group description: | |
| Sapanisertib 5 mg, unmilled API capsule, once daily in a 28-day cycle plus fulvestrant 500 mg, injection, intramuscularly (IM), once on Day 1 of each cycle (Up to 57 cycles). | |
| Reporting group title | Phase 1 (Part 2): Sapanisertib 3 mg + Exemestane |
| Reporting group description: | |
| Sapanisertib 3 mg, milled API capsule, once daily in a 28-day cycle plus exemestane 25 mg, tablets, once daily in a 28-day cycle (Up to 8 cycles). | |
| Reporting group title | Phase 1 (Part 2): Sapanisertib 3 mg + Fulvestrant |
| Reporting group description: | |
| Sapanisertib 3 mg, milled API capsule, once daily in a 28-day cycle up to 14 cycles plus fulvestrant 500 mg, injection, IM, once on Day 1 of each cycle (Up to 14 cycles). | |
| Reporting group title | Phase 1 (Part 2): Sapanisertib 4 mg + Exemestane |
| Reporting group description: | |
| Sapanisertib 4 mg, milled API capsule, once daily, in a 28-day cycle plus exemestane 25 mg, tablets, once daily in a 28-day cycle (Up to 18 cycles). | |
| Reporting group title | Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Sensitive) |
| Reporting group description: | |
| Sapanisertib 4 mg, milled API capsule once daily in a 28-day cycle plus exemestane 25 mg, tablets, once daily in a 28-day cycle (Up to 14 cycles) in everolimus sensitive participants. | |
| Reporting group title | Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Sensitive) |
| Reporting group description: | |
| Sapanisertib 4 mg, milled API capsule once daily in a 28-day cycle plus fulvestrant 500 mg, injection IM, once on Day 1 of each cycle (Up to 17 cycles) in everolimus sensitive participants. | |
| Reporting group title | Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Resistant) |
| Reporting group description: | |
| Sapanisertib 4 mg, milled API capsule, once daily, in a 28-day cycle plus exemestane 25 mg, tablets, once daily in a 28-day cycle (Up to 12 cycles) in everolimus resistant participants. | |
| Reporting group title | Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Resistant) |
| Reporting group description: | |
| Sapanisertib 4 mg, milled API capsule, once daily in a 28-day cycle plus fulvestrant 500 mg, injection IM, once on Day 1 of each cycle (Up to 9 cycles) in everolimus resistant participants. | |

### Primary: Phase 1: Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

| End point title | Phase 1: Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)[1][2] |
|---|---|
| End point description: | |
| An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug. A SAE is any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly/birth defect or is a medically important event. Relationship of | |

each AE to study drug will be determined by the Investigator. Safety Population included participants who received at least 1 dose of any study drug.

| End point type | Primary |
|---|---|

End point timeframe:

First dose of study drug through 30 days after the last dose (Up to 52 months)

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: This endpoint was performed in Phase 1 of the study.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was performed in Phase 1 of the study.

| **End point values** | Phase 1 (Part 1): Sapanisertib 5 mg + Exemestane | Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant | Phase 1 (Part 2): Sapanisertib 3 mg + Exemestane | Phase 1 (Part 2): Sapanisertib 3 mg + Fulvestrant |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 6 | 6 | 3 | 3 |
| Units: participants | | | | |
| Any AE | 6 | 6 | 3 | 3 |
| SAEs | 1 | 2 | 0 | 0 |

| **End point values** | Phase 1 (Part 2): Sapanisertib 4 mg + Exemestane | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 6 | | | |
| Units: participants | | | | |
| Any AE | 6 | | | |
| SAEs | 2 | | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Phase 2: Clinical Benefit Rate at 16 Weeks (CBR-16)

| End point title | Phase 2: Clinical Benefit Rate at 16 Weeks (CBR-16)[3][4] |
|---|---|

End point description:

CBR-16 was defined as the percentage of participants who achieved confirmed complete response (CR) or partial response (PR) of any duration or had confirmed stable disease (SD) as best response and the first 2 or more post baseline scans had PR/SD and the duration of SD was >112 days. Disease response was assessed for target lesions by computed tomography (CT) or magnetic resonance imaging (MRI) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines. CR is disappearance of all target lesions. PR is >=30% decrease in the sum of the longest diameter of target lesions. SD is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for disease progression (PD). Response-Evaluable Population included participants who received at least 1 dose of study drug and had measurable disease at baseline.

| End point type | Primary |
|---|---|

End point timeframe:

Week 16

Notes:

[3] - 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: This endpoint was performed in Phase 2 of the study.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was performed in Phase 2 of the study.

| **End point values** | Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Sensitive) | Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Sensitive) | Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Resistant) | Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Resistant) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 43 | 8 | 35 | 8 |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 44 (29.1 to 60.1) | 50 (15.7 to 84.3) | 23 (10.4 to 40.1) | 25 (3.2 to 65.1) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase 2: Clinical Benefit Rate at 24 Weeks (CBR-24)

| End point title | Phase 2: Clinical Benefit Rate at 24 Weeks (CBR-24)[5] |
|---|---|

End point description:

CBR-24 was defined as the percentage of participants who achieved confirmed CR or PR at any time or had confirmed SD as best response and the first 2 or more post baseline scans had PR/SD and the duration of stable disease was >168 days. Disease response was assessed for target lesions by CT or MRI according to RECIST version 1.1 guidelines. CR is disappearance of all target lesions. PR is >=30% decrease in the sum of the longest diameter of target lesions. SD is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Response-Evaluable Population included participants who received at least 1 dose of study drug and had measurable disease at baseline.

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

End point timeframe:

Week 24

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was performed in Phase 2 of the study.

| **End point values** | Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Sensitive) | Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Sensitive) | Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Resistant) | Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Resistant) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 43 | 8 | 35 | 8 |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 28 (15.3 to 43.7) | 38 (8.5 to 75.5) | 23 (10.4 to 40.1) | 25 (3.2 to 65.1) |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Phase 2: Overall Response Rate (ORR)

| End point title | Phase 2: Overall Response Rate (ORR)[6] |
|---|---|

End point description:

ORR is defined as the percentage of participants with confirmed CR or PR as per RECIST version1.1 guidelines. CR is disappearance of all target lesions. PR is >=30% decrease in the sum of the longest diameter of target lesions. Response-Evaluable Population included participants who received at least 1 dose of study drug and had measurable disease at baseline.

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

End point timeframe:

Baseline then every 2 cycles from Cycles 2 through 6, and every 3 cycles thereafter in a 28-day cycle up to End of Treatment (EOT) (Up to 24 months)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was performed in Phase 2 of the study.

| **End point values** | Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Sensitive) | Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Sensitive) | Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Resistant) | Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Resistant) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 43 | 8 | 35 | 8 |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 7 (1.5 to 19.1) | 13 (1 to 52.7) | 0 (0 to 0) | 13 (1 to 52.7) |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Phase 2: Progression-Free Survival (PFS)

| End point title | Phase 2: Progression-Free Survival (PFS)[7] |
|---|---|

End point description:

PFS is defined as the time in months from the date of first dose of study treatment to the date of the first documented disease progression or death. Disease progression was defined using Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.0) as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, including baseline; an absolute increase of at least 5 mm in the sum of diameters of target lesions; or the appearance of one or more new lesions. Safety Population included participants who received at least 1 dose of study drug. For a participant whose disease had not progressed and was last known to be alive, PFS was censored at the last response assessment that was stable disease or better. 99999: Upper limit of Confidence Interval (CI) was not reached due to low number of participants with events.

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

End point timeframe:

Baseline then every 2 cycles from Cycles 2 through 6, and every 3 cycles thereafter in a 28-day cycle, then every 3 months after EOT until disease progression or death (Up to 24 months)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was performed in Phase 2 of the study.

| **End point values** | Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Sensitive) | Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Sensitive) | Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Resistant) | Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Resistant) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 43 | 8 | 35 | 8 |
| Units: months | | | | |
| median (confidence interval 95%) | 4.1 (1.9 to 5.5) | 5.5 (1.8 to 99999) | 3.3 (1.9 to 3.7) | 5.4 (1.7 to 8.3) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase 2: Overall Survival (OS)

| End point title | Phase 2: Overall Survival (OS)[8] |
|---|---|

End point description:

OS is the time in months from start of study treatment to date of death due to any cause. Data for the analysis of OS included the censored data at the timepoint that the participant was last known to be alive. Safety Population included participants who received at least 1 dose of study drug. Participants without documentation of death at the time of analysis were censored at the date last known to be alive.

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

End point timeframe:

Up to 24 months

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was performed in Phase 2 of the study.

| **End point values** | Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Sensitive) | Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Sensitive) | Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Resistant) | Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Resistant) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 43 | 8 | 35 | 8 |
| Units: months | | | | |
| median (confidence interval 95%) | 15.9 (14.1 to 19.5) | 20.7 (8.6 to 20.7) | 14.0 (10.6 to 16.0) | 13.0 (4.1 to 21.3) |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Phase 2: Best Percent Change from Baseline in Tumor Size

| End point title | Phase 2: Best Percent Change from Baseline in Tumor Size[9] |
|---|---|

End point description:

Participants from Safety Population included participants who received at least 1 dose of study drug and provided both baseline and at least one post-baseline disease response.

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

End point timeframe:

Baseline to Month 24

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was performed in Phase 2 of the study.

| End point values | Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Sensitive) | Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Sensitive) | Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Resistant) | Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Resistant) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 36 | 7 | 27 | 7 |
| Units: percentage change in tumor size | | | | |
| arithmetic mean (standard deviation) | -0.46 (± 34.89) | 0.96 (± 38.98) | 1.76 (± 31.14) | -18.91 (± 19.71) |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Phase1: Cmax: Maximum Observed Plasma Concentration for Sapanisertib

| End point title | Phase1: Cmax: Maximum Observed Plasma Concentration for Sapanisertib[10] |
|---|---|

End point description:

Pharmacokinetic (PK) Population included participants with sufficient dosing and PK data to reliably estimate PK parameters. PK data was not available for Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant arm group at Cycle 1 Day 15. n= number analyzed is the number of participants with data available for analyses at the given timepoint.

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

End point timeframe:

Cycle 1 Day 15 and Cycle 2 Day 1 pre-dose and multiple timepoints (Up to 8 hours) post-dose

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was performed in Phase 1 of the study.

| End point values | Phase 1 (Part 1): Sapanisertib 5 mg + Exemestane | Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant | Phase 1 (Part 2): Sapanisertib 3 mg + Exemestane | Phase 1 (Part 2): Sapanisertib 3 mg + Fulvestrant |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 6 | 5 | 3 | 3 |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 15 (n=6,0,3,2,6) | 57.72 (± 9.927) | 9999 (± 9999) | 47.40 (± 6.583) | 50.90 (± 23.476) |
| Cycle 2 Day 1 (n=5,5,3,3,5) | 38.68 (± 20.551) | 44.96 (± 34.459) | 43.47 (± 0.874) | 45.30 (± 16.235) |

| End point values | Phase 1 (Part 2): Sapanisertib 4 mg + Exemestane | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 6 | | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 15 (n=6,0,3,2,6) | 45.37 (± 9.644) | | | |
| Cycle 2 Day 1 (n=5,5,3,3,5) | 44.68 (± 8.636) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase 1: Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Sapanisertib

| End point title | Phase 1: Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Sapanisertib[11] |
|---|---|

End point description:

PK Population included participants with sufficient dosing and PK data to reliably estimate PK parameters. PK data was not available for Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant arm group at Cycle 1 Day 15. n=number analyzed is the number of participants with data available for analyses at the given timepoint.

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

End point timeframe:

Cycle 1 Day 15 and Cycle 2 Day 1 pre-dose and multiple timepoints (Up to 8 hours) post-dose

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was performed in Phase 1 of the study.

| End point values | Phase 1 (Part 1): Sapanisertib 5 mg + Exemestane | Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant | Phase 1 (Part 2): Sapanisertib 3 mg + Exemestane | Phase 1 (Part 2): Sapanisertib 3 mg + Fulvestrant |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 6 | 5 | 3 | 3 |
| Units: hour | | | | |
| median (full range (min-max)) | | | | |
| Cycle 1 Day 15 (n=6,0,3,2,6) | 3.005 (0.58 to 7.30) | 9999 (9999 to 9999) | 0.600 (0.45 to 1.00) | 1.035 (1.00 to 1.07) |
| Cycle 2 Day 1 (n=5,5,3,3,5) | 2.280 (0.85 to 3.58) | 3.500 (0.92 to 4.03) | 0.980 (0.68 to 1.00) | 1.000 (0.48 to 1.12) |

| End point values | Phase 1 (Part 2): Sapanisertib 4 mg + Exemestane | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 6 | | | |
| Units: hour | | | | |
| median (full range (min-max)) | | | | |
| Cycle 1 Day 15 (n=6,0,3,2,6) | 2.000 (0.50 to 3.55) | | | |
| Cycle 2 Day 1 (n=5,5,3,3,5) | 2.000 (0.50 to 3.77) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase 1: AUC(0-24): Area under the Plasma Concentration-time Curve from Time 0 to Time 24 Hours, Calculated using the Observed Value of the Last Quantifiable Concentration Over the Dosing Interval for Sapanisertib

| End point title | Phase 1: AUC(0-24): Area under the Plasma Concentration-time Curve from Time 0 to Time 24 Hours, Calculated using the Observed Value of the Last Quantifiable Concentration Over the Dosing Interval for Sapanisertib[12] |
|---|---|

