# Clinical trial results:
# A phase Ib trial of LEE011 in combination with everolimus (RAD001) and exemestane in the treatment of postmenopausal women with hormone receptor positive, HER2 negative locally advanced or metastatic breast cancer

## Summary

| | |
|---|---|
| EudraCT number | 2012-005461-13 |
| Trial protocol | ES DE IT GB FR |
| Global end of trial date | 16 April 2020 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 22 April 2021 |
| First version publication date | 22 April 2021 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | CLEE011X2106 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01857193 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.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 | 16 April 2020 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 16 April 2020 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

Dose escalation:
- To estimate the maximum tolerated dose (MTD(s)) and/or recommended Phase 2 dose (RP2D) of LEE011 (ribociclib) in combination with everolimus and exemestane in patients with estrogen receptor-positive (ER-positive) human epidermal growth factor receptor 2-negative (HER2-negative) advanced breast cancer.*

Expansion:
- To characterize the safety and tolerability of the triplet combination of LEE011 (ribociclib) + everolimus + exemestane in patients naive or refractory to cyclin-dependent kinase 4/6 (CDK4/6) inhibitor based therapy.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 06 September 2013 |
| 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 | Belgium: 5 |
| Country: Number of subjects enrolled | France: 12 |
| Country: Number of subjects enrolled | Hong Kong: 4 |
| Country: Number of subjects enrolled | Spain: 14 |
| Country: Number of subjects enrolled | United States: 97 |
| Worldwide total number of subjects | 132 |
| EEA total number of subjects | 31 |

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) | 98 |
| From 65 to 84 years | 34 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Participants were enrolled in 13 centers across 5 countries: USA (8), Spain (2), France (1), Belgium (1), Hong Kong (1)

### Pre-assignment

Screening details:

Participants were divided into two phases: dose escalation and dose expansion. Each phase was further divided into three groups (two triplets and one doublet) depending on the varied dose levels.

### Period 1

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

Blinding implementation details:

Not applicable as this was an open-label study

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive |

Arm description:

Triplet combination of LEE011 200 mg + everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered in fasting to the naive to CDK4/6 inhibitors group

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | LEE011 (Ribociclib) + Everolimus + Exemestane |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

ribociclib (200 mg once daily 3 weeks on/1 week off), a reduced dose of everolimus (2.5 mg once daily) and exemestane (25 mg once daily)

| | |
|---|---|
| **Arm title** | LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory |

Arm description:

Triplet combination of LEE011 200 mg + everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | LEE011 (Ribociclib) + Everolimus + Exemestane |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

ribociclib (200 mg once daily 3 weeks on/1 week off), a reduced dose of everolimus (2.5 mg once daily) and exemestane (25 mg once daily)

| | |
|---|---|
| **Arm title** | LEE011(600 mg)+exe(25 mg) esc refractory |

Arm description:

Doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group

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

| | |
|---|---|
| Investigational medicinal product name | LEE011 (Ribociclib) + Exemestane |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

ribociclib (600 mg once daily 3 weeks on/1 week off) and exemestane (25 mg once daily)

| | |
|---|---|
| **Arm title** | LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive |

Arm description:

Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the naive to CDK4/6 inhibitors group

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | LEE011 (Ribociclib) + Everolimus + Exemestane |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

ribociclib (300 mg once daily 3 weeks on/1 week off), a reduced dose of everolimus (2.5 mg once daily) and exemestane (25 mg once daily)

| | |
|---|---|
| **Arm title** | LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory |

Arm description:

Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | LEE011 (Ribociclib) + Everolimus + Exemestane |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

ribociclib (300 mg once daily 3 weeks on/1 week off), a reduced dose of everolimus (2.5 mg once daily) and exemestane (25 mg once daily)

| | |
|---|---|
| **Arm title** | LEE011(600 mg)+exe(25 mg) exp refractory |

Arm description:

Following RP2D declaration for the doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group (except patients with disease refractory to prior LEE011)

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | LEE011 (Ribociclib) + Exemestane |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

ribociclib (600 mg once daily 3 weeks on/1 week off) and exemestane (25 mg once daily)

| **Number of subjects in period 1** | LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive | LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory | LEE011(600 mg)+exe(25 mg) esc refractory |
|---|---|---|---|
| Started | 41 | 42 | 14 |
| Completed | 0 | 0 | 0 |
| Not completed | 41 | 42 | 14 |
| Subject withdrew consent | 1 | 3 | 1 |
| Physician decision | 5 | 9 | - |
| Disease progression | 32 | 26 | 12 |
| Adverse event, non-fatal | 3 | 3 | 1 |
| Administrative problems | - | 1 | - |

| **Number of subjects in period 1** | LEE011(300 mg)+eve(2.5 mg)+exe (25mg) | LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory | LEE011(600 mg)+exe(25 mg) exp refractory |
|---|---|---|---|
| Started | 16 | 17 | 2 |
| Completed | 0 | 0 | 0 |
| Not completed | 16 | 17 | 2 |
| Subject withdrew consent | 1 | - | - |
| Physician decision | 2 | 2 | - |
| Disease progression | 11 | 14 | 1 |
| Adverse event, non-fatal | 2 | 1 | 1 |
| Administrative problems | - | - | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive |
| Reporting group description: | |
| Triplet combination of LEE011 200 mg + everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered in fasting to the naive to CDK4/6 inhibitors group | |
| Reporting group title | LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory |
| Reporting group description: | |
| Triplet combination of LEE011 200 mg + everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group | |
| Reporting group title | LEE011(600 mg)+exe(25 mg) esc refractory |
| Reporting group description: | |
| Doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group | |
| Reporting group title | LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive |
| Reporting group description: | |
| Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the naive to CDK4/6 inhibitors group | |
| Reporting group title | LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory |
| Reporting group description: | |
| Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group | |
| Reporting group title | LEE011(600 mg)+exe(25 mg) exp refractory |
| Reporting group description: | |
| Following RP2D declaration for the doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group (except patients with disease refractory to prior LEE011) | |

| **Reporting group values** | LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive | LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory | LEE011(600 mg)+exe(25 mg) esc refractory |
|---|---|---|---|
| Number of subjects | 41 | 42 | 14 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 30 | 33 | 9 |
| From 65-84 years | 11 | 9 | 5 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 57.2 | 56.6 | 60.4 |
| standard deviation | ± 11.03 | ± 9.89 | ± 9.31 |

| | | | |
|---|---|---|---|
| Sex: Female, Male<br>Units: Participants | | | |
| Female | 41 | 42 | 14 |
| Male | 0 | 0 | 0 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| Hispanic/Latino | 7 | 4 | 1 |
| Chinese | 3 | 3 | 0 |
| Other | 28 | 29 | 11 |
| Missing | 3 | 6 | 2 |

| **Reporting group values** | LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive | LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory | LEE011(600 mg)+exe(25 mg) exp refractory |
|---|---|---|---|
| Number of subjects | 16 | 17 | 2 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 10 | 15 | 1 |
| From 65-84 years | 6 | 2 | 1 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 60.6 | 52.9 | 64.0 |
| standard deviation | ± 6.90 | ± 11.48 | ± 11.31 |
| Sex: Female, Male<br>Units: Participants | | | |
| Female | 16 | 17 | 2 |
| Male | 0 | 0 | 0 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| Hispanic/Latino | 2 | 2 | 0 |
| Chinese | 0 | 0 | 0 |
| Other | 12 | 15 | 2 |
| Missing | 2 | 0 | 0 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 132 | | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 98 | | |
| From 65-84 years | 34 | | |
| 85 years and over | 0 | | |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Sex: Female, Male<br>Units: Participants | | | |
| Female | 132 | | |
| Male | 0 | | |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| Hispanic/Latino | 16 | | |
| Chinese | 6 | | |
| Other | 97 | | |
| Missing | 13 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive |
| Reporting group description: | |
| Triplet combination of LEE011 200 mg + everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered in fasting to the naive to CDK4/6 inhibitors group | |
| Reporting group title | LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory |
| Reporting group description: | |
| Triplet combination of LEE011 200 mg + everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group | |
| Reporting group title | LEE011(600 mg)+exe(25 mg) esc refractory |
| Reporting group description: | |
| Doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group | |
| Reporting group title | LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive |
| Reporting group description: | |
| Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the naive to CDK4/6 inhibitors group | |
| Reporting group title | LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory |
| Reporting group description: | |
| Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group | |
| Reporting group title | LEE011(600 mg)+exe(25 mg) exp refractory |
| Reporting group description: | |
| Following RP2D declaration for the doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group (except patients with disease refractory to prior LEE011) | |
| Subject analysis set title | Doublet Escalation: LEE011 (600 mg) exe (25 mg) (Fasting) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Doublet combination of LEE011 (600 mg) + exemestane (25 mg) (Fasting) | |
| Subject analysis set title | LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fasting) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Triplet combination of LEE011 (200 mg) + everolimus (RAD001, 2.5 mg) + exemestane (25 mg) (fasting) | |
| Subject analysis set title | LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fed) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Triplet combination of LEE011 (200 mg) + everolimus (RAD001, 2.5 mg) + exemestane (25 mg) (fed) | |
| Subject analysis set title | LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fasting) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Triplet combination of LEE011 (250 mg) + everolimus (RAD001, 2.5 mg) + exemestane (25 mg) (fasting) | |
| Subject analysis set title | LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fed) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Triplet combination of LEE011 (250 mg) + everolimus (RAD001, 2.5 mg) + exemestane (25 mg) (fed) | |
| Subject analysis set title | LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fasting) |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Triplet combination of LEE011 (300 mg) + everolimus (RAD001, 2.5 mg) + exemestane (25 mg) (fasting)

| | |
|---|---|
| Subject analysis set title | LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fed) |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Triplet combination of LEE011 (300 mg) + everolimus (RAD001, 2.5 mg) + exemestane (25 mg) (fed)

| | |
|---|---|
| Subject analysis set title | LEE011 (350 mg) + eve (1 mg) + exe (25mg) (fasting) |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Triplet combination of LEE011 (350 mg) + everolimus (RAD001, 1 mg) + exemestane (25 mg) (fasting)

| | |
|---|---|
| Subject analysis set title | LEE011 (350 mg) + eve (2.5 mg) + exe (25mg) (fed) |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Triplet combination of LEE011 (350 mg) + everolimus (RAD001, 2.5 mg) + exemestane (25 mg) (fed)

| | |
|---|---|
| Subject analysis set title | LEE011 (200 mg) + eve (5 mg) + exe (25 mg) (fed) |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Triplet combination of LEE011 (200 mg) + everolimus (RAD001, 5 mg) + exemestane (25 mg) (fed)

| | |
|---|---|
| Subject analysis set title | Triplet Escalation ALL |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Triplet Escalation ALL (FED and fasting)

## Primary: Dose Escalation: Incidence of Dose Limiting Toxicity (DLT)

| | |
|---|---|
| End point title | Dose Escalation: Incidence of Dose Limiting Toxicity (DLT)[1] |

End point description:

DLT is defined as treatment-related toxicity (classified according Common Toxicity Criteria for Adverse Events (CTCAE) Version 4) occurring during the first 28 treatment days and meeting specific protocol-predefined criteria.

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

End point timeframe:

28 days from dosing or cycle 1

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: No statistical analyses have been specified for this primary end point.

| **End point values** | Doublet Escalation: LEE011 (600 mg) exe (25 mg) (Fasting) | Triplet Escalation ALL | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 14 | 70 | | |
| Units: Participants | | | | |
| number (not applicable) | 2 | 7 | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Dose Expansion: Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

| End point title | Dose Expansion: Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)[2][3] |
|---|---|

End point description:

Adverse events were collected for approximately 4.5 years for dose expansion including the 30 days safety follow-up period.

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

End point timeframe:

Approximately 4.5 years after FPFV

Notes:

[2] - 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: No statistical analyses have been specified for this primary end point.

[3] - 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: No statistical analyses have been specified for this primary end point.

| **End point values** | LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive | LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory | LEE011(600 mg)+exe(25 mg) exp refractory | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 16 | 17 | 2 | |
| Units: Participants | | | | |
| Adverse Events (AEs) | 16 | 17 | 2 | |
| Serious Adverse Events (SAEs) | 4 | 1 | 1 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Dose Escalation: Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

| End point title | Dose Escalation: Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)[4] |
|---|---|

End point description:

Adverse events were collected for approximately 6.5 years for dose escalation including the 30 days safety follow-up period.

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

End point timeframe:

Approximately 6.5 years after FPFV

Notes:

[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: No statistical analyses have been specified for this primary end point.

| End point values | LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive | LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory | LEE011(600 mg)+exe(25 mg) esc refractory | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 41 | 42 | 14 | |
| Units: Participants | | | | |
| Adverse Events (AEs) | 41 | 42 | 14 | |
| Serious Adverse Events (SAEs) | 14 | 12 | 6 | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Dose Escalation and Expansion: Overall Response Rate (ORR)**

| End point title | Dose Escalation and Expansion: Overall Response Rate (ORR) |
|---|---|

End point description:

Overall Response Rate (ORR) is defined as the proportion of participants with a best overall response of complete response or partial response.

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

End point timeframe:

Approximately 6.5 years for Dose Escalation and 4.5 years for Dose Espansion after FPFV

| End point values | LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive | LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory | LEE011(600 mg)+exe(25 mg) esc refractory | LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 41 | 42 | 14 | 16 |
| Units: Participants | 4 | 5 | 2 | 0 |

| End point values | LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory | LEE011(600 mg)+exe(25 mg) exp refractory | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 17 | 2 | | |
| Units: Participants | 0 | 0 | | |

**Statistical analyses**

No statistical analyses for this end point

## Secondary: Dose Escalation and Expansion: Disease Control Rate (DCR)

| End point title | Dose Escalation and Expansion: Disease Control Rate (DCR) |
|---|---|

End point description:

Disease Control Rate (DCR) is the proportion of patients with a best overall response of Complete Response or Partial Response or Stable Disease.

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

End point timeframe:

Approximately 6.5 years for Dose Escalation and 4.5 years for Dose expansion after FPFV

| End point values | LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive | LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory | LEE011(600 mg)+exe(25 mg) esc refractory | LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 41 | 42 | 14 | 16 |
| Units: Participants | 27 | 33 | 12 | 13 |

| End point values | LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory | LEE011(600 mg)+exe(25 mg) exp refractory | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 17 | 2 | | |
| Units: Participants | 7 | 0 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Dose Escalation and Expansion: Clinical Benefit Rate (CBR)

| End point title | Dose Escalation and Expansion: Clinical Benefit Rate (CBR) |
|---|---|

End point description:

Clinical Benefit Rate (CBR) is the Complete Response, Partial Response, or Stable Disease lasting 24 weeks or longer

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

End point timeframe:

Approximately 6.5 years for Dose Escalation and 4.5 years for Dose Espansion after FPFV

| End point values | LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive | LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory | LEE011(600 mg)+exe(25 mg) esc refractory | LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 41 | 42 | 14 | 16 |
| Units: Participants | 18 | 20 | 10 | 10 |

| End point values | LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory | LEE011(600 mg)+exe(25 mg) exp refractory | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 17 | 2 | | |
| Units: Participants | 4 | 0 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Dose Expansion: Duration of Response (DOR)

| End point title | Dose Expansion: Duration of Response (DOR)[5] |
|---|---|

End point description:

Duration of Response (DOR) is calculated as the time from the date of first documented response (complete response (CR) or partial response (PR)) to the first documented date of progression or death due to underlying cancer. The DOR is not applicable as none of the patients in the expansion treatment groups (triplet treatment naive, triplet treatment refractory and doublet treatment refractory) had a CR or PR

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

End point timeframe:

Approximately 4.5 years after FPFV

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: No statistical analyses have been specified for this primary end point.

| End point values | LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive | LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory | LEE011(600 mg)+exe(25 mg) exp refractory | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 16 | 17 | 2 | |
| Units: Participants | 0 | 0 | 0 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Dose Expansion: Progression Free Survival (PFS)

| End point title | Dose Expansion: Progression Free Survival (PFS)[6] |
|---|---|

End point description:

Progression Free Survival (PFS) is defined as the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.

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

End point timeframe:

Approximately 4.5 years after FPFV

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: No statistical analyses have been specified for this primary end point.

| End point values | LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive | LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory | LEE011(600 mg)+exe(25 mg) exp refractory | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 16 | 17 | 2 | |
| Units: months | | | | |
| median (confidence interval 95%) | 12.7 (3.7 to 20.2) | 1.9 (1.7 to 7.3) | 1.7 (-999 to 999) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Dose Escalation: Pharmacokinetics (PK) parameter: AUC0-24h at Day 1 of Cycle 1

| End point title | Dose Escalation: Pharmacokinetics (PK) parameter: AUC0-24h at Day 1 of Cycle 1 |
|---|---|

End point description:

AUC0-24h is the area under the drug concentration-time curve during a dosing interval (mass x time x volume-1).

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

End point timeframe:

6 Cycles of treatment (28 day cycles): Cycle 1 Day 1

| End point values | LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fasting) | LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fed) | LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fasting) | LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fed) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6 | 2 | 18 | 6 |
| Units: hr*ng/mL | | | | |

| | | | | |
|---|---|---|---|---|
| arithmetic mean (standard deviation) | 2170 (± 854) | 2580 (± 2340) | 3750 (± 1840) | 2820 (± 1260) |

| **End point values** | LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fasting) | LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fed) | LEE011 (350 mg) + eve (1 mg) + exe (25mg) (fasting) | LEE011 (350 mg) + eve (2.5 mg) + exe (25mg) (fed) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 9 | 17 | 6 | 9 |
| Units: hr*ng/mL | | | | |
| arithmetic mean (standard deviation) | 6810 (± 2280) | 5440 (± 2810) | 6060 (± 2730) | 6380 (± 3630) |

| **End point values** | LEE011 (200 mg) + eve (5 mg) + exe (25 mg) (fed) | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 5 | | | |
| Units: hr*ng/mL | | | | |
| arithmetic mean (standard deviation) | 2440 (± 1270) | | | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Dose Escalation: Pharmacokinetics (PK) parameter: AUC0-24h at Day 15 of Cycle 1**

| End point title | Dose Escalation: Pharmacokinetics (PK) parameter: AUC0-24h at Day 15 of Cycle 1 |
|---|---|

End point description:

AUC0-24h is the area under the drug concentration-time curve during a dosing interval (mass x time x volume-1).

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

End point timeframe:

6 Cycles of treatment (28 day cycles): Cycle 1 Day 1

| **End point values** | LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fasting) | LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fed) | LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fasting) | LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fed) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 5 | 3 | 13 | 6 |
| Units: hr*ng/mL | | | | |
| arithmetic mean (standard deviation) | 5310 (± 3760) | 4770 (± 3590) | 11100 (± 6030) | 7120 (± 4240) |

| End point values | LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fasting) | LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fed) | LEE011 (350 mg) + eve (1 mg) + exe (25mg) (fasting) | LEE011 (350 mg) + eve (2.5 mg) + exe (25mg) (fed) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 8 | 16 | 5 | 8 |
| Units: hr*ng/mL | | | | |
| arithmetic mean (standard deviation) | 14600 (± 9320) | 11500 (± 6550) | 10800 (± 3820) | 15200 (± 8250) |

| End point values | LEE011 (200 mg) + eve (5 mg) + exe (25 mg) (fed) | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 5 | | | |
| Units: hr*ng/mL | | | | |
| arithmetic mean (standard deviation) | 6710 (± 2520) | | | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Dose Escalation: Pharmacokinetics (PK) parameter: Cmax at Day 1 of Cycle 1**

| End point title | Dose Escalation: Pharmacokinetics (PK) parameter: Cmax at Day 1 of Cycle 1 |
|---|---|

End point description:

Cmax is the maximum observed drug concentration after drug administration (mass x volume-1).

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

End point timeframe:

6 Cycles of treatment (28 day cycles): Cycle 1 Day 1

| End point values | LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fasting) | LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fed) | LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fasting) | LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fed) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6 | 2 | 18 | 6 |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 245 (± 148) | 238 (± 180) | 397 (± 205) | 358 (± 133) |

| End point values | LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fasting) | LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fed) | LEE011 (350 mg) + eve (1 mg) + exe (25mg) (fasting) | LEE011 (350 mg) + eve (2.5 mg) + exe (25mg) (fed) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 11 | 18 | 6 | 6 |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 510 (± 173) | 513 (± 206) | 512 (± 178) | 268 (± 178) |

| End point values | LEE011 (200 mg) + eve (5 mg) + exe (25 mg) (fed) | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 9 | | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 625 (± 310) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Dose Escalation: Pharmacokinetics (PK) parameter: Cmax at Day 15 of Cycle 1

| End point title | Dose Escalation: Pharmacokinetics (PK) parameter: Cmax at Day 15 of Cycle 1 |
|---|---|

End point description:

Cmax is the maximum observed drug concentration after drug administration (mass x volume-1).

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

End point timeframe:

6 Cycles of treatment (28 day cycles): Cycle 1 Day 15

| End point values | LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fasting) | LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fed) | LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fasting) | LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fed) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6 | 3 | 14 | 6 |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 473 (± 305) | 315 (± 163) | 840 (± 528) | 533 (± 277) |

| End point values | LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fasting) | LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fed) | LEE011 (350 mg) + eve (1 mg) + exe (25mg) (fasting) | LEE011 (350 mg) + eve (2.5 mg) + exe (25mg) (fed) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 8 | 16 | 5 | 8 |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 1250 (± 690) | 859 (± 459) | 893 (± 379) | 1030 (± 390) |

| End point values | LEE011 (200 mg) + eve (5 mg) + exe (25 mg) (fed) | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 6 | | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 550 (± 207) | | | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Dose Escalation: Pharmacokinetics (PK) parameter: Tmax at Day 1 of Cycle 1**

| End point title | Dose Escalation: Pharmacokinetics (PK) parameter: Tmax at Day 1 of Cycle 1 |
|---|---|

End point description:

Tmax is the time to reach maximum plasma/blood/serum drug concentration (time).

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

End point timeframe:

6 Cycles of treatment (28 day cycles): Cycle 1 Day 1

| End point values | LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fasting) | LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fed) | LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fasting) | LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fed) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6 | 2 | 18 | 6 |
| Units: hour | | | | |
| median (full range (min-max)) | 2.56 (1.02 to 4.2) | 4.03 (4 to 4.07) | 2.81 (0.967 to 4.5) | 1.13 (1 to 2.17) |

| End point values | LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fasting) | LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fed) | LEE011 (350 mg) + eve (1 mg) + exe (25mg) (fasting) | LEE011 (350 mg) + eve (2.5 mg) + exe (25mg) (fed) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 11 | 18 | 6 | 9 |
| Units: hour | | | | |
| median (full range (min-max)) | 4 (1 to 23) | 4 (1.95 to 8) | 2.82 (1 to 8) | 2.1 (1.02 to 4) |

| End point values | LEE011 (200 mg) + eve (5 mg) + exe (25 mg) (fed) | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 6 | | | |
| Units: hour | | | | |
| median (full range (min-max)) | 3.04 (1 to 4.02) | | | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Dose Escalation: Pharmacokinetics (PK) parameter: Tmax at Day 15 of Cycle 1**

| End point title | Dose Escalation: Pharmacokinetics (PK) parameter: Tmax at Day 15 of Cycle 1 |
|---|---|

End point description:

Tmax is the time to reach maximum plasma/blood/serum drug concentration (time).

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

End point timeframe:

6 Cycles of treatment (28 day cycles): Cycle 1 Day 15

| End point values | LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fasting) | LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fed) | LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fasting) | LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fed) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6 | 3 | 14 | 6 |
| Units: hour | | | | |
| median (full range (min-max)) | 2.03 (1.03 to 4.12) | 2.17 (2.12 to 4.02) | 2.19 (0.983 to 4.08) | 3.93 (2 to 4.03) |

| End point values | LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fasting) | LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fed) | LEE011 (350 mg) + eve (1 mg) + exe (25mg) (fasting) | LEE011 (350 mg) + eve (2.5 mg) + exe (25mg) (fed) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 8 | 16 | 5 | 8 |
| Units: hour | | | | |
| median (full range (min-max)) | 3 (1.03 to 4.33) | 3.07 (0.983 to 8) | 1.98 (1 to 4) | 4 (2.05 to 23.4) |

| End point values | LEE011 (200 mg) + eve (5 mg) + exe (25 mg) (fed) | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 6 | | | |
| Units: hour | | | | |
| median (full range (min-max)) | 2 (1 to 4.03) | | | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Dose Escalation: Pharmacokinetics (PK) parameter: Racc at Day 15 of Cycle 1**

| End point title | Dose Escalation: Pharmacokinetics (PK) parameter: Racc at Day 15 of Cycle 1 |
|---|---|
| End point description: | |
| Racc is the accumulation ratio calculated as AUCtau,ss / AUCtau,sd | |
| End point type | Secondary |
| End point timeframe: | |
| 6 Cycles of treatment (28 day cycles): Cycle 1 Day 15 | |

| End point values | LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fasting) | LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fed) | LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fasting) | LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fed) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 5 | 2 | 13 | 6 |
| Units: Ratio | | | | |
| arithmetic mean (standard deviation) | 2.22 (± 0.774) | 1.55 (± 1.09) | 3.54 (± 1.54) | 2.54 (± 0.94) |

| End point values | LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fasting) | LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fed) | LEE011 (350 mg) + eve (1 mg) + exe (25mg) (fasting) | LEE011 (350 mg) + eve (2.5 mg) + exe (25mg) (fed) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 7 | 16 | 5 | 8 |
| Units: Ratio | | | | |
| arithmetic mean (standard deviation) | 2.77 (± 0.846) | 2.55 (± 1.02) | 2.2 (± 0.618) | 2.85 (± 1.17) |

| End point values | LEE011 (200 mg) + eve (5 mg) + exe (25 mg) (fed) | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 5 | | | |
| Units: Ratio | | | | |
| arithmetic mean (standard deviation) | 3.61 (± 0.82) | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected for approximately 6.5 years for dose escalation and 4.5 years for dose expansion including the 30 days safety follow-up period.

Adverse event reporting additional description:

Any undesirable sign(s), symptom(s), or medical condition(s) that occurred after patient's signed informed consent up to roughly 6.5 years for dose escalation and 4.5 years for dose expansion including the 30 days safety follow-up period.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 23.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive |

Reporting group description:

Triplet combination of LEE011 200 mg + everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered in fasting to the naive to CDK4/6 inhibitors group

| | |
|---|---|
| Reporting group title | LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory |

Reporting group description:

Triplet combination of LEE011 200 mg + everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group

| | |
|---|---|
| Reporting group title | Triplet: ESCALATION ALL |

Reporting group description:

Triplet: ESCALATION ALL

| | |
|---|---|
| Reporting group title | LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive |

Reporting group description:

Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the naive to CDK4/6 inhibitors group

| | |
|---|---|
| Reporting group title | LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory |

Reporting group description:

Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group

| | |
|---|---|
| Reporting group title | LEE011(600 mg)+exe(25 mg) esc refractory |

Reporting group description:

Doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group

| | |
|---|---|
| Reporting group title | LEE011(600 mg)+exe(25 mg) exp refractory |

Reporting group description:

Following RP2D declaration for the doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group (except patients with disease refractory to prior LEE011)

| | |
|---|---|
| Reporting group title | All subjects |

Reporting group description:

All subjects

| **Serious adverse events** | LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive | LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory | Triplet: ESCALATION ALL |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 14 / 41 (34.15%) | 12 / 42 (28.57%) | 26 / 83 (31.33%) |
| number of deaths (all causes) | 4 | 2 | 6 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant peritoneal neoplasm | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to peritoneum | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Superior vena cava syndrome | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Peripheral swelling | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 0 / 42 (0.00%) | 2 / 83 (2.41%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |

| | | | |
|---|---|---|---|
| Aspiration | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (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 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Mental status changes | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (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 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (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 |

| | | | |
|---|---|---|---|
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (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 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (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 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (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 | | | |
| Transfusion reaction | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Central nervous system inflammation | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalopathy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal cord compression | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 42 (2.38%) | 2 / 83 (2.41%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (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 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 42 (2.38%) | 2 / 83 (2.41%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphopenia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 42 (2.38%) | 2 / 83 (2.41%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterocolitis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (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 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (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 |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Skin and subcutaneous tissue disorders** | | | |
| Rash | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Renal and urinary disorders** | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 42 (2.38%) | 2 / 83 (2.41%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infectious colitis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Localised infection | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumocystis jirovecii infection | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (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 |

| | | | |
|---|---|---|---|
| Pneumonia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 2 / 42 (4.76%) | 3 / 83 (3.61%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (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 |
| Wound infection | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (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 | | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 42 (2.38%) | 2 / 83 (2.41%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | LEE011(300 mg)+eve(2.5 mg)+exe (25mg) | LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory | LEE011(600 mg)+exe(25 mg) esc refractory |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 16 (25.00%) | 1 / 17 (5.88%) | 6 / 14 (42.86%) |
| number of deaths (all causes) | 0 | 0 | 3 |
| number of deaths resulting from adverse events | 0 | 0 | 1 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant peritoneal neoplasm | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 peritoneum | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 | | | |
| Superior vena cava syndrome | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 | | | |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Aspiration | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Dyspnoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (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 |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (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 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 | 2 / 16 (12.50%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Mental status changes | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (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 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Transfusion reaction | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 arrest | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 | | | |
| Central nervous system inflammation | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 |
| Spinal cord compression | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 |
| Enterocolitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 haemorrhage | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 14 (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 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 failure | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 | | | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 |
| Infectious colitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 |
| Localised infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 |
| Pneumocystis jirovecii infection | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 2 / 14 (14.29%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 14 (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 |
| Wound infection | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (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 |
| Metabolism and nutrition disorders | | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (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** | LEE011(600 mg)+exe(25 mg) exp refractory | All subjects | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 38 / 132 (28.79%) | |
| number of deaths (all causes) | 0 | 9 | |
| number of deaths resulting from adverse events | 0 | 1 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant peritoneal neoplasm | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to peritoneum | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Superior vena cava syndrome | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 3 / 132 (2.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 2 | |
| Aspiration | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoptysis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 4 / 132 (3.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Mental status changes | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Transfusion reaction | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Central nervous system inflammation | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord compression | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 3 / 132 (2.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infectious colitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Localised infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumocystis jirovecii infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 6 / 132 (4.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 2 (50.00%) | 2 / 132 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive | LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory | Triplet: ESCALATION ALL |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 41 / 41 (100.00%) | 42 / 42 (100.00%) | 83 / 83 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 2 / 42 (4.76%) | 3 / 83 (3.61%) |
| occurrences (all) | 1 | 2 | 3 |
| Malignant peritoneal neoplasm | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Vascular disorders | | | |

| | | | |
|---|---|---|---|
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Hot flush | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 3 / 42 (7.14%) | 3 / 83 (3.61%) |
| occurrences (all) | 0 | 4 | 4 |
| Hypertension | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 3 / 42 (7.14%) | 6 / 83 (7.23%) |
| occurrences (all) | 3 | 3 | 6 |
| Hypotension | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Lymphoedema | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 3 / 42 (7.14%) | 6 / 83 (7.23%) |
| occurrences (all) | 3 | 3 | 6 |
| Phlebitis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 7 / 41 (17.07%) | 7 / 42 (16.67%) | 14 / 83 (16.87%) |
| occurrences (all) | 9 | 12 | 21 |
| Axillary pain | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Chest pain | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Chills | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 1 / 42 (2.38%) | 3 / 83 (3.61%) |
| occurrences (all) | 2 | 1 | 3 |
| Fatigue | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 15 / 41 (36.59%) | 9 / 42 (21.43%) | 24 / 83 (28.92%) |
| occurrences (all) | 16 | 11 | 27 |
| Feeling cold | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Local swelling | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Malaise | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mass | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Mucosal dryness | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 1 / 42 (2.38%) | 3 / 83 (3.61%) |
| occurrences (all) | 2 | 1 | 3 |
| Oedema | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Oedema peripheral | | | |
| subjects affected / exposed | 10 / 41 (24.39%) | 5 / 42 (11.90%) | 15 / 83 (18.07%) |
| occurrences (all) | 12 | 6 | 18 |
| Pain | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 3 / 42 (7.14%) | 4 / 83 (4.82%) |
| occurrences (all) | 2 | 3 | 5 |
| Peripheral swelling | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Pyrexia | | | |
| subjects affected / exposed | 7 / 41 (17.07%) | 7 / 42 (16.67%) | 14 / 83 (16.87%) |
| occurrences (all) | 7 | 11 | 18 |
| Xerosis | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 0 / 42 (0.00%) | 2 / 83 (2.41%) |
| occurrences (all) | 2 | 0 | 2 |
| Immune system disorders | | | |
| Allergy to arthropod bite | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Seasonal allergy | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 2 | 0 | 2 |
| Reproductive system and breast disorders | | | |
| Breast haematoma | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Breast pain | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Menopausal symptoms | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Pelvic pain | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Vaginal discharge | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Vulval ulceration | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Vulvovaginal burning sensation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vulvovaginal dryness | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 2 | 2 |
| Vulvovaginal pain | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Allergic sinusitis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cough | | | |
| subjects affected / exposed | 12 / 41 (29.27%) | 11 / 42 (26.19%) | 23 / 83 (27.71%) |
| occurrences (all) | 14 | 11 | 25 |
| Dysphonia | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 0 / 42 (0.00%) | 3 / 83 (3.61%) |
| occurrences (all) | 4 | 0 | 4 |
| Dyspnoea | | | |
| subjects affected / exposed | 10 / 41 (24.39%) | 10 / 42 (23.81%) | 20 / 83 (24.10%) |
| occurrences (all) | 12 | 10 | 22 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 4 / 41 (9.76%) | 1 / 42 (2.38%) | 5 / 83 (6.02%) |
| occurrences (all) | 4 | 2 | 6 |
| Epistaxis | | | |
| subjects affected / exposed | 9 / 41 (21.95%) | 7 / 42 (16.67%) | 16 / 83 (19.28%) |
| occurrences (all) | 15 | 10 | 25 |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Hiccups | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Nasal congestion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 41 (7.32%) | 2 / 42 (4.76%) | 5 / 83 (6.02%) |
| occurrences (all) | 3 | 3 | 6 |
| Nasal discharge discolouration | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Nasal dryness | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 2 / 42 (4.76%) | 2 / 83 (2.41%) |
| occurrences (all) | 0 | 2 | 2 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 4 / 42 (9.52%) | 7 / 83 (8.43%) |
| occurrences (all) | 3 | 4 | 7 |
| Painful respiration | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 2 | 0 | 2 |
| Paranasal sinus discomfort | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 42 (2.38%) | 2 / 83 (2.41%) |
| occurrences (all) | 1 | 1 | 2 |
| Pharyngeal inflammation | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 2 / 42 (4.76%) | 3 / 83 (3.61%) |
| occurrences (all) | 1 | 2 | 3 |
| Pneumonitis | | | |
| subjects affected / exposed | 4 / 41 (9.76%) | 5 / 42 (11.90%) | 9 / 83 (10.84%) |
| occurrences (all) | 4 | 7 | 11 |
| Productive cough | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 2 | 2 |
| Pulmonary congestion | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Reflux laryngitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 2 / 42 (4.76%) | 2 / 83 (2.41%) |
| occurrences (all) | 0 | 2 | 2 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 42 (2.38%) | 2 / 83 (2.41%) |
| occurrences (all) | 1 | 1 | 2 |
| Sinus congestion | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Sinus pain | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Throat irritation | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Upper-airway cough syndrome | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Wheezing | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 0 / 42 (0.00%) | 2 / 83 (2.41%) |
| occurrences (all) | 3 | 0 | 3 |
| Delirium | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Depression | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 42 (2.38%) | 2 / 83 (2.41%) |
| occurrences (all) | 2 | 2 | 4 |
| Depressive symptom | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |

| | | | |
|---|---|---|---|
| Insomnia | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 6 / 42 (14.29%) | 8 / 83 (9.64%) |
| occurrences (all) | 2 | 7 | 9 |
| Irritability | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nightmare | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Restlessness | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sleep disorder | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 42 (2.38%) | 2 / 83 (2.41%) |
| occurrences (all) | 1 | 1 | 2 |
| Investigations | | | |
| Alanine aminotransferase decreased | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 12 / 41 (29.27%) | 13 / 42 (30.95%) | 25 / 83 (30.12%) |
| occurrences (all) | 19 | 19 | 38 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 18 / 41 (43.90%) | 16 / 42 (38.10%) | 34 / 83 (40.96%) |
| occurrences (all) | 30 | 24 | 54 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 11 / 41 (26.83%) | 7 / 42 (16.67%) | 18 / 83 (21.69%) |
| occurrences (all) | 18 | 11 | 29 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Blood calcium decreased | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 2 / 42 (4.76%) | 2 / 83 (2.41%) |
| occurrences (all) | 0 | 6 | 6 |
| Blood chloride decreased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Blood cholesterol increased | | | |
| subjects affected / exposed | 4 / 41 (9.76%) | 3 / 42 (7.14%) | 7 / 83 (8.43%) |
| occurrences (all) | 6 | 8 | 14 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 4 / 41 (9.76%) | 5 / 42 (11.90%) | 9 / 83 (10.84%) |
| occurrences (all) | 10 | 10 | 20 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 2 / 42 (4.76%) | 5 / 83 (6.02%) |
| occurrences (all) | 3 | 2 | 5 |
| Blood phosphorus decreased | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 42 (2.38%) | 2 / 83 (2.41%) |
| occurrences (all) | 1 | 1 | 2 |
| Blood phosphorus increased | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood sodium decreased | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Blood thyroid stimulating hormone decreased | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood thyroid stimulating hormone increased | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 3 | 0 | 3 |
| Blood triglycerides increased | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 2 / 42 (4.76%) | 3 / 83 (3.61%) |
| occurrences (all) | 2 | 3 | 5 |
| Blood urea decreased | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ejection fraction decreased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 0 / 42 (0.00%) | 2 / 83 (2.41%) |
| occurrences (all) | 2 | 0 | 2 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 5 / 41 (12.20%) | 5 / 42 (11.90%) | 10 / 83 (12.05%) |
| occurrences (all) | 7 | 5 | 12 |
| Haematocrit | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 0 / 42 (0.00%) | 2 / 83 (2.41%) |
| occurrences (all) | 2 | 0 | 2 |
| International normalised ratio increased | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 12 / 41 (29.27%) | 11 / 42 (26.19%) | 23 / 83 (27.71%) |
| occurrences (all) | 19 | 30 | 49 |
| Lymphocyte count increased | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 20 / 41 (48.78%) | 16 / 42 (38.10%) | 36 / 83 (43.37%) |
| occurrences (all) | 40 | 48 | 88 |
| Neutrophil count increased | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Platelet count decreased | | | |
| subjects affected / exposed | 9 / 41 (21.95%) | 8 / 42 (19.05%) | 17 / 83 (20.48%) |
| occurrences (all) | 16 | 10 | 26 |
| Platelet count increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Thyroxine decreased | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Thyroxine free increased | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Transaminases increased | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Tri-iodothyronine increased | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Weight decreased | | | |
| subjects affected / exposed | 6 / 41 (14.63%) | 3 / 42 (7.14%) | 9 / 83 (10.84%) |
| occurrences (all) | 8 | 3 | 11 |
| Weight increased | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 42 (2.38%) | 2 / 83 (2.41%) |
| occurrences (all) | 1 | 1 | 2 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 20 / 41 (48.78%) | 17 / 42 (40.48%) | 37 / 83 (44.58%) |
| occurrences (all) | 36 | 32 | 68 |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Contusion | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Fall | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Ligament sprain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle rupture | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Radiation skin injury | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Wound | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Wound secretion | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Wrist fracture | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Diastolic dysfunction | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Palpitations | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 42 (2.38%) | 2 / 83 (2.41%) |
| occurrences (all) | 1 | 1 | 2 |

| | | | |
|---|---|---|---|
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 2 / 42 (4.76%) | 2 / 83 (2.41%) |
| occurrences (all) | 0 | 2 | 2 |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Amnesia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Aphonia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Ataxia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Cognitive disorder | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Dizziness | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 1 / 42 (2.38%) | 4 / 83 (4.82%) |
| occurrences (all) | 3 | 1 | 4 |
| Dysaesthesia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Dysgeusia | | | |
| subjects affected / exposed | 8 / 41 (19.51%) | 4 / 42 (9.52%) | 12 / 83 (14.46%) |
| occurrences (all) | 8 | 4 | 12 |
| Headache | | | |
| subjects affected / exposed | 6 / 41 (14.63%) | 11 / 42 (26.19%) | 17 / 83 (20.48%) |
| occurrences (all) | 6 | 16 | 22 |
| Hyperaesthesia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Intracranial aneurysm | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Migraine | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 42 (2.38%) | 2 / 83 (2.41%) |
| occurrences (all) | 1 | 1 | 2 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 0 / 42 (0.00%) | 2 / 83 (2.41%) |
| occurrences (all) | 2 | 0 | 2 |
| Restless legs syndrome | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Sciatica | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Somnolence | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Tremor | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 26 / 41 (63.41%) | 22 / 42 (52.38%) | 48 / 83 (57.83%) |
| occurrences (all) | 43 | 48 | 91 |

| | | | |
|---|---|---|---|
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 3 / 42 (7.14%) | 4 / 83 (4.82%) |
| occurrences (all) | 1 | 3 | 4 |
| Lymphopenia | | | |
| subjects affected / exposed | 11 / 41 (26.83%) | 5 / 42 (11.90%) | 16 / 83 (19.28%) |
| occurrences (all) | 14 | 6 | 20 |
| Neutropenia | | | |
| subjects affected / exposed | 18 / 41 (43.90%) | 22 / 42 (52.38%) | 40 / 83 (48.19%) |
| occurrences (all) | 33 | 40 | 73 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 12 / 41 (29.27%) | 12 / 42 (28.57%) | 24 / 83 (28.92%) |
| occurrences (all) | 20 | 31 | 51 |
| Ear and labyrinth disorders | | | |
| Cerumen impaction | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear discomfort | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear pain | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 0 / 42 (0.00%) | 2 / 83 (2.41%) |
| occurrences (all) | 2 | 0 | 2 |
| Vertigo | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Chalazion | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Dry eye | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 41 (4.88%) | 1 / 42 (2.38%) | 3 / 83 (3.61%) |
| occurrences (all) | 2 | 1 | 3 |
| Eye pruritus | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Eyelid oedema | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 42 (2.38%) | 2 / 83 (2.41%) |
| occurrences (all) | 1 | 1 | 2 |
| Lacrimation increased | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Myopia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Visual impairment | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 41 (9.76%) | 5 / 42 (11.90%) | 9 / 83 (10.84%) |
| occurrences (all) | 4 | 9 | 13 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 1 / 42 (2.38%) | 4 / 83 (4.82%) |
| occurrences (all) | 6 | 1 | 7 |
| Anal haemorrhage | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |

| | | | |
|---|---|---|---|
| Anal incontinence | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Aphthous ulcer | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 2 / 42 (4.76%) | 2 / 83 (2.41%) |
| occurrences (all) | 0 | 2 | 2 |
| Ascites | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 3 / 42 (7.14%) | 3 / 83 (3.61%) |
| occurrences (all) | 0 | 7 | 7 |
| Atrophic glossitis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Cheilitis | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Colitis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Constipation | | | |
| subjects affected / exposed | 10 / 41 (24.39%) | 4 / 42 (9.52%) | 14 / 83 (16.87%) |
| occurrences (all) | 12 | 7 | 19 |
| Dental caries | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 9 / 41 (21.95%) | 13 / 42 (30.95%) | 22 / 83 (26.51%) |
| occurrences (all) | 12 | 19 | 31 |
| Dry mouth | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 5 / 42 (11.90%) | 7 / 83 (8.43%) |
| occurrences (all) | 2 | 5 | 7 |
| Dyspepsia | | | |
| subjects affected / exposed | 4 / 41 (9.76%) | 4 / 42 (9.52%) | 8 / 83 (9.64%) |
| occurrences (all) | 4 | 4 | 8 |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |

| | | | |
|---|---|---|---|
| Eructation | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Flatulence | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Food poisoning | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 1 / 42 (2.38%) | 3 / 83 (3.61%) |
| occurrences (all) | 2 | 1 | 3 |
| Gingival pain | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Gingival ulceration | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 3 / 42 (7.14%) | 4 / 83 (4.82%) |
| occurrences (all) | 1 | 4 | 5 |
| Lip oedema | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 2 | 2 |
| Lip swelling | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Lip ulceration | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Mouth ulceration | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 42 (2.38%) | 2 / 83 (2.41%) |
| occurrences (all) | 2 | 5 | 7 |

| | | | |
|---|---|---|---|
| Nausea | | | |
| subjects affected / exposed | 15 / 41 (36.59%) | 12 / 42 (28.57%) | 27 / 83 (32.53%) |
| occurrences (all) | 23 | 15 | 38 |
| Odynophagia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 3 / 42 (7.14%) | 4 / 83 (4.82%) |
| occurrences (all) | 1 | 4 | 5 |
| Oral pain | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Steatorrhoea | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Stomatitis | | | |
| subjects affected / exposed | 23 / 41 (56.10%) | 25 / 42 (59.52%) | 48 / 83 (57.83%) |
| occurrences (all) | 39 | 43 | 82 |
| Toothache | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 42 (2.38%) | 2 / 83 (2.41%) |
| occurrences (all) | 1 | 1 | 2 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Vomiting | | | |
| subjects affected / exposed | 12 / 41 (29.27%) | 7 / 42 (16.67%) | 19 / 83 (22.89%) |
| occurrences (all) | 16 | 17 | 33 |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Hepatic necrosis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hepatocellular injury | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 41 (4.88%) | 2 / 42 (4.76%) | 4 / 83 (4.82%) |
| occurrences (all) | 2 | 2 | 4 |
| Hepatomegaly | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Alopecia | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 3 / 42 (7.14%) | 5 / 83 (6.02%) |
| occurrences (all) | 2 | 3 | 5 |
| Angioedema | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 4 | 4 |
| Dermal cyst | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dermatitis | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 42 (2.38%) | 2 / 83 (2.41%) |
| occurrences (all) | 1 | 1 | 2 |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 2 / 42 (4.76%) | 3 / 83 (3.61%) |
| occurrences (all) | 1 | 2 | 3 |
| Dry skin | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 2 / 42 (4.76%) | 5 / 83 (6.02%) |
| occurrences (all) | 3 | 3 | 6 |
| Ecchymosis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eczema | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |

| | | | |
|---|---|---|---|
| Erythema | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 2 / 42 (4.76%) | 4 / 83 (4.82%) |
| occurrences (all) | 2 | 2 | 4 |
| Hair texture abnormal | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Madarosis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nail discolouration | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nail disorder | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 1 / 42 (2.38%) | 4 / 83 (4.82%) |
| occurrences (all) | 3 | 1 | 4 |
| Nail dystrophy | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nail toxicity | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Night sweats | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 1 / 42 (2.38%) | 3 / 83 (3.61%) |
| occurrences (all) | 2 | 1 | 3 |
| Onychoclasis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 2 / 42 (4.76%) | 2 / 83 (2.41%) |
| occurrences (all) | 0 | 2 | 2 |
| Onychomalacia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pain of skin | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Palmar-plantar erythrodysaesthesia syndrome | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 42 (2.38%) | 2 / 83 (2.41%) |
| occurrences (all) | 1 | 1 | 2 |
| Palmoplantar keratoderma | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pigmentation disorder | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Pruritus | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 3 / 42 (7.14%) | 6 / 83 (7.23%) |
| occurrences (all) | 3 | 3 | 6 |
| Rash | | | |
| subjects affected / exposed | 8 / 41 (19.51%) | 10 / 42 (23.81%) | 18 / 83 (21.69%) |
| occurrences (all) | 11 | 11 | 22 |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Rash macular | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 4 / 42 (9.52%) | 7 / 83 (8.43%) |
| occurrences (all) | 4 | 5 | 9 |
| Rash vesicular | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rosacea | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin hyperpigmentation | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Skin hypopigmentation | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Skin lesion | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin mass | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin toxicity | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Yellow skin | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 1 / 42 (2.38%) | 3 / 83 (3.61%) |
| occurrences (all) | 2 | 1 | 3 |
| Leukocyturia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Micturition urgency | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Proteinuria | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Renal failure | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 42 (2.38%) | 2 / 83 (2.41%) |
| occurrences (all) | 1 | 1 | 2 |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 42 (2.38%) | 2 / 83 (2.41%) |
| occurrences (all) | 1 | 1 | 2 |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 5 / 41 (12.20%) | 9 / 42 (21.43%) | 14 / 83 (16.87%) |
| occurrences (all) | 7 | 10 | 17 |
| Arthropathy | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Back pain | | | |
| subjects affected / exposed | 6 / 41 (14.63%) | 3 / 42 (7.14%) | 9 / 83 (10.84%) |
| occurrences (all) | 6 | 6 | 12 |
| Bone cyst | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bone pain | | | |
| subjects affected / exposed | 5 / 41 (12.20%) | 2 / 42 (4.76%) | 7 / 83 (8.43%) |
| occurrences (all) | 5 | 2 | 7 |
| Bursitis | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Intervertebral disc degeneration | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle contracture | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Muscle fatigue | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Muscle spasms | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 1 / 42 (2.38%) | 3 / 83 (3.61%) |
| occurrences (all) | 2 | 1 | 3 |
| Musculoskeletal chest pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 41 (4.88%) | 2 / 42 (4.76%) | 4 / 83 (4.82%) |
| occurrences (all) | 2 | 3 | 5 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 1 / 42 (2.38%) | 4 / 83 (4.82%) |
| occurrences (all) | 3 | 1 | 4 |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Myalgia | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 3 / 42 (7.14%) | 5 / 83 (6.02%) |
| occurrences (all) | 2 | 3 | 5 |
| Neck pain | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 0 / 42 (0.00%) | 2 / 83 (2.41%) |
| occurrences (all) | 2 | 0 | 2 |
| Osteitis | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Osteopenia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Osteoporosis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 2 / 42 (4.76%) | 5 / 83 (6.02%) |
| occurrences (all) | 7 | 2 | 9 |
| Pain in jaw | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 41 (0.00%) | 2 / 42 (4.76%) | 2 / 83 (2.41%) |
| occurrences (all) | 0 | 2 | 2 |
| Trigger finger | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Infections and infestations | | | |
| Angular cheilitis | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 2 | 0 | 2 |
| Atypical pneumonia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Bronchitis | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 0 / 42 (0.00%) | 2 / 83 (2.41%) |
| occurrences (all) | 2 | 0 | 2 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 2 | 2 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear infection | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |

| | | | |
|---|---|---|---|
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 2 | 2 |
| Folliculitis | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 42 (2.38%) | 2 / 83 (2.41%) |
| occurrences (all) | 1 | 1 | 2 |
| Fungal infection | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Genital herpes | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Gingivitis | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 42 (2.38%) | 2 / 83 (2.41%) |
| occurrences (all) | 5 | 1 | 6 |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Influenza | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Lung infection | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Mastitis | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Nail infection | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Neutropenic infection | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Onychomycosis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Paronychia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 2 / 42 (4.76%) | 3 / 83 (3.61%) |
| occurrences (all) | 2 | 2 | 4 |
| Pneumonia | | | |
| subjects affected / exposed | 4 / 41 (9.76%) | 2 / 42 (4.76%) | 6 / 83 (7.23%) |
| occurrences (all) | 4 | 2 | 6 |
| Rash pustular | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 0 / 42 (0.00%) | 2 / 83 (2.41%) |
| occurrences (all) | 3 | 0 | 3 |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |

| | | | |
|---|---|---|---|
| Sepsis | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Sinusitis | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 2 / 42 (4.76%) | 4 / 83 (4.82%) |
| occurrences (all) | 2 | 2 | 4 |
| Skin infection | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tooth abscess | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 42 (2.38%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 | 1 |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 4 / 42 (9.52%) | 5 / 83 (6.02%) |
| occurrences (all) | 3 | 10 | 13 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 3 / 42 (7.14%) | 5 / 83 (6.02%) |
| occurrences (all) | 2 | 3 | 5 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 4 / 42 (9.52%) | 5 / 83 (6.02%) |
| occurrences (all) | 1 | 6 | 7 |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Wound infection | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 10 / 41 (24.39%) | 6 / 42 (14.29%) | 16 / 83 (19.28%) |
| occurrences (all) | 12 | 7 | 19 |
| Dehydration | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 0 | 1 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 10 / 41 (24.39%) | 14 / 42 (33.33%) | 24 / 83 (28.92%) |
| occurrences (all) | 15 | 23 | 38 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 2 / 42 (4.76%) | 4 / 83 (4.82%) |
| occurrences (all) | 2 | 2 | 4 |
| Hypermagnesaemia | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 0 / 42 (0.00%) | 2 / 83 (2.41%) |
| occurrences (all) | 2 | 0 | 2 |
| Hyperphosphataemia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 42 (2.38%) | 2 / 83 (2.41%) |
| occurrences (all) | 1 | 1 | 2 |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 2 / 42 (4.76%) | 4 / 83 (4.82%) |
| occurrences (all) | 2 | 2 | 4 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 4 / 41 (9.76%) | 5 / 42 (11.90%) | 9 / 83 (10.84%) |
| occurrences (all) | 5 | 8 | 13 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 0 / 42 (0.00%) | 2 / 83 (2.41%) |
| occurrences (all) | 3 | 0 | 3 |
| Hypokalaemia | | | |
| subjects affected / exposed | 5 / 41 (12.20%) | 6 / 42 (14.29%) | 11 / 83 (13.25%) |
| occurrences (all) | 6 | 7 | 13 |
| Hypomagnesaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 5 / 41 (12.20%) | 4 / 42 (9.52%) | 9 / 83 (10.84%) |
| occurrences (all) | 9 | 7 | 16 |
| Hyponatraemia | | | |
| subjects affected / exposed | 5 / 41 (12.20%) | 7 / 42 (16.67%) | 12 / 83 (14.46%) |
| occurrences (all) | 7 | 7 | 14 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 10 / 41 (24.39%) | 12 / 42 (28.57%) | 22 / 83 (26.51%) |
| occurrences (all) | 22 | 17 | 39 |
| Increased appetite | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 42 (0.00%) | 0 / 83 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Iron deficiency | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 3 / 42 (7.14%) | 3 / 83 (3.61%) |
| occurrences (all) | 0 | 3 | 3 |

| **Non-serious adverse events** | LEE011(300 mg)+eve(2.5 mg)+exe (25mg) | LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory | LEE011(600 mg)+exe(25 mg) esc refractory |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 16 / 16 (100.00%) | 17 / 17 (100.00%) | 14 / 14 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Malignant peritoneal neoplasm | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hot flush | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 2 / 17 (11.76%) | 3 / 14 (21.43%) |
| occurrences (all) | 1 | 2 | 4 |

| | | | |
|---|---|---|---|
| Hypertension | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 1 / 17 (5.88%) | 2 / 14 (14.29%) |
| occurrences (all) | 1 | 1 | 2 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lymphoedema | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Phlebitis | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 3 / 16 (18.75%) | 1 / 17 (5.88%) | 2 / 14 (14.29%) |
| occurrences (all) | 10 | 1 | 7 |
| Axillary pain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Chest discomfort | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Chills | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 2 / 17 (11.76%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 5 / 16 (31.25%) | 9 / 17 (52.94%) | 5 / 14 (35.71%) |
| occurrences (all) | 5 | 11 | 5 |
| Feeling cold | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gait disturbance | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 2 / 14 (14.29%) |
| occurrences (all) | 0 | 0 | 2 |
| Local swelling | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Malaise | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Mass | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mucosal dryness | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oedema | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 5 / 16 (31.25%) | 5 / 17 (29.41%) | 2 / 14 (14.29%) |
| occurrences (all) | 5 | 5 | 2 |
| Pain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 16 (18.75%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 5 | 0 | 1 |
| Xerosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Immune system disorders | | | |
| Allergy to arthropod bite | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Seasonal allergy | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Reproductive system and breast disorders | | | |
| Breast haematoma | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Breast pain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Menopausal symptoms | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pelvic pain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vaginal discharge | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vulval ulceration | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vulvovaginal burning sensation | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vulvovaginal dryness | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vulvovaginal pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Allergic sinusitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Cough | | | |
| subjects affected / exposed | 3 / 16 (18.75%) | 3 / 17 (17.65%) | 4 / 14 (28.57%) |
| occurrences (all) | 3 | 3 | 4 |
| Dysphonia | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 4 / 16 (25.00%) | 1 / 17 (5.88%) | 2 / 14 (14.29%) |
| occurrences (all) | 4 | 1 | 2 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 1 / 17 (5.88%) | 4 / 14 (28.57%) |
| occurrences (all) | 2 | 1 | 4 |
| Epistaxis | | | |
| subjects affected / exposed | 4 / 16 (25.00%) | 3 / 17 (17.65%) | 1 / 14 (7.14%) |
| occurrences (all) | 4 | 4 | 1 |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hiccups | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Nasal discharge discolouration | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal dryness | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 2 / 17 (11.76%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 2 | 1 |
| Painful respiration | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Paranasal sinus discomfort | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pharyngeal inflammation | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 6 / 16 (37.50%) | 1 / 17 (5.88%) | 1 / 14 (7.14%) |
| occurrences (all) | 6 | 1 | 1 |
| Productive cough | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Pulmonary congestion | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Reflux laryngitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinorrhoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 16 (18.75%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Sinus congestion | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Sinus pain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Throat irritation | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper-airway cough syndrome | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Wheezing | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 3 | 0 | 1 |
| Delirium | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Depression | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 1 / 17 (5.88%) | 0 / 14 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Depressive symptom | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 2 / 17 (11.76%) | 2 / 14 (14.29%) |
| occurrences (all) | 0 | 3 | 6 |
| Irritability | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|---|---|---|
| Nightmare | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Restlessness | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Sleep disorder | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Investigations | | | |
| Alanine aminotransferase decreased | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 5 / 16 (31.25%) | 4 / 17 (23.53%) | 5 / 14 (35.71%) |
| occurrences (all) | 6 | 6 | 5 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 4 / 16 (25.00%) | 5 / 17 (29.41%) | 8 / 14 (57.14%) |
| occurrences (all) | 5 | 14 | 10 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 1 / 17 (5.88%) | 4 / 14 (28.57%) |
| occurrences (all) | 1 | 4 | 4 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 2 / 14 (14.29%) |
| occurrences (all) | 0 | 1 | 2 |
| Blood calcium decreased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood chloride decreased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood cholesterol increased | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 6 | 0 | 0 |
| Blood creatinine increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 16 (12.50%) | 1 / 17 (5.88%) | 2 / 14 (14.29%) |
| occurrences (all) | 5 | 4 | 7 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood phosphorus decreased | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood phosphorus increased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood sodium decreased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood thyroid stimulating hormone decreased | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Blood thyroid stimulating hormone increased | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood triglycerides increased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood urea decreased | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 2 / 14 (14.29%) |
| occurrences (all) | 0 | 1 | 3 |
| Gamma-glutamyltransferase increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 16 (18.75%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Haematocrit | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| International normalised ratio increased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 6 / 16 (37.50%) | 1 / 17 (5.88%) | 4 / 14 (28.57%) |
| occurrences (all) | 15 | 1 | 5 |
| Lymphocyte count increased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 10 / 16 (62.50%) | 8 / 17 (47.06%) | 9 / 14 (64.29%) |
| occurrences (all) | 29 | 30 | 23 |
| Neutrophil count increased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 3 / 17 (17.65%) | 3 / 14 (21.43%) |
| occurrences (all) | 1 | 6 | 3 |
| Platelet count increased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Thyroxine decreased | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Thyroxine free increased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tri-iodothyronine increased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Weight decreased | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Weight increased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 2 | 1 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 5 / 16 (31.25%) | 6 / 17 (35.29%) | 12 / 14 (85.71%) |
| occurrences (all) | 10 | 16 | 15 |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Contusion | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Muscle rupture | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Radiation skin injury | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Wound | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Wound secretion | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Wrist fracture | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Diastolic dysfunction | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Palpitations | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

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|---|---|---|---|
| Nervous system disorders | | | |
| Amnesia | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Aphonia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ataxia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cognitive disorder | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 2 / 17 (11.76%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Dysaesthesia | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dysgeusia | | | |
| subjects affected / exposed | 4 / 16 (25.00%) | 2 / 17 (11.76%) | 0 / 14 (0.00%) |
| occurrences (all) | 4 | 2 | 0 |
| Headache | | | |
| subjects affected / exposed | 3 / 16 (18.75%) | 3 / 17 (17.65%) | 3 / 14 (21.43%) |
| occurrences (all) | 10 | 3 | 3 |
| Hyperaesthesia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Intracranial aneurysm | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Migraine | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Restless legs syndrome | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sciatica | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tremor | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 10 / 16 (62.50%) | 5 / 17 (29.41%) | 9 / 14 (64.29%) |
| occurrences (all) | 18 | 6 | 13 |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 2 / 17 (11.76%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 2 | 1 |
| Lymphopenia | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 1 / 17 (5.88%) | 4 / 14 (28.57%) |
| occurrences (all) | 6 | 1 | 6 |

| | | | |
|---|---|---|---|
| Neutropenia | | | |
| subjects affected / exposed | 10 / 16 (62.50%) | 11 / 17 (64.71%) | 6 / 14 (42.86%) |
| occurrences (all) | 27 | 15 | 17 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 6 / 16 (37.50%) | 4 / 17 (23.53%) | 4 / 14 (28.57%) |
| occurrences (all) | 12 | 14 | 7 |
| Ear and labyrinth disorders | | | |
| Cerumen impaction | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ear discomfort | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Ear pain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vertigo | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Chalazion | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dry eye | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Eye pruritus | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eyelid oedema | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Lacrimation increased | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Myopia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 2 / 17 (11.76%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Visual impairment | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 2 / 17 (11.76%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 2 / 14 (14.29%) |
| occurrences (all) | 1 | 0 | 2 |
| Anal haemorrhage | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Anal incontinence | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Aphthous ulcer | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Ascites | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Atrophic glossitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cheilitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Colitis | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Constipation | | | |
| subjects affected / exposed | 3 / 16 (18.75%) | 3 / 17 (17.65%) | 6 / 14 (42.86%) |
| occurrences (all) | 3 | 3 | 8 |
| Dental caries | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 5 / 17 (29.41%) | 8 / 14 (57.14%) |
| occurrences (all) | 3 | 7 | 13 |
| Dry mouth | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 1 / 17 (5.88%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 1 | 1 |
| Dyspepsia | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 2 / 17 (11.76%) | 1 / 14 (7.14%) |
| occurrences (all) | 2 | 3 | 1 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eructation | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Flatulence | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Food poisoning | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 4 / 16 (25.00%) | 0 / 17 (0.00%) | 3 / 14 (21.43%) |
| occurrences (all) | 4 | 0 | 3 |
| Gingival pain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gingival ulceration | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Lip oedema | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lip swelling | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lip ulceration | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Nausea | | | |
| subjects affected / exposed | 5 / 16 (31.25%) | 9 / 17 (52.94%) | 6 / 14 (42.86%) |
| occurrences (all) | 9 | 10 | 7 |
| Odynophagia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oral pain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|---|---|---|
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Steatorrhoea | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Stomatitis | | | |
| subjects affected / exposed | 9 / 16 (56.25%) | 11 / 17 (64.71%) | 4 / 14 (28.57%) |
| occurrences (all) | 25 | 14 | 5 |
| Toothache | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 3 / 16 (18.75%) | 6 / 17 (35.29%) | 4 / 14 (28.57%) |
| occurrences (all) | 4 | 9 | 4 |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hepatic necrosis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Hepatocellular injury | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hepatomegaly | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 2 / 17 (11.76%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|---|---|---|
| Acne | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Alopecia | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 1 / 17 (5.88%) | 3 / 14 (21.43%) |
| occurrences (all) | 1 | 1 | 3 |
| Angioedema | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dermal cyst | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 2 |
| Dermatitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Dry skin | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 1 / 17 (5.88%) | 2 / 14 (14.29%) |
| occurrences (all) | 2 | 1 | 3 |
| Ecchymosis | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eczema | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Erythema | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hair texture abnormal | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Madarosis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|---|---|---|
| Nail discolouration | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Nail disorder | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 2 | 0 | 2 |
| Nail dystrophy | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nail toxicity | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Night sweats | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Onychoclasis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Onychomalacia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Pain of skin | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Palmoplantar keratoderma | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Pigmentation disorder | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pruritus | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Rash | | | |
| subjects affected / exposed | 5 / 16 (31.25%) | 4 / 17 (23.53%) | 1 / 14 (7.14%) |
| occurrences (all) | 6 | 5 | 1 |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash macular | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash vesicular | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Rosacea | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin hyperpigmentation | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin hypopigmentation | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin lesion | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Skin mass | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin toxicity | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Yellow skin | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Leukocyturia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Micturition urgency | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Proteinuria | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 5 / 17 (29.41%) | 2 / 14 (14.29%) |
| occurrences (all) | 2 | 5 | 3 |
| Arthropathy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Back pain | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 1 / 17 (5.88%) | 3 / 14 (21.43%) |
| occurrences (all) | 2 | 1 | 5 |
| Bone cyst | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Bone pain | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Bursitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Intervertebral disc degeneration | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Muscle contracture | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle fatigue | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 1 / 17 (5.88%) | 2 / 14 (14.29%) |
| occurrences (all) | 1 | 1 | 5 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 1 / 17 (5.88%) | 1 / 14 (7.14%) |
| occurrences (all) | 2 | 1 | 1 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 1 / 17 (5.88%) | 1 / 14 (7.14%) |
| occurrences (all) | 2 | 3 | 1 |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Myalgia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 2 / 14 (14.29%) |
| occurrences (all) | 0 | 3 | 2 |
| Neck pain | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 1 / 17 (5.88%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Osteitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Osteonecrosis | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Osteopenia | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Osteoporosis | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 1 / 17 (5.88%) | 1 / 14 (7.14%) |
| occurrences (all) | 2 | 1 | 1 |
| Pain in jaw | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Trigger finger | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| Angular cheilitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Atypical pneumonia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Ear infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Folliculitis | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Fungal infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Genital herpes | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Gingivitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lung infection | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Mastitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nail infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 2 | 0 | 1 |

| | | | |
|---|---|---|---|
| Neutropenic infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Onychomycosis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Paronychia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash pustular | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 4 | 1 |
| Skin infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|---|---|---|
| Tooth abscess | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tooth infection | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 1 / 17 (5.88%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 1 / 17 (5.88%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 3 / 17 (17.65%) | 1 / 14 (7.14%) |
| occurrences (all) | 2 | 6 | 1 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Wound infection | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 5 / 16 (31.25%) | 6 / 17 (35.29%) | 1 / 14 (7.14%) |
| occurrences (all) | 5 | 6 | 1 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperglycaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 16 (18.75%) | 4 / 17 (23.53%) | 5 / 14 (35.71%) |
| occurrences (all) | 3 | 4 | 6 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Hypermagnesaemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperphosphataemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 2 | 0 | 1 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 2 / 14 (14.29%) |
| occurrences (all) | 0 | 0 | 2 |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 1 / 17 (5.88%) | 3 / 14 (21.43%) |
| occurrences (all) | 1 | 1 | 3 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 1 / 17 (5.88%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 1 | 2 |
| Hyponatraemia | | | |
| subjects affected / exposed | 3 / 16 (18.75%) | 0 / 17 (0.00%) | 2 / 14 (14.29%) |
| occurrences (all) | 3 | 0 | 3 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 5 / 16 (31.25%) | 4 / 17 (23.53%) | 3 / 14 (21.43%) |
| occurrences (all) | 8 | 8 | 5 |
| Increased appetite | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Iron deficiency | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| **Non-serious adverse events** | LEE011(600 mg)+exe(25 mg) exp refractory | All subjects | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 2 / 2 (100.00%) | 132 / 132 (100.00%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 3 / 132 (2.27%) | |
| occurrences (all) | 0 | 3 | |
| Malignant peritoneal neoplasm | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Hot flush | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 10 / 132 (7.58%) | |
| occurrences (all) | 1 | 12 | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 10 / 132 (7.58%) | |
| occurrences (all) | 0 | 10 | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Lymphoedema | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 8 / 132 (6.06%) | |
| occurrences (all) | 0 | 8 | |

| | | | |
|---|---|---|---|
| Phlebitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 20 / 132 (15.15%) | |
| occurrences (all) | 0 | 39 | |
| Axillary pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Chills | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 6 / 132 (4.55%) | |
| occurrences (all) | 1 | 6 | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 43 / 132 (32.58%) | |
| occurrences (all) | 0 | 48 | |
| Feeling cold | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 3 / 132 (2.27%) | |
| occurrences (all) | 0 | 3 | |
| Local swelling | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Malaise | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Mass | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Mucosal dryness | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 3 / 132 (2.27%) | |
| occurrences (all) | 0 | 3 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 4 / 132 (3.03%) | |
| occurrences (all) | 0 | 4 | |
| Oedema | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 27 / 132 (20.45%) | |
| occurrences (all) | 0 | 30 | |
| Pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 5 / 132 (3.79%) | |
| occurrences (all) | 0 | 6 | |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 2 (100.00%) | 20 / 132 (15.15%) | |
| occurrences (all) | 2 | 26 | |
| Xerosis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Immune system disorders | | | |
| Allergy to arthropod bite | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Seasonal allergy | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 2 | |

| | | | |
|---|---|---|---|
| Reproductive system and breast disorders | | | |
| Breast haematoma | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Breast pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Menopausal symptoms | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Pelvic pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Vaginal discharge | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Vulval ulceration | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Vulvovaginal burning sensation | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Vulvovaginal dryness | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 2 | |
| Vulvovaginal pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Allergic sinusitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Cough | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 34 / 132 (25.76%) | |
| occurrences (all) | 1 | 36 | |
| Dysphonia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 2 (0.00%) | 4 / 132 (3.03%) | |
| occurrences (all) | 0 | 5 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 27 / 132 (20.45%) | |
| occurrences (all) | 0 | 29 | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 12 / 132 (9.09%) | |
| occurrences (all) | 0 | 13 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 24 / 132 (18.18%) | |
| occurrences (all) | 0 | 34 | |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Hiccups | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 7 / 132 (5.30%) | |
| occurrences (all) | 0 | 8 | |
| Nasal discharge discolouration | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Nasal dryness | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 10 / 132 (7.58%) | |
| occurrences (all) | 0 | 10 | |
| Painful respiration | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 2 | |
| Paranasal sinus discomfort | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Pharyngeal inflammation | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 3 / 132 (2.27%) | |
| occurrences (all) | 0 | 3 | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 17 / 132 (12.88%) | |
| occurrences (all) | 0 | 19 | |
| Productive cough | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 3 / 132 (2.27%) | |
| occurrences (all) | 0 | 4 | |
| Pulmonary congestion | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Reflux laryngitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 5 / 132 (3.79%) | |
| occurrences (all) | 0 | 7 | |
| Sinus congestion | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Sinus pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Throat irritation | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Upper-airway cough syndrome | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Wheezing | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 4 / 132 (3.03%) | |
| occurrences (all) | 0 | 7 | |
| Delirium | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Depression | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 5 / 132 (3.79%) | |
| occurrences (all) | 0 | 7 | |
| Depressive symptom | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 12 / 132 (9.09%) | |
| occurrences (all) | 0 | 18 | |
| Irritability | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Nightmare | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Restlessness | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Sleep disorder | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Investigations | | | |
| Alanine aminotransferase decreased | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 39 / 132 (29.55%) | |
| occurrences (all) | 0 | 55 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 51 / 132 (38.64%) | |
| occurrences (all) | 0 | 83 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 24 / 132 (18.18%) | |
| occurrences (all) | 0 | 38 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 4 / 132 (3.03%) | |
| occurrences (all) | 0 | 4 | |
| Blood calcium decreased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 6 | |
| Blood chloride decreased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Blood cholesterol increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 9 / 132 (6.82%) | |
| occurrences (all) | 0 | 20 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 15 / 132 (11.36%) | |
| occurrences (all) | 1 | 37 | |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 5 / 132 (3.79%) | |
| occurrences (all) | 0 | 5 | |
| Blood phosphorus decreased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 3 / 132 (2.27%) | |
| occurrences (all) | 0 | 3 | |
| Blood phosphorus increased | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Blood sodium decreased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Blood thyroid stimulating hormone decreased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 2 | |
| Blood thyroid stimulating hormone increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 4 | |
| Blood triglycerides increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 3 / 132 (2.27%) | |
| occurrences (all) | 0 | 5 | |
| Blood urea decreased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 5 / 132 (3.79%) | |
| occurrences (all) | 0 | 6 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 13 / 132 (9.85%) | |
| occurrences (all) | 0 | 16 | |
| Haematocrit | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 3 / 132 (2.27%) | |
| occurrences (all) | 0 | 3 | |
| International normalised ratio increased | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 34 / 132 (25.76%) | |
| occurrences (all) | 0 | 70 | |
| Lymphocyte count increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 64 / 132 (48.48%) | |
| occurrences (all) | 1 | 171 | |
| Neutrophil count increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 24 / 132 (18.18%) | |
| occurrences (all) | 0 | 36 | |
| Platelet count increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Thyroxine decreased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Thyroxine free increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Tri-iodothyronine increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 11 / 132 (8.33%) | |
| occurrences (all) | 0 | 13 | |
| Weight increased | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 2 (0.00%) | 4 / 132 (3.03%) | |
| occurrences (all) | 0 | 5 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 60 / 132 (45.45%) | |
| occurrences (all) | 0 | 109 | |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Contusion | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Fall | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Muscle rupture | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Radiation skin injury | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Wound | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Wound secretion | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Wrist fracture | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Diastolic dysfunction | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Palpitations | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 3 / 132 (2.27%) | |
| occurrences (all) | 0 | 3 | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 3 / 132 (2.27%) | |
| occurrences (all) | 0 | 3 | |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Nervous system disorders | | | |
| Amnesia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Aphonia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Ataxia | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Cognitive disorder | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 6 / 132 (4.55%) | |
| occurrences (all) | 0 | 6 | |
| Dysaesthesia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 18 / 132 (13.64%) | |
| occurrences (all) | 0 | 18 | |
| Headache | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 27 / 132 (20.45%) | |
| occurrences (all) | 1 | 39 | |
| Hyperaesthesia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Intracranial aneurysm | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Migraine | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Peripheral sensory neuropathy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Restless legs syndrome | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Sciatica | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Tremor | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 72 / 132 (54.55%) | |
| occurrences (all) | 0 | 128 | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 8 / 132 (6.06%) | |
| occurrences (all) | 0 | 8 | |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 23 / 132 (17.42%) | |
| occurrences (all) | 0 | 33 | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 67 / 132 (50.76%) | |
| occurrences (all) | 0 | 132 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 38 / 132 (28.79%) | |
| occurrences (all) | 0 | 84 | |
| Ear and labyrinth disorders | | | |
| Cerumen impaction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Ear discomfort | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Ear pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Chalazion | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Dry eye | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 4 / 132 (3.03%) | |
| occurrences (all) | 0 | 4 | |
| Eye pruritus | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Eyelid oedema | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 3 / 132 (2.27%) | |
| occurrences (all) | 0 | 3 | |
| Lacrimation increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 3 / 132 (2.27%) | |
| occurrences (all) | 0 | 3 | |
| Myopia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 3 / 132 (2.27%) | |
| occurrences (all) | 0 | 4 | |

| | | | |
|---|---|---|---|
| Visual impairment | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 3 / 132 (2.27%) | |
| occurrences (all) | 0 | 3 | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 11 / 132 (8.33%) | |
| occurrences (all) | 0 | 17 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 7 / 132 (5.30%) | |
| occurrences (all) | 0 | 10 | |
| Anal haemorrhage | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Anal incontinence | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Aphthous ulcer | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 4 / 132 (3.03%) | |
| occurrences (all) | 0 | 5 | |
| Ascites | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 3 / 132 (2.27%) | |
| occurrences (all) | 0 | 7 | |
| Atrophic glossitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Cheilitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Colitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 27 / 132 (20.45%) | |
| occurrences (all) | 1 | 34 | |
| Dental caries | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 37 / 132 (28.03%) | |
| occurrences (all) | 0 | 54 | |
| Dry mouth | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 10 / 132 (7.58%) | |
| occurrences (all) | 0 | 10 | |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 14 / 132 (10.61%) | |
| occurrences (all) | 1 | 15 | |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Eructation | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Flatulence | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 3 / 132 (2.27%) | |
| occurrences (all) | 0 | 3 | |
| Food poisoning | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 10 / 132 (7.58%) | |
| occurrences (all) | 0 | 10 | |
| Gingival pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Gingival ulceration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 5 / 132 (3.79%) | |
| occurrences (all) | 0 | 7 | |
| Lip oedema | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 2 | |
| Lip swelling | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Lip ulceration | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 4 / 132 (3.03%) | |
| occurrences (all) | 0 | 9 | |
| Nausea | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 48 / 132 (36.36%) | |
| occurrences (all) | 1 | 65 | |
| Odynophagia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 4 / 132 (3.03%) | |
| occurrences (all) | 0 | 5 | |
| Oral pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Steatorrhoea | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Stomatitis | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 2 (0.00%) | 72 / 132 (54.55%) | |
| occurrences (all) | 0 | 126 | |
| Toothache | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 33 / 132 (25.00%) | |
| occurrences (all) | 1 | 51 | |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Hepatic necrosis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Hepatocellular injury | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 4 / 132 (3.03%) | |
| occurrences (all) | 0 | 4 | |
| Hepatomegaly | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Alopecia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 10 / 132 (7.58%) | |
| occurrences (all) | 0 | 10 | |
| Angioedema | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 4 | |
| Dermal cyst | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 2 | |
| Dermatitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 3 / 132 (2.27%) | |
| occurrences (all) | 0 | 3 | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 4 / 132 (3.03%) | |
| occurrences (all) | 0 | 4 | |
| Dry skin | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 10 / 132 (7.58%) | |
| occurrences (all) | 0 | 12 | |
| Ecchymosis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Eczema | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Erythema | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 4 / 132 (3.03%) | |
| occurrences (all) | 0 | 4 | |
| Hair texture abnormal | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Madarosis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Nail discolouration | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Nail disorder | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 7 / 132 (5.30%) | |
| occurrences (all) | 0 | 8 | |
| Nail dystrophy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Nail toxicity | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Night sweats | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 3 / 132 (2.27%) | |
| occurrences (all) | 0 | 3 | |
| Onychoclasis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Onychomalacia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Pain of skin | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Palmoplantar keratoderma | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Pigmentation disorder | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Pruritus | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 8 / 132 (6.06%) | |
| occurrences (all) | 0 | 8 | |
| Rash | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 28 / 132 (21.21%) | |
| occurrences (all) | 0 | 34 | |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |

| | | | |
|---|---|---|---|
| Rash macular | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 3 | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 7 / 132 (5.30%) | |
| occurrences (all) | 0 | 9 | |
| Rash vesicular | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 2 | |
| Rosacea | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Skin hyperpigmentation | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Skin hypopigmentation | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Skin lesion | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Skin mass | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Skin toxicity | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Yellow skin | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 4 / 132 (3.03%) | |
| occurrences (all) | 1 | 4 | |
| Leukocyturia | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Micturition urgency | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 3 | |
| Proteinuria | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 3 / 132 (2.27%) | |
| occurrences (all) | 0 | 3 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 22 / 132 (16.67%) | |
| occurrences (all) | 0 | 27 | |
| Arthropathy | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Back pain | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 16 / 132 (12.12%) | |
| occurrences (all) | 1 | 21 | |
| Bone cyst | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 9 / 132 (6.82%) | |
| occurrences (all) | 0 | 9 | |
| Bursitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Intervertebral disc degeneration | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Muscle contracture | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Muscle fatigue | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 7 / 132 (5.30%) | |
| occurrences (all) | 0 | 10 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 7 / 132 (5.30%) | |
| occurrences (all) | 0 | 9 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 8 / 132 (6.06%) | |
| occurrences (all) | 0 | 10 | |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 8 / 132 (6.06%) | |
| occurrences (all) | 0 | 10 | |
| Neck pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 4 / 132 (3.03%) | |
| occurrences (all) | 0 | 4 | |
| Osteitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Osteopenia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Osteoporosis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 9 / 132 (6.82%) | |
| occurrences (all) | 0 | 13 | |
| Pain in jaw | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Trigger finger | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Infections and infestations | | | |
| Angular cheilitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 2 | |
| Atypical pneumonia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 3 / 132 (2.27%) | |
| occurrences (all) | 0 | 5 | |

| | | | |
|---|---|---|---|
| Cellulitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 2 | |
| Cystitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Device related infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Ear infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 2 | |
| Folliculitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 3 / 132 (2.27%) | |
| occurrences (all) | 0 | 3 | |
| Fungal infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |

| | | | |
|---|---|---|---|
| Gastrointestinal infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Genital herpes | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Gingivitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 6 | |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Lung infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Mastitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Nail infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 3 / 132 (2.27%) | |
| occurrences (all) | 0 | 4 | |
| Neutropenic infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Onychomycosis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |

| | | | |
|---|---|---|---|
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Paronychia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 3 / 132 (2.27%) | |
| occurrences (all) | 0 | 4 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 6 / 132 (4.55%) | |
| occurrences (all) | 0 | 6 | |
| Rash pustular | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 3 | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 3 | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 6 / 132 (4.55%) | |
| occurrences (all) | 0 | 9 | |
| Skin infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Tooth abscess | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |

| | | | |
|---|---|---|---|
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 7 / 132 (5.30%) | |
| occurrences (all) | 0 | 15 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 10 / 132 (7.58%) | |
| occurrences (all) | 0 | 14 | |
| Viral infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 7 / 132 (5.30%) | |
| occurrences (all) | 0 | 9 | |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Wound infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 28 / 132 (21.21%) | |
| occurrences (all) | 0 | 31 | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 36 / 132 (27.27%) | |
| occurrences (all) | 0 | 51 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 6 / 132 (4.55%) | |
| occurrences (all) | 0 | 6 | |
| Hypermagnesaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Hyperphosphataemia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 2 | |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 132 (1.52%) | |
| occurrences (all) | 0 | 3 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 4 / 132 (3.03%) | |
| occurrences (all) | 0 | 4 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 10 / 132 (7.58%) | |
| occurrences (all) | 0 | 14 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 4 / 132 (3.03%) | |
| occurrences (all) | 0 | 5 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 16 / 132 (12.12%) | |
| occurrences (all) | 0 | 18 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 12 / 132 (9.09%) | |
| occurrences (all) | 0 | 20 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 17 / 132 (12.88%) | |
| occurrences (all) | 0 | 20 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 34 / 132 (25.76%) | |
| occurrences (all) | 0 | 60 | |
| Increased appetite | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 132 (0.76%) | |
| occurrences (all) | 0 | 1 | |
| Iron deficiency | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 3 / 132 (2.27%) | |
| occurrences (all) | 0 | 3 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 20 December 2013 | Addition of a cohort of patients during dose escalation to allow a preliminary exploration of the PK and safety of ribociclib when given with food in combination with everolimus and exemestane.<br>Optional biopsies for both pharmacodynamics and for the study of mechanisms of tumor resistance. Extensive examination of the genetic alterations of the tumors treated in the pivotal study of everolimus and exemestane indicated that CDK4/6 activity could be responsible for resistance to hormonal plus mTOR treatment in a number of patients. In order to test this hypothesis as well as to correlate efficacy and resistance with inhibition of the CDK4/6 and mTOR pathways, optional paired biopsies and a biopsy at the time of disease progression were to be performed, if accessible and medically feasible. The ontreatment biopsies measure suppression of the mTOR and CDK 4/6 pathways.<br>Addition of guidelines regarding management of hepatitis B and C infections. Reactivation of hepatitis B (HBV) had been observed in patients with cancer receiving chemotherapy. Sporadic cases of hepatitis B reactivation were also seen in this setting with everolimus. Use of antiviral treatments during anti-cancer therapy had shown<br>to reduce the risk of hepatitis B virus reactivation and associated morbidity and mortality. |
| 26 October 2015 | The study design was changed to replace the randomized Phase II part with an expansion part in approximately 45 patients. Additional changes to the protocol include recommendations for dose modification, safety monitoring, concomitant medications, PK sampling, biomarker assessments, inclusion/exclusion criteria. Everolimus exposure increased 2- to 4-fold in the presence of ribociclib. In the expansion triplet combination groups, dose modification guidelines were updated. D Since prolongation of the QT interval is one of the potential toxicities for ribociclib, the eligibility criteria related to cardiac function were modified. Updates were made to the dose adjustment guidelines for QTcF prolongation, hepatobiliary toxicities, hyperglycemia, nausea, emesis and diarrhea, in order to enhance and clarify safety monitoring of patients. D however, for the expansion part of the study both ER-positive and/or PR-positive (HR-positive) breast cancer patients were included in order to be aligned with the overall development strategy for ribociclib. D No clinically significant thyroid adverse events have been reported in ribociclib clinical trials so far. The risk to thyroid gland was removed from the reference safety information for the compound. D Potential risk of hepatic toxicity was observed in patients treated with ribociclib. Updates to monitoring and dose adjustment guidelines for hepatobiliary toxicities including ALT, AST, and TBIL were added. D Additional blood collections for exploratory liver biomarkers to further characterize potential drug-induced liver injury and for circulating tumor DNA to explore molecular alterations were added. D The lists of prohibited concomitant medications were updated. D Survival follow-up was not needed since the Phase II part of the study was being removed with this amendment. |

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| 04 January 2017 | The RP2D for the triplet combination was determined to be ribociclib 300 mg (once daily, 3 weeks on/1 week off in a 4 week cycle) + everolimus 2.5 mg (once daily) + exemestane 25 mg (once daily) taken with food. Enrollment to the first two expansion groups of the triplet combination (Group 1: CDK4/6i naive patients; Group 2: CDK4/6i refractory patients) had been completed with 16 patients treated in Group 1 and 17 in Group 2 on RP2D.<br>The RP2D for the doublet combination had been confirmed to be ribociclib 600 mg (once daily, 3 weeks on/1 week off in a 4 week cycle) + exemestane 25 mg (once daily) taken without food.<br>Enrollment to the expansion group of the doublet combination (Group 3: CDK4/6i refractory patients excluding patients treated with prior ribociclib) had been completed with 2 patients treated in Group 3 on RP2D.<br>The purpose of this amendment was to close further enrollment to the expansion Group 3 (doublet combination) due to the Sponsor’s decision based on another ongoing study CLEE011XUS18T addressing the same question of the role of CDK4/6 inhibition after failure of prior CDK4/6 inhibitor treatment. This decision was not due to safety reasons. On 14-Oct-2016, an Investigator letter was released to inform Investigators about the closure of enrollment to Group 3. Patients who had been allocated by 21-Oct-2016 were allowed to be screened and enrolled. All patients enrolled in the study were to continue on treatment and post-treatment follow-up until they experienced disease progression or withdrew for other reasons outlined in the protocol. This amendment outlined the reduction in scope of the expansion part of the study and the decrease in the number of patients to be enrolled in Group 3.<br>With this amendment, potential interim analyses had been added to allow early analysis of the data as needed for health authority submission purposes. |

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| 06 August 2018 | The dose adjustment and management recommendations for QTcF prolongation weer<br>updated. Analyses of preclinical and clinical data with ribociclib demonstrated that ribociclib prolongs the QT interval in a concentration-dependent manner. Moreover, based<br>on the ribociclib exposure-ΔQTcF relationship and the clinical experience in studies CLEE011A2301, CLEE011F2301 and CLEE011E2301, ribociclib dose reduction is an effective strategy for managing ribociclib therapy in patients experiencing QTcF prolongation. Therefore, in order to reduce the risk of subsequent QTcF prolongation in<br>patients experiencing a QTcF between 481-500 msec, ribociclib dosing was to be reduced<br>by 1 dose level with the first occurrence of QTcF ≥ 481 msec.<br>The prohibited concomitant medications were updated according to the Oncology Clinical<br>Pharmacology guidance, drug-drug interaction and co-medication considerations (v07,<br>release date: Jan 2018). Updated the withdrawal of consent language to align with the new Global Data Protection<br>Requirements.<br>Reduced the frequency of tumor evaluations as ongoing patients had been on-treatment for<br>more than 18 months. For dose escalation part, tumor evaluations were to be performed<br>within ± 7 days of Day 1 of Cycles 3, 5, and 7. Subsequent evaluations were to be performed<br>within ± 7 days of Day 1 of every fourth Cycle untill 36 months, then as clinically indicated<br>or sooner if there is clinical evidence of disease progression. For the dose expansion part,<br>tumor evaluations were to be performed every 8 weeks (within ± 7 days of Day 1 of Cycles<br>3, 5, 7, 9, 11 and so on) during the first 18 months. Subsequent evaluations were to be<br>performed every 12 weeks (within ±7 days) until 36 months, then as clinically indicated or<br>sooner if there was clinical evidence of disease progression. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

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| Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results. |

Notes: