



Clinical trial results:

An open-label, multicenter, Phase I/II dose escalation study of oral GW572016 in combination with docetaxel (Taxotere) plus trastuzumab (Herceptin) in subjects previously untreated for ErbB2-overexpressing metastatic breast cancer

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2005-000846-35 |
| Trial protocol | IE |
| Global end of trial date | 22 June 2022 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 20 March 2023 |
| First version publication date | 20 March 2023 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | EGF100161 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|------------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00251433 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Novartis: CLAP016A2101 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | Novartis Campus, Basel, Switzerland, 4002 |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com |
| 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 | 22 June 2022 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|--------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 22 June 2022 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The purpose of this Phase I/II dose escalation study, LAP016A2101/EGF100161, was to evaluate the tumor response rate, as well as the safety, tolerability, and efficacy of this combination in subjects with previously untreated metastatic breast cancer (MBC) whose tumors over-express Human epidermal growth factor receptor 2 (HER2)/ epidermal growth factor receptor 2 (ErbB2) receptors.

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 | 26 September 2005 |
| 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 | France: 22 |
| Country: Number of subjects enrolled | Ireland: 28 |
| Country: Number of subjects enrolled | United States: 3 |
| Worldwide total number of subjects | 53 |
| EEA total number of subjects | 50 |

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) | 49 |

| | |
|---------------------|---|
| From 65 to 84 years | 4 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study was conducted in 5 centers in 3 countries: France (2), Ireland (2), United States (1)

Period 1

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

Arms

| | |
|------------------------------|-----------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Phase I: Dose Level 0 |

Arm description:

Lapatinib 500 mg once daily (OD) with Docetaxel 60 mg/m² once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).

| | |
|--|----------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Lapatinib |
| Investigational medicinal product code | |
| Other name | GW572016 |
| Pharmaceutical forms | Film-coated tablet, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

500mg OD

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

Dosage and administration details:

60mg/m² q3weeks

| | |
|--|---|
| Investigational medicinal product name | Trastuzumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for infusion, Powder for concentrate, Powder for concentrate for solution for infusion, Powder for concentrate for solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Loading dose: 4mg/kg during first week, 2mg/kg once a week

| | |
|------------------|-----------------------|
| Arm title | Phase I: Dose Level 1 |
|------------------|-----------------------|

Arm description:

Lapatinib 500 mg once daily (OD) with Docetaxel 75 mg/m² once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).

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

| | |
|---|---|
| Investigational medicinal product name | Lapatinib |
| Investigational medicinal product code | |
| Other name | GW572016 |
| Pharmaceutical forms | Film-coated tablet, Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: 500mg OD | |
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection, Solution for injection/infusion, Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: 75mg/m2 q3weeks | |
| Investigational medicinal product name | Trastuzumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for infusion, Powder for concentrate, Powder for concentrate for solution for infusion, Powder for concentrate for solution for injection/infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: Loading dose: 4mg/kg during first week, 2mg/kg once a week | |
| Arm title | Phase I: Dose Level 1A |
| Arm description: Lapatinib 750 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week). | |
| Arm type | Experimental |
| Investigational medicinal product name | Lapatinib |
| Investigational medicinal product code | |
| Other name | GW572016 |
| Pharmaceutical forms | Film-coated tablet, Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: 750mg OD | |
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection, Solution for injection/infusion, Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: 75mg/m2 q3weeks | |
| Investigational medicinal product name | Trastuzumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for infusion, Powder for concentrate, Powder for concentrate for solution for infusion, Powder for concentrate for solution for injection/infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: Loading dose: 4mg/kg during first week, 2mg/kg once a week | |

| | |
|--|---|
| Arm title | Phase I: Dose Level 1B |
| Arm description: | |
| Lapatinib 1000 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week). | |
| Arm type | Experimental |
| Investigational medicinal product name | Lapatinib |
| Investigational medicinal product code | |
| Other name | GW572016 |
| Pharmaceutical forms | Film-coated tablet, Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 1000mg OD | |
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection, Solution for injection/infusion, Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 75mg/m2 q3weeks | |
| Investigational medicinal product name | Trastuzumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for infusion, Powder for concentrate, Powder for concentrate for solution for infusion, Powder for concentrate for solution for injection/infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Loading dose: 4mg/kg during first week, 2mg/kg once a week | |
| Arm title | Phase I: Dose Level 1C |
| Arm description: | |
| Lapatinib 1250 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week). | |
| Arm type | Experimental |
| Investigational medicinal product name | Lapatinib |
| Investigational medicinal product code | |
| Other name | GW572016 |
| Pharmaceutical forms | Film-coated tablet, Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 1250mg OD | |
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection, Solution for injection/infusion, Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 75mg/m2 q3weeks | |
| Investigational medicinal product name | Trastuzumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for infusion, Powder for concentrate, Powder for |

| | |
|--|---|
| | concentrate for solution for infusion, Powder for concentrate for solution for injection/infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Loading dose: 4mg/kg during first week, 2mg/kg once a week | |
| Arm title | Phase I: Dose Level 1D |
| Arm description: | |
| Lapatinib 1500 mg once daily (OD) with Docetaxel 75 mg/m ² once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week). | |
| Arm type | Experimental |
| Investigational medicinal product name | Lapatinib |
| Investigational medicinal product code | |
| Other name | GW572016 |
| Pharmaceutical forms | Film-coated tablet, Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 1500mg OD | |
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection, Solution for injection/infusion, Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 75mg/m ² q3weeks | |
| Investigational medicinal product name | Trastuzumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for infusion, Powder for concentrate, Powder for concentrate for solution for infusion, Powder for concentrate for solution for injection/infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Loading dose: 4mg/kg during first week, 2mg/kg once a week | |
| Arm title | Phase I: Dose Level 2 |
| Arm description: | |
| Lapatinib 500 mg once daily (OD) with Docetaxel 100 mg/m ² once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week). | |
| Arm type | Experimental |
| Investigational medicinal product name | Lapatinib |
| Investigational medicinal product code | |
| Other name | GW572016 |
| Pharmaceutical forms | Film-coated tablet, Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 500mg OD | |
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection, Solution for injection/infusion, Solution for infusion |
| Routes of administration | Intravenous use |

| | |
|---|---|
| Dosage and administration details: 100mg/m2 q3weeks | |
| Investigational medicinal product name | Trastuzumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for infusion, Powder for concentrate, Powder for concentrate for solution for infusion, Powder for concentrate for solution for injection/infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: Loading dose: 4mg/kg during first week, 2mg/kg once a week | |
| Arm title | Phase I: Dose Level 3 |
| Arm description: Lapatinib 750 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week). | |
| Arm type | Experimental |
| Investigational medicinal product name | Lapatinib |
| Investigational medicinal product code | |
| Other name | GW572016 |
| Pharmaceutical forms | Film-coated tablet, Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: 750mg OD | |
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection, Solution for injection/infusion, Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: 100mg/m2 q3weeks | |
| Investigational medicinal product name | Trastuzumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for infusion, Powder for concentrate, Powder for concentrate for solution for infusion, Powder for concentrate for solution for injection/infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: Loading dose: 4mg/kg during first week, 2mg/kg once a week | |
| Arm title | Phase I: Dose Level 4 |
| Arm description: Lapatinib 1000 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week). | |
| Arm type | Experimental |
| Investigational medicinal product name | Lapatinib |
| Investigational medicinal product code | |
| Other name | GW572016 |
| Pharmaceutical forms | Film-coated tablet, Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: 1000mg OD | |

| | |
|---|---|
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection, Solution for injection/infusion, Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: 100mg/m2 q3weeks | |
| Investigational medicinal product name | Trastuzumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for infusion, Powder for concentrate, Powder for concentrate for solution for infusion, Powder for concentrate for solution for injection/infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: Loading dose: 4mg/kg during first week, 2mg/kg once a week | |
| Arm title | Phase I: Dose Level 5 |
| Arm description: Lapatinib 1250 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week). | |
| Arm type | Experimental |
| Investigational medicinal product name | Lapatinib |
| Investigational medicinal product code | |
| Other name | GW572016 |
| Pharmaceutical forms | Film-coated tablet, Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: 1250mg OD | |
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection, Solution for injection/infusion, Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: 100mg/m2 q3weeks | |
| Investigational medicinal product name | Trastuzumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for infusion, Powder for concentrate, Powder for concentrate for solution for infusion, Powder for concentrate for solution for injection/infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: Loading dose: 4mg/kg during first week, 2mg/kg once a week | |

| Number of subjects in period 1 | Phase I: Dose Level 0 | Phase I: Dose Level 1 | Phase I: Dose Level 1A |
|---|-----------------------|-----------------------|------------------------|
| Started | 6 | 3 | 12 |
| Completed | 6 | 1 | 5 |
| Not completed | 0 | 2 | 7 |
| Adverse event, non-fatal | - | - | - |
| Other pre-specified reasons defined in protocol | - | 2 | 7 |

| Number of subjects in period 1 | Phase I: Dose Level 1B | Phase I: Dose Level 1C | Phase I: Dose Level 1D |
|---|------------------------|------------------------|------------------------|
| Started | 5 | 4 | 3 |
| Completed | 3 | 1 | 1 |
| Not completed | 2 | 3 | 2 |
| Adverse event, non-fatal | - | 1 | - |
| Other pre-specified reasons defined in protocol | 2 | 2 | 2 |

| Number of subjects in period 1 | Phase I: Dose Level 2 | Phase I: Dose Level 3 | Phase I: Dose Level 4 |
|---|-----------------------|-----------------------|-----------------------|
| Started | 5 | 6 | 6 |
| Completed | 4 | 3 | 0 |
| Not completed | 1 | 3 | 6 |
| Adverse event, non-fatal | 1 | 1 | 1 |
| Other pre-specified reasons defined in protocol | - | 2 | 5 |

| Number of subjects in period 1 | Phase I: Dose Level 5 |
|---|-----------------------|
| Started | 3 |
| Completed | 2 |
| Not completed | 1 |
| Adverse event, non-fatal | - |
| Other pre-specified reasons defined in protocol | 1 |

Baseline characteristics

Reporting groups

| | |
|---|------------------------|
| Reporting group title | Phase I: Dose Level 0 |
| Reporting group description: Lapatinib 500 mg once daily (OD) with Docetaxel 60 mg/m ² once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week). | |
| Reporting group title | Phase I: Dose Level 1 |
| Reporting group description: Lapatinib 500 mg once daily (OD) with Docetaxel 75 mg/m ² once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week). | |
| Reporting group title | Phase I: Dose Level 1A |
| Reporting group description: Lapatinib 750 mg once daily (OD) with Docetaxel 75 mg/m ² once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week). | |
| Reporting group title | Phase I: Dose Level 1B |
| Reporting group description: Lapatinib 1000 mg once daily (OD) with Docetaxel 75 mg/m ² once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week). | |
| Reporting group title | Phase I: Dose Level 1C |
| Reporting group description: Lapatinib 1250 mg once daily (OD) with Docetaxel 75 mg/m ² once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week). | |
| Reporting group title | Phase I: Dose Level 1D |
| Reporting group description: Lapatinib 1500 mg once daily (OD) with Docetaxel 75 mg/m ² once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week). | |
| Reporting group title | Phase I: Dose Level 2 |
| Reporting group description: Lapatinib 500 mg once daily (OD) with Docetaxel 100 mg/m ² once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week). | |
| Reporting group title | Phase I: Dose Level 3 |
| Reporting group description: Lapatinib 750 mg once daily (OD) with Docetaxel 100 mg/m ² once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week). | |
| Reporting group title | Phase I: Dose Level 4 |
| Reporting group description: Lapatinib 1000 mg once daily (OD) with Docetaxel 100 mg/m ² once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week). | |
| Reporting group title | Phase I: Dose Level 5 |
| Reporting group description: Lapatinib 1250 mg once daily (OD) with Docetaxel 100 mg/m ² once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week). | |

| Reporting group values | Phase I: Dose Level 0 | Phase I: Dose Level 1 | Phase I: Dose Level 1A |
|--|-----------------------|-----------------------|------------------------|
| Number of subjects | 6 | 3 | 12 |
| Age categorical | | | |
| 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) | 6 | 3 | 11 |
| From 65-84 years | 0 | 0 | 1 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | 45.2 | 49.7 | 46.2 |
| standard deviation | ± 11.92 | ± 7.51 | ± 9.43 |
| Sex: Female, Male | | | |
| Units: Participants | | | |
| Female | 6 | 3 | 12 |
| Male | 0 | 0 | 0 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| White | 6 | 3 | 12 |
| Asian | 0 | 0 | 0 |

| Reporting group values | Phase I: Dose Level 1B | Phase I: Dose Level 1C | Phase I: Dose Level 1D |
|--|------------------------|------------------------|------------------------|
| Number of subjects | 5 | 4 | 3 |
| Age categorical | | | |
| 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) | 4 | 4 | 3 |
| From 65-84 years | 1 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | 54.4 | 44.0 | 53.0 |
| standard deviation | ± 12.74 | ± 10.03 | ± 7.00 |
| Sex: Female, Male | | | |
| Units: Participants | | | |
| Female | 5 | 4 | 3 |
| Male | 0 | 0 | 0 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| White | 5 | 4 | 3 |
| Asian | 0 | 0 | 0 |

| Reporting group values | Phase I: Dose Level 2 | Phase I: Dose Level 3 | Phase I: Dose Level 4 |
|------------------------|-----------------------|-----------------------|-----------------------|
| Number of subjects | 5 | 6 | 6 |

| | | | |
|---|---------|--------|---------|
| Age categorical 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) | 5 | 6 | 4 |
| From 65-84 years | 0 | 0 | 2 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: Years | | | |
| arithmetic mean | 50.0 | 53.7 | 55.8 |
| standard deviation | ± 10.70 | ± 8.04 | ± 10.93 |
| Sex: Female, Male Units: Participants | | | |
| Female | 5 | 6 | 6 |
| Male | 0 | 0 | 0 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| White | 5 | 5 | 6 |
| Asian | 0 | 1 | 0 |

| Reporting group values | Phase I: Dose Level 5 | Total | |
|---|--------------------------|-------|--|
| Number of subjects | 3 | 53 | |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 3 | 49 | |
| From 65-84 years | 0 | 4 | |
| 85 years and over | 0 | 0 | |
| Age Continuous Units: Years | | | |
| arithmetic mean | 43.3 | - | |
| standard deviation | ± 11.02 | - | |
| Sex: Female, Male Units: Participants | | | |
| Female | 3 | 53 | |
| Male | 0 | 0 | |
| Race/Ethnicity, Customized Units: Subjects | | | |
| White | 3 | 52 | |

| | | | |
|-------|---|---|--|
| Asian | 0 | 1 | |
|-------|---|---|--|

End points

End points reporting groups

| | |
|---|------------------------|
| Reporting group title | Phase I: Dose Level 0 |
| Reporting group description: Lapatinib 500 mg once daily (OD) with Docetaxel 60 mg/m ² once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week). | |
| Reporting group title | Phase I: Dose Level 1 |
| Reporting group description: Lapatinib 500 mg once daily (OD) with Docetaxel 75 mg/m ² once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week). | |
| Reporting group title | Phase I: Dose Level 1A |
| Reporting group description: Lapatinib 750 mg once daily (OD) with Docetaxel 75 mg/m ² once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week). | |
| Reporting group title | Phase I: Dose Level 1B |
| Reporting group description: Lapatinib 1000 mg once daily (OD) with Docetaxel 75 mg/m ² once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week). | |
| Reporting group title | Phase I: Dose Level 1C |
| Reporting group description: Lapatinib 1250 mg once daily (OD) with Docetaxel 75 mg/m ² once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week). | |
| Reporting group title | Phase I: Dose Level 1D |
| Reporting group description: Lapatinib 1500 mg once daily (OD) with Docetaxel 75 mg/m ² once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week). | |
| Reporting group title | Phase I: Dose Level 2 |
| Reporting group description: Lapatinib 500 mg once daily (OD) with Docetaxel 100 mg/m ² once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week). | |
| Reporting group title | Phase I: Dose Level 3 |
| Reporting group description: Lapatinib 750 mg once daily (OD) with Docetaxel 100 mg/m ² once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week). | |
| Reporting group title | Phase I: Dose Level 4 |
| Reporting group description: Lapatinib 1000 mg once daily (OD) with Docetaxel 100 mg/m ² once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week). | |
| Reporting group title | Phase I: Dose Level 5 |
| Reporting group description: Lapatinib 1250 mg once daily (OD) with Docetaxel 100 mg/m ² once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week). | |

Primary: Phase I: Determination of the optimally tolerated regimen (OTR)

| | |
|-----------------|--|
| End point title | Phase I: Determination of the optimally tolerated regimen (OTR) ^[1] |
|-----------------|--|

End point description:

Enrollment to the Phase I part of the study was halted on 04 August 2010 after 3 subjects were enrolled into the cohort dose level 5 (lapatinib 1250 mg) that was opened for enrollment on 23 November 2009 and completed enrollment by 03 June 2010. No subjects experienced a DLT at this dose level, thus the optimally tolerated regimen (OTR) dose regimen of lapatinib with the higher docetaxel dose (100 mg/m²) was not determined. The Phase II part of the study did not proceed.

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

End point timeframe:

From first initiated treatment on 19-Jan-2006 to the data cut-off date for primary CSR on 9 Dec 2009, assessed approximately up to 4 years.

Notes:

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

Justification: Only descriptive analysis performed

| End point values | Phase I: Dose Level 0 | Phase I: Dose Level 1 | Phase I: Dose Level 1A | Phase I: Dose Level 1B |
|-----------------------------|-----------------------|-----------------------|------------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 0 ^[2] | 0 ^[3] | 0 ^[4] | 0 ^[5] |
| Units: Participants | | | | |

Notes:

[2] - Not estimable due to early termination of the study

[3] - Not estimable due to early termination of the study

[4] - Not estimable due to early termination of the study

[5] - Not estimable due to early termination of the study

| End point values | Phase I: Dose Level 1C | Phase I: Dose Level 1D | Phase I: Dose Level 2 | Phase I: Dose Level 3 |
|-----------------------------|------------------------|------------------------|-----------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 0 ^[6] | 0 ^[7] | 0 ^[8] | 0 ^[9] |
| Units: Participants | | | | |

Notes:

[6] - Not estimable due to early termination of the study

[7] - Not estimable due to early termination of the study

[8] - Not estimable due to early termination of the study

[9] - Not estimable due to early termination of the study

| End point values | Phase I: Dose Level 4 | Phase I: Dose Level 5 | | |
|-----------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[10] | 0 ^[11] | | |
| Units: Participants | | | | |

Notes:

[10] - Not estimable due to early termination of the study

[11] - Not estimable due to early termination of the study

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I: Overall Response Rate (ORR)

| | |
|-----------------|--------------------------------------|
| End point title | Phase I: Overall Response Rate (ORR) |
|-----------------|--------------------------------------|

End point description:

Overall response rate (ORR) was defined as the percentage of subjects achieving either a confirmed complete response (CR) or partial response (PR). This was based on confirmed responses from the Investigator assessment of best overall response (the best response from the start of the treatment until disease progression/recurrence).

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

End point timeframe:

From first initiated treatment on 19-Jan-2006 to the data cut-off date for primary CSR on 9 Dec 2009, assessed approximately up to 4 years.

| End point values | Phase I: Dose Level 0 | Phase I: Dose Level 1 | Phase I: Dose Level 1A | Phase I: Dose Level 1B |
|--|-----------------------|-----------------------|------------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 6 | 2 | 10 | 4 |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | | | | |
| Best Response with Bone Scan Confirmation | 67 (22.3 to 95.7) | 50 (1.3 to 98.7) | 30 (6.7 to 65.2) | 999 (999 to 999) |
| Best Response without Bone Scan Confirmation | 67 (22.3 to 95.7) | 100 (15.8 to 100.0) | 60 (26.2 to 87.8) | 25 (0.6 to 80.6) |

| End point values | Phase I: Dose Level 1C | Phase I: Dose Level 1D | Phase I: Dose Level 2 | Phase I: Dose Level 3 |
|--|------------------------|------------------------|-----------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 3 | 3 | 5 |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | | | | |
| Best Response with Bone Scan Confirmation | 67 (9.4 to 99.2) | 33 (0.8 to 90.6) | 33 (0.8 to 90.6) | 40 (5.3 to 85.3) |
| Best Response without Bone Scan Confirmation | 100 (29.2 to 100.0) | 67 (9.4 to 99.2) | 33 (0.8 to 90.6) | 100 (47.8 to 100.0) |

| End point values | Phase I: Dose Level 4 | Phase I: Dose Level 5 | | |
|--|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 | 3 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | | | | |
| Best Response with Bone Scan Confirmation | 33 (4.3 to 77.7) | 999 (999 to 999) | | |
| Best Response without Bone Scan Confirmation | 83 (35.9 to 99.6) | 67 (9.4 to 99.2) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I: Duration of Response (DoR)

| | |
|-----------------|-------------------------------------|
| End point title | Phase I: Duration of Response (DoR) |
|-----------------|-------------------------------------|

End point description:

For subjects who did show CR or PR, duration of response was defined to be the time from first documented evidence of PR or CR until the first documented sign of disease progression or death due to breast cancer. Disease progression was based on the assessments from the blinded, independent review of objective evidence (e.g., radiological scans and medical photographs). For subjects who did not

progress, or die, duration of response was censored at the time of the last independently-assessed radiological scan preceding the initiation of any alternative anti-cancer therapy.

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

End point timeframe:

From first initiated treatment on 19-Jan-2006 to the data cut-off date for primary CSR on 9 Dec 2009, assessed approximately up to 4 years.

| End point values | Phase I: Dose Level 0 | Phase I: Dose Level 1 | Phase I: Dose Level 1A | Phase I: Dose Level 1B |
|---------------------------------------|-----------------------|------------------------|------------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 2 | 6 | 1 |
| Units: Weeks | | | | |
| median (inter-quartile range (Q1-Q3)) | 31.1 (24.9 to 184.4) | 117.0 (108.3 to 125.7) | 203.9 (143.3 to 241.7) | 999 (999 to 999) |

| End point values | Phase I: Dose Level 1C | Phase I: Dose Level 1D | Phase I: Dose Level 2 | Phase I: Dose Level 3 |
|---------------------------------------|------------------------|------------------------|-----------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 2 | 1 | 5 |
| Units: Weeks | | | | |
| median (inter-quartile range (Q1-Q3)) | 54.1 (42.6 to 62.1) | 77.1 (60.7 to 93.6) | 64.3 (64.3 to 64.3) | 61.6 (31.1 to 152.1) |

| End point values | Phase I: Dose Level 4 | Phase I: Dose Level 5 | | |
|---------------------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 5 | 2 | | |
| Units: Weeks | | | | |
| median (inter-quartile range (Q1-Q3)) | 999 (39.3 to 999) | 999 (57.0 to 999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I: Time to Response

| | |
|-----------------|---------------------------|
| End point title | Phase I: Time to Response |
|-----------------|---------------------------|

End point description:

Time to response was defined as the time from randomization until first documented evidence of partial or complete tumor response (whichever status is recorded first) and was based on responses confirmed at a repeat assessment, with the time to response taken as the first time the response was observed. For subjects who withdrew with no tumor response, the time was censored at the time of withdrawal from the study.

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

End point timeframe:

Week 8, Week 12, Week 16, Week 24, Week 32

| End point values | Phase I: Dose Level 0 | Phase I: Dose Level 1 | Phase I: Dose Level 1A | Phase I: Dose Level 1B |
|-----------------------------|-----------------------|-----------------------|------------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 2 | 6 | 1 |
| Units: Participants | | | | |
| CR or PR by Week 8 | 2 | 0 | 3 | 1 |
| CR or PR by Week 12 | 1 | 1 | 1 | 0 |
| CR or PR by Week 16 | 1 | 1 | 1 | 0 |
| CR or PR by Week 24 | 0 | 0 | 0 | 0 |
| CR or PR by Week 32 | 0 | 0 | 1 | 0 |

| End point values | Phase I: Dose Level 1C | Phase I: Dose Level 1D | Phase I: Dose Level 2 | Phase I: Dose Level 3 |
|-----------------------------|------------------------|------------------------|-----------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 2 | 1 | 5 |
| Units: Participants | | | | |
| CR or PR by Week 8 | 2 | 1 | 1 | 3 |
| CR or PR by Week 12 | 0 | 0 | 0 | 2 |
| CR or PR by Week 16 | 1 | 1 | 0 | 0 |
| CR or PR by Week 24 | 0 | 0 | 0 | 0 |
| CR or PR by Week 32 | 0 | 0 | 0 | 0 |

| End point values | Phase I: Dose Level 4 | Phase I: Dose Level 5 | | |
|-----------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 5 | 2 | | |
| Units: Participants | | | | |
| CR or PR by Week 8 | 4 | 1 | | |
| CR or PR by Week 12 | 1 | 0 | | |
| CR or PR by Week 16 | 0 | 0 | | |
| CR or PR by Week 24 | 0 | 1 | | |
| CR or PR by Week 32 | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I: Time to Progression

| | |
|-----------------|------------------------------|
| End point title | Phase I: Time to Progression |
|-----------------|------------------------------|

End point description:

Time to progression was defined as the interval between the date of randomization and the earliest date of disease progression or death due to breast cancer, if sooner. Disease progression was based on the assessments from the blinded, independent review of objective evidence (e.g., radiological scans and medical photographs). For subjects who withdrew without disease progression, it was censored at the time of last contact.

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

End point timeframe:

From first initiated treatment on 19-Jan-2006 to the data cut-off date for primary CSR on 9 Dec 2009, assessed approximately up to 4 years.

| End point values | Phase I: Dose Level 0 | Phase I: Dose Level 1 | Phase I: Dose Level 1A | Phase I: Dose Level 1B |
|---------------------------------------|-----------------------|-----------------------|------------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 6 | 2 | 9 | 3 |
| Units: Weeks | | | | |
| median (inter-quartile range (Q1-Q3)) | 34.1 (32.0 to 50.9) | 137.9 (119.6 to 999) | 148.5 (27.5 to 999) | 54.9 (17.1 to 999) |

| End point values | Phase I: Dose Level 1C | Phase I: Dose Level 1D | Phase I: Dose Level 2 | Phase I: Dose Level 3 |
|---------------------------------------|------------------------|------------------------|-----------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 2 | 5 | 5 |
| Units: Weeks | | | | |
| median (inter-quartile range (Q1-Q3)) | 67.1 (53.6 to 999) | 86.6 (73.9 to 99.3) | 71.4 (50.3 to 130.9) | 113.7 (37.9 to 165.0) |

| End point values | Phase I: Dose Level 4 | Phase I: Dose Level 5 | | |
|---------------------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2 | 2 | | |
| Units: Weeks | | | | |
| median (inter-quartile range (Q1-Q3)) | 999 (45.6 to 999) | 66.0 (63.9 to 999) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From study treatment start date till 30 days safety follow-up, assessed approximately up to 17 years.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 25.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Dose Level 0 |
|-----------------------|--------------|

Reporting group description:

Dose Level 0

| | |
|-----------------------|---------------|
| Reporting group title | Dose Level 1A |
|-----------------------|---------------|

Reporting group description:

Dose Level 1A

| | |
|-----------------------|---------------|
| Reporting group title | Dose Level 1B |
|-----------------------|---------------|

Reporting group description:

Dose Level 1B

| | |
|-----------------------|--------------|
| Reporting group title | Dose Level 5 |
|-----------------------|--------------|

Reporting group description:

Dose Level 5

| | |
|-----------------------|---------------|
| Reporting group title | Dose Level 1D |
|-----------------------|---------------|

Reporting group description:

Dose Level 1D

| | |
|-----------------------|--------------|
| Reporting group title | Dose Level 2 |
|-----------------------|--------------|

Reporting group description:

Dose Level 2

| | |
|-----------------------|--------------|
| Reporting group title | Dose Level 3 |
|-----------------------|--------------|

Reporting group description:

Dose Level 3

| | |
|-----------------------|--------------|
| Reporting group title | Dose Level 4 |
|-----------------------|--------------|

Reporting group description:

Dose Level 4

| | |
|-----------------------|--------------|
| Reporting group title | Dose Level 1 |
|-----------------------|--------------|

Reporting group description:

Dose Level 1

| | |
|-----------------------|---------------|
| Reporting group title | Dose Level 1C |
|-----------------------|---------------|

Reporting group description:

Dose Level 1C

| Serious adverse events | Dose Level 0 | Dose Level 1A | Dose Level 1B |
|---|----------------|-----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 6 / 12 (50.00%) | 1 / 5 (20.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Investigations | | | |
| Blood calcium increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (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 |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 12 (0.00%) | 0 / 5 (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 |
| Oxygen saturation decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (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 | | | |
| Urinary retention postoperative | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (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 | | | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (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 | | | |
| Transient ischaemic attack | | | |

| | | | |
|---|---------------|-----------------|----------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (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 | | | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 5 / 12 (41.67%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 10 / 12 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (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 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 1 / 5 (20.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (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 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (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 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (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 | | | |
| Colitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (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 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (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 | | | |
| Emphysema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (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 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (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 disorder | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (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 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (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 | | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (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 |
| Neutropenic sepsis | | | |

| | | | |
|---|---------------|----------------|---------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (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 device infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (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 |

| Serious adverse events | Dose Level 5 | Dose Level 1D | Dose Level 2 |
|---|----------------|----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 1 / 3 (33.33%) | 4 / 5 (80.00%) |
| number of deaths (all causes) | 0 | 1 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Investigations | | | |
| Blood calcium increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (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 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (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 |
| Oxygen saturation decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 5 (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 |
| Injury, poisoning and procedural complications | | | |
| Urinary retention postoperative | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (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 | | | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (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 | | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 5 (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 |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 3 / 5 (60.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 5 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 5 (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 |
| Mucosal inflammation | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (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 / 3 (0.00%) | 0 / 3 (0.00%) | 2 / 5 (40.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Colitis | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 5 (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 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (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 | | | |
| Emphysema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 5 (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 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory disorder | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------------------------|---------------------------------|----------------------------------|
| Infections and infestations Lower respiratory tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 3 (0.00%) 0 / 0 0 / 0 | 0 / 3 (0.00%) 0 / 0 0 / 0 | 1 / 5 (20.00%) 0 / 1 0 / 0 |
| Cellulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 3 (0.00%) 0 / 0 0 / 0 | 0 / 3 (0.00%) 0 / 0 0 / 0 | 1 / 5 (20.00%) 0 / 2 0 / 0 |
| Neutropenic sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 3 (0.00%) 0 / 0 0 / 0 | 0 / 3 (0.00%) 0 / 0 0 / 0 | 1 / 5 (20.00%) 1 / 1 0 / 0 |
| Vascular device infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 3 (33.33%) 0 / 1 0 / 0 | 0 / 3 (0.00%) 0 / 0 0 / 0 | 0 / 5 (0.00%) 0 / 0 0 / 0 |

| Serious adverse events | Dose Level 3 | Dose Level 4 | Dose Level 1 |
|--|----------------------------------|---------------------------------|----------------------------------|
| Total subjects affected by serious adverse events subjects affected / exposed number of deaths (all causes) number of deaths resulting from adverse events | 5 / 6 (83.33%) 0 0 | 3 / 6 (50.00%) 0 0 | 2 / 3 (66.67%) 0 0 |
| Investigations Blood calcium increased subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 6 (0.00%) 0 / 0 0 / 0 | 0 / 6 (0.00%) 0 / 0 0 / 0 | 0 / 3 (0.00%) 0 / 0 0 / 0 |
| Ejection fraction decreased subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 2 / 6 (33.33%) 2 / 2 0 / 0 | 0 / 6 (0.00%) 0 / 0 0 / 0 | 1 / 3 (33.33%) 6 / 6 0 / 0 |
| Haemoglobin decreased | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oxygen saturation decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Urinary retention postoperative | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (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 |
| Nervous system disorders | | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |

| | | | |
|--|---------------|----------------|---------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Colitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Emphysema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |

| | | | |
|---|----------------|---------------|---------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory disorder | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular device infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---------------|--|--|
| Serious adverse events | Dose Level 1C | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

| | | | |
|---|---------------|--|--|
| Investigations | | | |
| Blood calcium increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oxygen saturation decreased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Urinary retention postoperative | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |

| | | | |
|--|---------------|--|--|
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Colitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|---------------|--|--|
| Respiratory, thoracic and mediastinal disorders | | | |
| Emphysema | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory disorder | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular device infection | | | |

| | | | |
|---|---------------|--|--|
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Dose Level 0 | Dose Level 1A | Dose Level 1B |
|---|-----------------|-------------------|-----------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 6 / 6 (100.00%) | 12 / 12 (100.00%) | 5 / 5 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Hot flush | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 12 (16.67%) | 0 / 5 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lymphoedema | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Surgical and medical procedures | | | |
| Cataract operation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|--|----------------|-----------------|----------------|
| General disorders and administration site conditions | | | |
| Catheter site haematoma | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Asthenia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 7 / 12 (58.33%) | 2 / 5 (40.00%) |
| occurrences (all) | 4 | 20 | 5 |
| Axillary pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 12 (16.67%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Catheter site bruise | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Catheter site erythema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Catheter site pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Catheter site inflammation | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypothermia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 3 / 12 (25.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 9 | 5 | 1 |
| General physical health deterioration | | | |

| | | | |
|-----------------------------|----------------|----------------|---------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Granuloma | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Face oedema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Injection site erythema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infusion site vesicles | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injection site haemorrhage | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nodule | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mucosal dryness | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Injection site rash | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oedema | | | |

| | | | |
|---|---------------------|----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Oedema peripheral subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 2 / 12 (16.67%) 3 | 0 / 5 (0.00%) 0 |
| Xerosis subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 5 (0.00%) 0 |
| Pyrexia subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 5 / 12 (41.67%) 5 | 2 / 5 (40.00%) 2 |
| Peripheral swelling subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Pain subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 5 (20.00%) 2 |
| Hypersensitivity subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Social circumstances Menopause subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 5 (0.00%) 0 |
| Reproductive system and breast disorders Intermenstrual bleeding subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 12 (8.33%) 2 | 0 / 5 (0.00%) 0 |
| Genital haemorrhage subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 5 (20.00%) 1 |
| Breast pain | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 4 | 0 |
| Breast oedema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Amenorrhoea | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vulvovaginal pruritus | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vulvovaginal dryness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pelvic pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Menopausal symptoms | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 4 / 12 (33.33%) | 3 / 5 (60.00%) |
| occurrences (all) | 0 | 7 | 3 |
| Allergic sinusitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysphonia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dyspnoea | | | |

| | | | |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 12 (16.67%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Emphysema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 6 / 12 (50.00%) | 2 / 5 (40.00%) |
| occurrences (all) | 3 | 8 | 2 |
| Nasal dryness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 12 (16.67%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 3 | 1 |
| Nasal discomfort | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal obstruction | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal inflammation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Sinus congestion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 7 / 12 (58.33%) | 1 / 5 (20.00%) |
| occurrences (all) | 4 | 13 | 2 |
| Pulmonary fibrosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Productive cough | | | |

| | | | |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pharyngeal erythema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pharyngeal oedema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 12 (16.67%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Tachypnoea | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| Abnormal dreams | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tearfulness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Anxiety | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 3 / 12 (25.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 1 | 6 | 1 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Depression | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 12 (16.67%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 5 / 6 (83.33%) | 3 / 12 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 8 | 7 | 0 |

| | | | |
|--|--------------------|----------------------|---------------------|
| Mood altered subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Investigations | | | |
| Alanine aminotransferase subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 12 (8.33%) 1 | 1 / 5 (20.00%) 1 |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 2 / 12 (16.67%) 2 | 2 / 5 (40.00%) 2 |
| Aspartate aminotransferase subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Blood albumin decreased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Blood calcium decreased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Blood glucose increased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Blood magnesium decreased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Ejection fraction decreased | | | |

| | | | |
|--|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 12 (16.67%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 1 | 1 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Radiation skin injury | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 12 (16.67%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Post procedural complication | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pelvic fracture | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin laceration | | | |

| | | | |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Thermal burn | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Wound secretion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Intracardiac mass | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Ageusia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 12 (16.67%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Allodynia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Headache | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 6 / 12 (50.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 5 | 9 | 1 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysgeusia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Electric shock sensation | | | |

| | | | |
|-------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Coma | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hyperaesthesia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Horner's syndrome | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Memory impairment | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 3 / 12 (25.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 5 | 3 | 1 |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Motor dysfunction | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Migraine | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Presyncope | | | |

| | | | |
|--------------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Restless legs syndrome | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Taste disorder | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 0 / 12 (0.00%) | 2 / 5 (40.00%) |
| occurrences (all) | 9 | 0 | 2 |
| Sciatica | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Anaemia | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 5 / 12 (41.67%) | 1 / 5 (20.00%) |
| occurrences (all) | 6 | 9 | 2 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Splenic vein thrombosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Neutropenia | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 6 / 12 (50.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 13 | 18 | 1 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |

| | | | |
|--------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ear disorder | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Eye disorders | | | |
| Conjunctival irritation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Conjunctival haemorrhage | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dry eye | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 3 / 12 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Lacrimation increased | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 2 / 12 (16.67%) | 0 / 5 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| Foreign body sensation in eyes | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eyelid oedema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Eye pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Erythema of eyelid | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ocular hyperaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|-----------------------------|----------------|-----------------|---------------|
| Orbital oedema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Visual impairment | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Visual acuity reduced | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Scintillating scotoma | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Photopsia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Aerophagia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 4 / 12 (33.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 5 | 5 | 0 |
| Anal fissure | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Diarrhoea | | | |

| | | | |
|----------------------------------|----------------|------------------|-----------------|
| subjects affected / exposed | 5 / 6 (83.33%) | 11 / 12 (91.67%) | 5 / 5 (100.00%) |
| occurrences (all) | 27 | 43 | 10 |
| Constipation | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 3 / 12 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 7 | 4 | 0 |
| Breath odour | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Aphthous ulcer | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 4 / 12 (33.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 5 | 0 |
| Anal haemorrhage | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 12 (16.67%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Dyschezia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dry mouth | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastritis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 12 (16.67%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 4 / 12 (33.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 4 | 0 |
| Gingival bleeding | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Gingival pain | | | |

| | | | |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypoaesthesia oral | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hiatus hernia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 12 (16.67%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Haematochezia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 7 / 12 (58.33%) | 4 / 5 (80.00%) |
| occurrences (all) | 13 | 14 | 7 |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mesenteric vein thrombosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lip pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Noninfective gingivitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Odynophagia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Rectal haemorrhage | | | |

| | | | |
|--|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 12 (16.67%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Oral mucosal blistering | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oral pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Periodontal disease | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Stomatitis | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 2 / 12 (16.67%) | 0 / 5 (0.00%) |
| occurrences (all) | 7 | 2 | 0 |
| Tongue ulceration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Toothache | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 5 / 12 (41.67%) | 1 / 5 (20.00%) |
| occurrences (all) | 2 | 9 | 2 |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 3 / 12 (25.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 1 | 7 | 1 |
| Drug eruption | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Dermatitis allergic | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|-----------------------------|----------------|-----------------|----------------|
| Dermatitis acneiform | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 5 / 12 (41.67%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 7 | 0 |
| Blister | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Alopecia | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 6 / 12 (50.00%) | 3 / 5 (60.00%) |
| occurrences (all) | 4 | 6 | 3 |
| Acne | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 3 / 12 (25.00%) | 2 / 5 (40.00%) |
| occurrences (all) | 3 | 8 | 2 |
| Onycholysis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 12 (16.67%) | 0 / 5 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |
| Onychoclasia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Onychalgia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nail toxicity | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Eczema | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 12 (16.67%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Nail disorder | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 6 / 12 (50.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 2 | 11 | 1 |
| Nail ridging | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Erythema | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 12 (16.67%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |

| | | | |
|--|----------------|-----------------|----------------|
| Ecchymosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Onychomadesis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 12 (16.67%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 5 / 12 (41.67%) | 1 / 5 (20.00%) |
| occurrences (all) | 12 | 5 | 1 |
| Purpura | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pruritus allergic | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Pruritus | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 4 / 12 (33.33%) | 1 / 5 (20.00%) |
| occurrences (all) | 2 | 5 | 1 |
| Pain of skin | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 3 / 12 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Skin fissures | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 3 / 12 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 2 | 11 | 0 |
| Skin exfoliation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin disorder | | | |

| | | | |
|-----------------------------|---------------|-----------------|----------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin discolouration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash macular | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash pruritic | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Scab | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 12 (16.67%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rash papular | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Xeroderma | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vascular skin disorder | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 1 | 1 |
| Neurogenic bladder | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|----------------|-----------------|----------------|
| Renal failure | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 7 / 12 (58.33%) | 2 / 5 (40.00%) |
| occurrences (all) | 3 | 9 | 3 |
| Arthritis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Back pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 3 / 12 (25.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 1 | 4 | 1 |
| Bone pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 3 / 12 (25.00%) | 2 / 5 (40.00%) |
| occurrences (all) | 0 | 3 | 2 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 4 / 12 (33.33%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 4 | 3 |
| Joint swelling | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal discomfort | | | |

| | | | |
|------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 4 / 12 (33.33%) | 2 / 5 (40.00%) |
| occurrences (all) | 1 | 5 | 4 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Osteopenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Spinal pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 1 | 2 |
| Pain in jaw | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 2 / 12 (16.67%) | 1 / 5 (20.00%) |
| occurrences (all) | 5 | 2 | 1 |
| Systemic lupus erythematosus | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| Eye infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|-----------------------------|----------------|-----------------|----------------|
| Folliculitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 12 (16.67%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 2 | 1 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dermatitis infected | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infected cyst | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hordeolum | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Herpes virus infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Fungal skin infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|-----------------------------------|----------------|-----------------|----------------|
| Fungal foot infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 12 (16.67%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 7 / 12 (58.33%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 8 | 2 |
| Nail infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nail bed infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mastitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Localised infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 12 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 2 | 0 | 1 |
| Laryngitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Influenza | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 3 / 12 (25.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 2 | 5 | 1 |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 1 | 1 |
| Rash pustular | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|-----------------------------|----------------|-----------------|----------------|
| Pustule | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 12 (8.33%) | 1 / 5 (20.00%) |
| occurrences (all) | 1 | 1 | 1 |
| Paronychia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 12 (16.67%) | 2 / 5 (40.00%) |
| occurrences (all) | 1 | 7 | 3 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 3 / 12 (25.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 5 | 1 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Septic rash | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tooth abscess | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Skin infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Tracheitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|--------------------|----------------------|---------------------|
| Vascular device infection subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Vaginal infection subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 5 (0.00%) 0 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 2 / 12 (16.67%) 2 | 0 / 5 (0.00%) 0 |
| Vulvovaginal candidiasis subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Hyperkalaemia subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Dehydration subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Decreased appetite subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 4 / 12 (33.33%) 5 | 2 / 5 (40.00%) 2 |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 2 / 12 (16.67%) 2 | 0 / 5 (0.00%) 0 |
| Hyponatraemia subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Hypokalaemia | | | |

| | | | |
|-----------------------------|---------------|----------------|----------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 12 (8.33%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 1 | 1 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| Non-serious adverse events | Dose Level 5 | Dose Level 1D | Dose Level 2 |
|---|-----------------|-----------------|-----------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 3 / 3 (100.00%) | 3