End point description:

AUC(0-24) is the area under the plasma concentration-time curve of the samples collected up to 8 hours and extrapolated up to 24 hours. Participants from PK Population included participants with sufficient dosing and PK data to reliably estimate PK parameters. PK data was not available for Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant arm group at Cycle 1 Day 15. Number analyzed is the number of participants with data available for analyses at the given timepoint.

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

End point timeframe:

Cycle 1 Day 15 pre-dose and multiple timepoints (Up to 8 hours) post-dose, extrapolated to 24 hours post-dose

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was performed in Phase 1 of the study.

| End point values | Phase 1 (Part 1): Sapanisertib 5 mg + Exemestane | Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant | Phase 1 (Part 2): Sapanisertib 3 mg + Exemestane | Phase 1 (Part 2): Sapanisertib 3 mg + Fulvestrant |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 6 | 0[13] | 3 | 2 |
| Units: h*ng/mL | | | | |
| arithmetic mean (standard deviation) | 577.081 (± 331.9813) | () | 178.063 (± 46.1416) | 332.618 (± 228.5641) |

Notes:

[13] - PK data was not available at Cycle 1 Day 15.

| End point values | Phase 1 (Part 2): Sapanisertib 4 mg + Exemestane | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 5 | | | |
| Units: h*ng/mL | | | | |
| arithmetic mean (standard deviation) | 277.626 (± 64.0661) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase 1: AUC(0-last): Area under the Plasma Concentration-time Curve from Time 0 to Time tau Over the Dosing Interval for MLN0128

| End point title | Phase 1: AUC(0-last): Area under the Plasma Concentration-time Curve from Time 0 to Time tau Over the Dosing Interval for MLN0128[14] |
|---|---|

End point description:

AUC(0-last) is the area under the plasma concentration-time curve of the samples collected up to 8 hours and extrapolated up to last time point. PK Population included participants with sufficient dosing and PK data to reliably estimate PK parameters. PK data was not available for Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant arm group at Cycle 1 Day 15. n=number analyzed is the number of participants with data available for analyses at the given timepoint.

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

End point timeframe:

Cycle 1 Day 15 pre-dose and multiple timepoints (Up to 8 hours) post-dose, extrapolated to last timepoint

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was performed in Phase 1 of the study.

| End point values | Phase 1 (Part 1): Sapanisertib 5 mg + Exemestane | Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant | Phase 1 (Part 2): Sapanisertib 3 mg + Exemestane | Phase 1 (Part 2): Sapanisertib 3 mg + Fulvestrant |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 6 | 5 | 3 | 3 |
| Units: h*ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 15 (n=6,0,3,2,6) | 577.081 (± 331.9813) | 9999 (± 9999) | 164.123 (± 52.6287) | 332.618 (± 228.5641) |
| Cycle 1 Day 2 (n=5,5,3,3,5) | 101.599 (± 51.0248) | 109.496 (± 82.3968) | 89.576 (± 15.0117) | 109.548 (± 52.8500) |

| End point values | Phase 1 (Part 2): Sapanisertib 4 mg + Exemestane | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 6 | | | |
| Units: h*ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 15 (n=6,0,3,2,6) | 251.165 (± 83.7121) | | | |
| Cycle 1 Day 2 (n=5,5,3,3,5) | 116.557 (± 8.6059) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase 1: Terminal Elimination Half-life (T1/2) for Sapanisertib

| End point title | Phase 1: Terminal Elimination Half-life (T1/2) for |
|---|---|

End point description:

Participants from PK Population, participants with sufficient dosing and PK data to reliably estimate PK parameters. PK data was not available for Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant arm group at Cycle 1 Day 15.

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

End point timeframe:

Cycle 1 Day 15 pre-dose and multiple timepoints (Up to 8 hours) post-dose

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was performed in Phase 1 of the study.

| End point values | Phase 1 (Part 1): Sapanisertib 5 mg + Exemestane | Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant | Phase 1 (Part 2): Sapanisertib 3 mg + Exemestane | Phase 1 (Part 2): Sapanisertib 3 mg + Fulvestrant |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 2 | 0[16] | 3 | 2 |
| Units: hour | | | | |
| arithmetic mean (standard deviation) | 6.639 (± 1.2176) | () | 3.161 (± 1.6585) | 7.777 (± 2.9177) |

Notes:

[16] - PK data was not available at Cycle 1 Day 15.

| End point values | Phase 1 (Part 2): Sapanisertib 4 mg + Exemestane | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 4 | | | |
| Units: hour | | | | |
| arithmetic mean (standard deviation) | 5.370 (± 1.4638) | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

First dose up to 30 days post last dose of study drug (Up to 52 months)

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 21.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Phase 1 (Part 1): Sapanisertib 5 mg + Exemestane |

Reporting group description:

Sapanisertib 5 mg, unmilled active pharmaceutical ingredient (API) capsule, once daily in a 28-day cycle plus exemestane 25 mg, tablets, once daily in a 28-day cycle (Up to 12 cycles).

| | |
|---|---|
| Reporting group title | Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant |

Reporting group description:

Sapanisertib 5 mg, unmilled API capsule, once daily in a 28-day cycle plus fulvestrant 500 mg, injection, intramuscularly (IM), once on Day 1 of each cycle (Up to 57 cycles).

| | |
|---|---|
| Reporting group title | Phase 1 (Part 2): Sapanisertib 3 mg + Exemestane |

Reporting group description:

Sapanisertib 3 mg, milled API capsule, once daily in a 28-day cycle plus exemestane 25 mg, tablets, once daily in a 28-day cycle (Up to 8 cycles).

| | |
|---|---|
| Reporting group title | Phase 1 (Part 2): Sapanisertib 3 mg + Fulvestrant |

Reporting group description:

Sapanisertib 3 mg, milled API capsule, once daily in a 28-day cycle up to 14 cycles plus fulvestrant 500 mg, injection, IM, once on Day 1 of each cycle (Up to 14 cycles).

| | |
|---|---|
| Reporting group title | Phase 1 (Part 2): Sapanisertib 4 mg + Exemestane |

Reporting group description:

Sapanisertib 4 mg, milled API capsule, once daily, in a 28-day cycle plus exemestane 25 mg, tablets, once daily in a 28-day cycle (Up to 18 cycles).

| | |
|---|---|
| Reporting group title | Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Sensitive) |

Reporting group description:

Sapanisertib 4 mg, milled API capsule once daily in a 28-day cycle plus exemestane 25 mg, tablets, once daily in a 28-day cycle (Up to 14 cycles) in everolimus sensitive participants.

| | |
|---|---|
| Reporting group title | Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Resistant) |

Reporting group description:

Sapanisertib 4 mg, milled API capsule, once daily, in a 28-day cycle plus fulvestrant 500 mg, injection IM, once on Day 1 of each cycle (Up to 12 cycles) in everolimus resistant participants.

| | |
|---|---|
| Reporting group title | Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Sensitive) |

Reporting group description:

Sapanisertib 4 mg, milled API capsule once daily in a 28-day cycle plus fulvestrant 500 mg, injection IM, once on Day 1 of each cycle (Up to 17 cycles) in everolimus sensitive participants.

| | |
|---|---|
| Reporting group title | Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Resistant) |

Reporting group description:

Sapanisertib 4 mg, milled API capsule, once daily in a 28-day cycle plus fulvestrant 500 mg, injection IM, once on Day 1 of each cycle (Up to 9 cycles) in everolimus resistant participants.

| **Serious adverse events** | Phase 1 (Part 1): Sapanisertib 5 mg + Exemestane | Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant | Phase 1 (Part 2): Sapanisertib 3 mg + Exemestane |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 6 (33.33%) | 0 / 3 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer metastatic | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to bone | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Generalised oedema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Mental status changes | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Clostridium test positive | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Injury, poisoning and procedural complications | | | |
| Alcohol poisoning | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Ataxia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Diplopia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast cellulitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Failure to thrive | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Phase 1 (Part 2): Sapanisertib 3 mg + Fulvestrant | Phase 1 (Part 2): Sapanisertib 4 mg + Exemestane | Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Sensitive) |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 6 (33.33%) | 11 / 43 (25.58%) |
| number of deaths (all causes) | 0 | 1 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer metastatic | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to bone | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Generalised oedema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Mental status changes | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Clostridium test positive | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Alcohol poisoning | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Ataxia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Diplopia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 2 / 43 (4.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast cellulitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Failure to thrive | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Resistant) | Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Sensitive) | Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Resistant) |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 35 (14.29%) | 3 / 8 (37.50%) | 2 / 8 (25.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer metastatic | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to bone | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration | | | |

| | | | |
|---|---|---|---|
| site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Generalised oedema | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Mental status changes | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Clostridium test positive | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Alcohol poisoning | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Ataxia | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Diplopia | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast cellulitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Failure to thrive | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 2 %

| **Non-serious adverse events** | Phase 1 (Part 1): Sapanisertib 5 mg + Exemestane | Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant | Phase 1 (Part 2): Sapanisertib 3 mg + Exemestane |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 6 / 6 (100.00%) | 6 / 6 (100.00%) | 3 / 3 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Seborrhoeic keratosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 6 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Hypotension | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 6 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Flushing | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lymphoedema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Venous thrombosis limb | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 6 / 6 (100.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 7 | 6 | 1 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 6 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Injection site pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injection site rash | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oedema peripheral | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Asthenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Malaise | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Immune system disorders | | | |
| Contrast media allergy | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Reproductive system and breast disorders | | | |
| Breast pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vulvovaginal dryness | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Genital rash | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pelvic pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 3 / 6 (50.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 4 | 0 |
| Cough | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysphonia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pleurisy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Wheezing | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sinus congestion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper-airway cough syndrome | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal dryness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pleuritic pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Productive cough | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiration abnormal | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 6 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dysphoria | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Stress | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Depression | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Irritability | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hallucination | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hallucinations, mixed | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Initial insomnia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Panic attack | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Product issues | | | |
| Thrombosis in device | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 2 / 6 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Amylase increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood cholesterol increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|---|---|---|
| Glycosylated haemoglobin increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| International normalised ratio increased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| White blood cells urine positive | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood phosphorus increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood phosphorus decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood triglycerides increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Activated partial thromboplastin time prolonged | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood urea increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Amylase decreased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood albumin decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood calcium increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood glucose increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood potassium increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood sodium decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| International normalised ratio decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Low density lipoprotein increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Protein total increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Protein urine | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| **Injury, poisoning and procedural complications** | | | |
| Upper limb fracture | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Contusion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Animal bite | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fracture | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Procedural nausea | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Thoracic vertebral fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tachyarrhythmia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Dysgeusia | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Headache | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Tremor | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 2 | 0 | 1 |
| Ataxia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Disturbance in attention | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hyperaesthesia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Restless legs syndrome | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Serotonin syndrome | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| VIth nerve paralysis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Cognitive disorder | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ageusia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dystonia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoglossal nerve disorder | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sciatica | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eosinophilia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lymphadenopathy | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear and labyrinth disorders | | | |
| Deafness neurosensory | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ear pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tinnitus | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye disorders | | | |

| | | | |
|---|---|---|---|
| Cataract | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Diplopia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dry eye | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Visual impairment | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vitreous floaters | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Conjunctival haemorrhage | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Retinal scar | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 5 / 6 (83.33%) | 2 / 3 (66.67%) |
| occurrences (all) | 5 | 11 | 2 |
| Nausea | | | |
| subjects affected / exposed | 6 / 6 (100.00%) | 4 / 6 (66.67%) | 1 / 3 (33.33%) |
| occurrences (all) | 7 | 5 | 1 |
| Stomatitis | | | |

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|---|---|---|---|
| subjects affected / exposed | 5 / 6 (83.33%) | 3 / 6 (50.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 10 | 5 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 6 (33.33%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 2 | 2 |
| Constipation | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 6 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 2 / 3 (66.67%) |
| occurrences (all) | 0 | 0 | 2 |
| Toothache | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 6 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 1 / 6 (16.67%) | 3 / 3 (100.00%) |
| occurrences (all) | 2 | 1 | 3 |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Flatulence | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastroesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gingival pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Glossodynia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Mouth ulceration | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dry mouth | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eructation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lip dry | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 3 / 6 (50.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 4 | 3 | 1 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 1 / 3 (33.33%) |
| occurrences (all) | 8 | 1 | 1 |
| Rash pruritic | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Rash | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 6 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |

| | | | |
|---|---|---|---|
| Rash macular | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Acne | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dermatitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Drug reaction with eosinophilia and systemic symptoms | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dry skin | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ingrowing nail | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Night sweats | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pruritus generalised | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Psoriasis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rash papular | | | |

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| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin exfoliation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin irritation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Alopecia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Erythema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nail ridging | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Onychoclasis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin lesion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Decubitus ulcer | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ecchymosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eczema | | | |

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| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pain of skin | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin hyperpigmentation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Swelling face | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal and urinary disorders | | | |
| Proteinuria | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dysuria | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oliguria | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Azotaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Chronic kidney disease | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Leukocyturia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Micturition urgency | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urinary tract pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Endocrine disorders | | | |
| Thyroid disorder | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 1 / 6 (16.67%) | 2 / 3 (66.67%) |
| occurrences (all) | 2 | 2 | 2 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 2 | 1 |
| Joint swelling | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Back pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Muscle fatigue | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neck pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Osteopenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pain in jaw | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bone pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bursitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Flank pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Joint range of motion decreased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Joint stiffness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle twitching | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pathological fracture | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Synovial cyst | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tenosynovitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Arthritis infective | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bacterial infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fungal infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fungal skin infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hepatic infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Otitis media | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Pharyngitis streptococcal | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash pustular | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sphingomonas paucimobilis infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Streptococcal infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vulvovaginal candidiasis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 3 / 6 (50.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 2 | 4 | 1 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 4 / 6 (66.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 3 | 5 | 0 |
| Dehydration | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Hypercholesterolaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 6 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hyperlipidaemia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Lactic acidosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypernatraemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperuricaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Food intolerance | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypermagnesaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| **Non-serious adverse events** | Phase 1 (Part 2): Sapanisertib 3 mg + Fulvestrant | Phase 1 (Part 2): Sapanisertib 4 mg + Exemestane | Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Sensitive) |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 3 / 3 (100.00%) | 6 / 6 (100.00%) | 43 / 43 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Seborrhoeic keratosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 6 (0.00%) | 2 / 43 (4.65%) |
| occurrences (all) | 1 | 0 | 3 |
| Hypotension | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 3 / 43 (6.98%) |
| occurrences (all) | 0 | 0 | 7 |
| Flushing | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lymphoedema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Venous thrombosis limb | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 2 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 3 / 3 (100.00%) | 4 / 6 (66.67%) | 19 / 43 (44.19%) |
| occurrences (all) | 3 | 4 | 30 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 3 / 43 (6.98%) |
| occurrences (all) | 0 | 0 | 3 |
| Injection site pain | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Injection site rash | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oedema peripheral | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Asthenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 3 / 43 (6.98%) |
| occurrences (all) | 0 | 0 | 5 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 3 / 43 (6.98%) |
| occurrences (all) | 0 | 0 | 4 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 3 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Malaise | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 5 |
| Pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Immune system disorders | | | |
| Contrast media allergy | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Reproductive system and breast disorders | | | |
| Breast pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 3 / 43 (6.98%) |
| occurrences (all) | 0 | 0 | 3 |
| Vulvovaginal dryness | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 2 / 43 (4.65%) |
| occurrences (all) | 0 | 0 | 3 |
| Genital rash | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Pelvic pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 8 / 43 (18.60%) |
| occurrences (all) | 0 | 1 | 11 |
| Cough | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 7 / 43 (16.28%) |
| occurrences (all) | 0 | 1 | 9 |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 2 / 43 (4.65%) |
| occurrences (all) | 0 | 1 | 2 |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dysphonia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Pleurisy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 2 / 43 (4.65%) |
| occurrences (all) | 0 | 0 | 2 |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Wheezing | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Sinus congestion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper-airway cough syndrome | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Nasal dryness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Pleuritic pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Productive cough | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiration abnormal | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 3 / 43 (6.98%) |
| occurrences (all) | 0 | 1 | 3 |
| Insomnia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 3 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysphoria | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Stress | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Depression | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 2 / 43 (4.65%) |
| occurrences (all) | 0 | 0 | 2 |
| Irritability | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hallucination | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Hallucinations, mixed | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Initial insomnia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Panic attack | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Product issues | | | |
| Thrombosis in device | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 3 / 6 (50.00%) | 6 / 43 (13.95%) |
| occurrences (all) | 2 | 3 | 8 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 6 / 43 (13.95%) |
| occurrences (all) | 0 | 0 | 8 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 2 / 43 (4.65%) |
| occurrences (all) | 0 | 0 | 2 |
| Amylase increased | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 6 (16.67%) | 1 / 43 (2.33%) |
| occurrences (all) | 1 | 1 | 1 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 6 (0.00%) | 3 / 43 (6.98%) |
| occurrences (all) | 1 | 0 | 3 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 4 / 43 (9.30%) |
| occurrences (all) | 0 | 1 | 4 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 4 / 43 (9.30%) |
| occurrences (all) | 0 | 0 | 5 |
| Blood cholesterol increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 3 / 43 (6.98%) |
| occurrences (all) | 0 | 1 | 3 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Glycosylated haemoglobin increased | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 6 (0.00%) | 3 / 43 (6.98%) |
| occurrences (all) | 1 | 0 | 3 |
| International normalised ratio increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| White blood cells urine positive | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 4 / 43 (9.30%) |
| occurrences (all) | 0 | 0 | 9 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 4 / 43 (9.30%) |
| occurrences (all) | 0 | 0 | 6 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 4 / 43 (9.30%) |
| occurrences (all) | 0 | 0 | 5 |
| Blood phosphorus increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 2 / 43 (4.65%) |
| occurrences (all) | 0 | 0 | 2 |
| Blood phosphorus decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 3 / 43 (6.98%) |
| occurrences (all) | 0 | 0 | 3 |
| Blood triglycerides increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Activated partial thromboplastin time prolonged | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood urea increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Amylase decreased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood albumin decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood calcium increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Blood glucose increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood potassium increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood sodium decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| International normalised ratio decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Low density lipoprotein increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Protein total increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Protein urine | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Injury, poisoning and procedural complications | | | |
| Upper limb fracture | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Contusion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Animal bite | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fracture | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Procedural nausea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Thoracic vertebral fracture | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 3 / 43 (6.98%) |
| occurrences (all) | 0 | 0 | 3 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 2 / 43 (4.65%) |
| occurrences (all) | 0 | 0 | 2 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tachyarrhythmia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Nervous system disorders | | | |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 8 / 43 (18.60%) |
| occurrences (all) | 0 | 0 | 9 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 7 / 43 (16.28%) |
| occurrences (all) | 0 | 1 | 11 |
| Headache | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 11 / 43 (25.58%) |
| occurrences (all) | 0 | 1 | 13 |
| Tremor | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 5 / 43 (11.63%) |
| occurrences (all) | 0 | 1 | 6 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ataxia | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Disturbance in attention | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperaesthesia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Restless legs syndrome | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Serotonin syndrome | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| VIth nerve paralysis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cognitive disorder | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 2 / 43 (4.65%) |
| occurrences (all) | 0 | 0 | 2 |
| Ageusia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dystonia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypoglossal nerve disorder | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sciatica | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 6 / 43 (13.95%) |
| occurrences (all) | 0 | 1 | 8 |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eosinophilia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Lymphadenopathy | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 2 / 43 (4.65%) |
| occurrences (all) | 0 | 0 | 2 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear and labyrinth disorders | | | |
| Deafness neurosensory | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Tinnitus | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Eye disorders | | | |

| | | | |
|---|---|---|---|
| Cataract | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Diplopia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dry eye | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 6 (0.00%) | 2 / 43 (4.65%) |
| occurrences (all) | 1 | 0 | 3 |
| Eye pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Visual impairment | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 2 / 43 (4.65%) |
| occurrences (all) | 0 | 0 | 2 |
| Vitreous floaters | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Conjunctival haemorrhage | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Retinal scar | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 4 / 6 (66.67%) | 17 / 43 (39.53%) |
| occurrences (all) | 4 | 5 | 27 |
| Nausea | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 3 / 6 (50.00%) | 23 / 43 (53.49%) |
| occurrences (all) | 2 | 5 | 29 |
| Stomatitis | | | |

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| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 6 (33.33%) | 10 / 43 (23.26%) |
| occurrences (all) | 0 | 3 | 11 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 3 / 6 (50.00%) | 10 / 43 (23.26%) |
| occurrences (all) | 0 | 4 | 13 |
| Constipation | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 6 (16.67%) | 6 / 43 (13.95%) |
| occurrences (all) | 1 | 1 | 7 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 5 / 43 (11.63%) |
| occurrences (all) | 0 | 1 | 5 |
| Toothache | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 4 / 43 (9.30%) |
| occurrences (all) | 0 | 0 | 4 |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 2 / 43 (4.65%) |
| occurrences (all) | 0 | 1 | 2 |
| Flatulence | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 6 (0.00%) | 2 / 43 (4.65%) |
| occurrences (all) | 1 | 0 | 3 |
| Gastroesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Gingival pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Glossodynia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mouth ulceration | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dry mouth | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 7 / 43 (16.28%) |
| occurrences (all) | 0 | 0 | 7 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 2 / 43 (4.65%) |
| occurrences (all) | 0 | 0 | 2 |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Eructation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lip dry | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 3 / 3 (100.00%) | 3 / 6 (50.00%) | 11 / 43 (25.58%) |
| occurrences (all) | 4 | 3 | 14 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 6 (33.33%) | 5 / 43 (11.63%) |
| occurrences (all) | 1 | 6 | 6 |
| Rash pruritic | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rash | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|---|---|---|
| Rash macular | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Acne | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 6 (0.00%) | 3 / 43 (6.98%) |
| occurrences (all) | 1 | 0 | 4 |
| Dermatitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 6 (0.00%) | 4 / 43 (9.30%) |
| occurrences (all) | 1 | 0 | 5 |
| Drug reaction with eosinophilia and systemic symptoms | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dry skin | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 3 / 43 (6.98%) |
| occurrences (all) | 0 | 0 | 3 |
| Ingrowing nail | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Night sweats | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pruritus generalised | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Psoriasis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash papular | | | |

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| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Skin exfoliation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin irritation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Alopecia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 2 / 43 (4.65%) |
| occurrences (all) | 0 | 0 | 3 |
| Erythema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Nail ridging | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Onychoclasis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 2 / 43 (4.65%) |
| occurrences (all) | 0 | 0 | 2 |
| Skin lesion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Decubitus ulcer | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ecchymosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eczema | | | |

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| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pain of skin | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin hyperpigmentation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Swelling face | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Renal and urinary disorders | | | |
| Proteinuria | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysuria | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Oliguria | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Azotaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Chronic kidney disease | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Leukocyturia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Micturition urgency | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Urinary tract pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Endocrine disorders | | | |
| Thyroid disorder | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 3 / 43 (6.98%) |
| occurrences (all) | 0 | 0 | 3 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 2 / 43 (4.65%) |
| occurrences (all) | 0 | 1 | 2 |
| Joint swelling | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 6 (16.67%) | 0 / 43 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 3 / 43 (6.98%) |
| occurrences (all) | 0 | 0 | 3 |
| Back pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 8 / 43 (18.60%) |
| occurrences (all) | 0 | 0 | 12 |
| Muscle fatigue | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 3 / 43 (6.98%) |
| occurrences (all) | 0 | 1 | 3 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 2 / 43 (4.65%) |
| occurrences (all) | 0 | 0 | 2 |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Osteopenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pain in jaw | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 6 / 43 (13.95%) |
| occurrences (all) | 0 | 0 | 6 |
| Bone pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Bursitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Flank pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Joint range of motion decreased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Joint stiffness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle twitching | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pathological fracture | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Synovial cyst | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tenosynovitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 7 / 43 (16.28%) |
| occurrences (all) | 0 | 1 | 8 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 1 | 0 | 1 |

| | | | |
|---|---|---|---|
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Arthritis infective | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bacterial infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fungal infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Fungal skin infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hepatic infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Otitis media | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|---|---|---|
| Pharyngitis streptococcal | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash pustular | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 3 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Sphingomonas paucimobilis infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Streptococcal infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vulvovaginal candidiasis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 6 (16.67%) | 16 / 43 (37.21%) |
| occurrences (all) | 2 | 1 | 19 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 11 / 43 (25.58%) |
| occurrences (all) | 0 | 2 | 25 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 3 / 43 (6.98%) |
| occurrences (all) | 0 | 0 | 3 |
| Hypercholesterolaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 6 (16.67%) | 7 / 43 (16.28%) |
| occurrences (all) | 0 | 1 | 8 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 3 / 43 (6.98%) |
| occurrences (all) | 0 | 0 | 3 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Hyperlipidaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lactic acidosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 3 / 43 (6.98%) |
| occurrences (all) | 0 | 0 | 3 |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 3 / 43 (6.98%) |
| occurrences (all) | 0 | 0 | 3 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 3 / 43 (6.98%) |
| occurrences (all) | 0 | 0 | 4 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Hypernatraemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 2 / 43 (4.65%) |
| occurrences (all) | 0 | 0 | 2 |
| Hyperuricaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 2 / 43 (4.65%) |
| occurrences (all) | 0 | 0 | 2 |
| Food intolerance | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypermagnesaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 6 (0.00%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 1 |

| **Non-serious adverse events** | Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Resistant) | Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Sensitive) | Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Resistant) |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 35 / 35 (100.00%) | 8 / 8 (100.00%) | 8 / 8 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Seborrhoeic keratosis | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tumour pain | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypotension | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 35 (2.86%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hypertension | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Flushing | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Lymphoedema | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Venous thrombosis limb | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 16 / 35 (45.71%) | 6 / 8 (75.00%) | 2 / 8 (25.00%) |
| occurrences (all) | 16 | 6 | 2 |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Injection site pain | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injection site rash | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Oedema peripheral | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Asthenia | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | 1 / 8 (12.50%) | 2 / 8 (25.00%) |
| occurrences (all) | 4 | 1 | 2 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Peripheral swelling | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 1 |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Malaise | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pain | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Immune system disorders | | | |
| Contrast media allergy | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Reproductive system and breast disorders | | | |
| Breast pain | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vulvovaginal dryness | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Genital rash | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pelvic pain | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 2 / 8 (25.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Cough | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | 3 / 8 (37.50%) | 2 / 8 (25.00%) |
| occurrences (all) | 4 | 4 | 2 |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysphonia | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 1 |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pleurisy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Wheezing | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Sinus congestion | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Upper-airway cough syndrome | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal dryness | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pleuritic pain | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Productive cough | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiration abnormal | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Confusional state | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 1 |
| Dysphoria | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Stress | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Depression | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Irritability | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 1 |
| Hallucination | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hallucinations, mixed | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Initial insomnia | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Panic attack | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|---|---|---|
| Product issues | | | |
| Thrombosis in device | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | 2 / 8 (25.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 5 | 2 | 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 5 / 35 (14.29%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 6 | 0 | 2 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | 0 / 8 (0.00%) | 2 / 8 (25.00%) |
| occurrences (all) | 5 | 0 | 3 |
| Amylase increased | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 3 | 0 | 1 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 6 / 35 (17.14%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 7 | 0 | 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 2 / 8 (25.00%) |
| occurrences (all) | 2 | 0 | 2 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 8 (0.00%) | 2 / 8 (25.00%) |
| occurrences (all) | 2 | 0 | 2 |
| Blood cholesterol increased | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 2 | 0 | 1 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Glycosylated haemoglobin increased | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| International normalised ratio increased | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| White blood cells urine positive | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 8 (0.00%) | 2 / 8 (25.00%) |
| occurrences (all) | 2 | 0 | 2 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 1 / 8 (12.50%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 1 | 1 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood phosphorus increased | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 1 |
| Blood phosphorus decreased | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood triglycerides increased | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Activated partial thromboplastin time prolonged | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood urea increased | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Amylase decreased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood albumin decreased | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood calcium increased | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood glucose increased | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Blood potassium increased | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood sodium decreased | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| International normalised ratio decreased | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Low density lipoprotein increased | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Protein total increased | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Protein urine | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|---|---|---|
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| **Injury, poisoning and procedural complications** | | | |
| Upper limb fracture | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Contusion | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Animal bite | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Fall | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Fracture | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Procedural nausea | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Thoracic vertebral fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Sinus tachycardia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tachyarrhythmia | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Dysgeusia | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Dizziness | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | 2 / 8 (25.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tremor | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ataxia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Disturbance in attention | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperaesthesia | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Restless legs syndrome | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Serotonin syndrome | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| VIth nerve paralysis | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cognitive disorder | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ageusia | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Dystonia | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoglossal nerve disorder | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Sciatica | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 6 / 35 (17.14%) | 0 / 8 (0.00%) | 2 / 8 (25.00%) |
| occurrences (all) | 8 | 0 | 2 |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 2 / 8 (25.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 2 | 2 | 1 |
| Eosinophilia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Lymphadenopathy | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Ear and labyrinth disorders | | | |
| Deafness neurosensory | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear pain | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tinnitus | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye disorders | | | |

| | | | |
|---|---|---|---|
| Cataract | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Diplopia | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dry eye | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Eye pain | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vision blurred | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Visual impairment | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vitreous floaters | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Conjunctival haemorrhage | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Retinal scar | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 9 / 35 (25.71%) | 3 / 8 (37.50%) | 6 / 8 (75.00%) |
| occurrences (all) | 10 | 3 | 9 |
| Nausea | | | |
| subjects affected / exposed | 15 / 35 (42.86%) | 7 / 8 (87.50%) | 4 / 8 (50.00%) |
| occurrences (all) | 21 | 8 | 5 |
| Stomatitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 8 / 35 (22.86%) | 3 / 8 (37.50%) | 2 / 8 (25.00%) |
| occurrences (all) | 11 | 3 | 2 |
| Vomiting | | | |
| subjects affected / exposed | 10 / 35 (28.57%) | 1 / 8 (12.50%) | 5 / 8 (62.50%) |
| occurrences (all) | 13 | 2 | 7 |
| Constipation | | | |
| subjects affected / exposed | 5 / 35 (14.29%) | 1 / 8 (12.50%) | 2 / 8 (25.00%) |
| occurrences (all) | 5 | 1 | 2 |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Toothache | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 2 | 0 | 1 |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Flatulence | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastroesophageal reflux disease | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Gingival pain | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Glossodynia | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mouth ulceration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dry mouth | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eructation | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Lip dry | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 6 / 35 (17.14%) | 1 / 8 (12.50%) | 1 / 8 (12.50%) |
| occurrences (all) | 8 | 1 | 1 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Rash pruritic | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rash | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |

| | | | |
|---|---|---|---|
| Rash macular | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Acne | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 1 |
| Dermatitis | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 1 / 8 (12.50%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 1 | 1 |
| Drug reaction with eosinophilia and systemic symptoms | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dry skin | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ingrowing nail | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Night sweats | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pruritus generalised | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Psoriasis | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash papular | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Skin exfoliation | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin irritation | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Alopecia | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Erythema | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Nail ridging | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Onychoclasis | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin lesion | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Urticaria | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Decubitus ulcer | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ecchymosis | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Eczema | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Pain of skin | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin hyperpigmentation | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Swelling face | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal and urinary disorders | | | |
| Proteinuria | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysuria | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Haematuria | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oliguria | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pollakiuria | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 1 |
| Azotaemia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|---|---|---|
| Chronic kidney disease | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Leukocyturia | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Micturition urgency | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urinary tract pain | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Endocrine disorders | | | |
| Thyroid disorder | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 2 / 8 (25.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 2 | 2 | 1 |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 1 |
| Joint swelling | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 2 / 8 (25.00%) |
| occurrences (all) | 1 | 0 | 2 |
| Back pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 35 (11.43%) | 0 / 8 (0.00%) | 2 / 8 (25.00%) |
| occurrences (all) | 5 | 0 | 2 |
| Muscle fatigue | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neck pain | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 2 | 0 | 1 |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Osteopenia | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pain in jaw | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bone pain | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 1 / 8 (12.50%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 1 | 1 |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Bursitis | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Flank pain | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Joint range of motion decreased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Joint stiffness | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Muscle twitching | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pathological fracture | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Synovial cyst | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tenosynovitis | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 5 / 35 (14.29%) | 3 / 8 (37.50%) | 1 / 8 (12.50%) |
| occurrences (all) | 5 | 3 | 1 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin infection | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|---|---|---|
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tooth infection | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Arthritis infective | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Bacterial infection | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Catheter site infection | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Fungal infection | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fungal skin infection | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hepatic infection | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Otitis media | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Pharyngitis streptococcal | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Rash pustular | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sphingomonas paucimobilis infection | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Streptococcal infection | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vulvovaginal candidiasis | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 9 / 35 (25.71%) | 1 / 8 (12.50%) | 2 / 8 (25.00%) |
| occurrences (all) | 10 | 1 | 2 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 16 / 35 (45.71%) | 0 / 8 (0.00%) | 4 / 8 (50.00%) |
| occurrences (all) | 29 | 0 | 8 |
| Dehydration | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Hypercholesterolaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 35 (8.57%) | 1 / 8 (12.50%) | 1 / 8 (12.50%) |
| occurrences (all) | 3 | 1 | 1 |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 1 / 8 (12.50%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 1 | 1 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 1 / 8 (12.50%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hyperlipidaemia | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Lactic acidosis | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | 0 / 8 (0.00%) | 3 / 8 (37.50%) |
| occurrences (all) | 3 | 0 | 3 |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 2 | 0 | 1 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 1 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Hypernatraemia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hyperuricaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 1 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 2 | 0 | 1 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 8 (0.00%) | 2 / 8 (25.00%) |
| occurrences (all) | 2 | 0 | 3 |
| Food intolerance | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypermagnesaemia | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 8 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 16 June 2014 | • The primary purpose of this amendment was to expand the number of investigative sites to include sites in the US, Belgium, and France. In conjunction with this expansion, the sponsor agreed to provide exemestane and fulvestrant to sites outside of the US, and references to the Summary of Product Characteristics (SmPC) for each agent were added.<br>• This amendment also incorporated procedural clarifications contained in prior administrative letters and clarified posttreatment follow-up procedures, including a specification for an overall study ending timepoint no later than 6 months after the last patient completed the end of treatment (EOT) visit.<br>• To optimize analysis of the phase 2 exploratory endpoint of changes in tumor volume, collection of the most recent prebaseline computed tomography (CT) scan (if available) was added to the screening procedures; availability of the historical prebaseline scan was not a prerequisite for study eligibility.<br>• Several eligibility criteria were clarified: the inclusion criterion for HER2-status was simplified to reference the updated ASCO/CAP testing criteria, and the exclusion criterion for treatment with cytochrome P450 (CYP) inhibitors was aligned with prohibited concomitant medications. |
| 15 September 2014 | • The primary purpose of Amendment 2 was to evaluate the safety, tolerability, and pharmacokinetic (PK) of a new sapanisertib capsule based on milled API before initiation of the phase 2 portion of the study. The new capsules based on milled API were to be taken on an empty stomach. |
| 12 March 2015 | • The primary purpose of Amendment 3 was to clarify that enrolled patients in France or Belgium would not have had prior combination therapy with fulvestrant and everolimus and would not receive this combination in the study. Additionally, this amendment clarified the timing of sapanisertib and exemestane administration to allow for exemestane to be administered after a meal in accordance with the product label. A guide for managing patients with noninfectious pneumonitis was added, and the vendor and contact information to report product complaints was updated. |
| 22 October 2015 | • The primary purpose of Amendment 4 was to modify the eligibility criteria to expand the pool of potential study participants and clarify disease status confirmation requirements, and to decrease the number of PK samples required in phase 2. This amendment also revised the excluded medications section of the protocol based on characterization of PK from the phase 1 portion of this study and other clinical studies in the sapanisertib development program. The starting dose for the phase 2 portion of this study was confirmed as 4 mg (milled) sapanisertib + either exemestane 25 mg or fulvestrant 500 mg, based on a safety and tolerability review of patients in cohort 2 of phase 1b part 2. It was not anticipated that these modifications would affect the scientific integrity of the study or the safety of study participants. Administrative changes were also made, such as introducing the new compound code for the study drug, adding the suspected unexpected serious adverse reactions (SUSAR) language, and<br>• revising the product complaints vendor and contact information. |
| 12 May 2017 | • The primary purpose of Amendment 5 was to allow the use of ondansetron and granisetron for antiemetic therapy and prophylaxis, update the definition of the response-evaluable population, and remove the PK/tumor-pharmacodynamic cohort. |

| | |
|---|---|
| 26 October 2017 | • The primary purpose of Amendment 6 was to update sections affected by new nonclinical data for sapanisertib metabolism by specific cytochrome P450 (CYP) isoforms. Exclusion criteria, the list of prohibited concomitant medications and CYP inhibitors, dietary restrictions related to CYP inhibitors and inducers, the use of contrast with MRI, and the description of potential DDIs were updated accordingly. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported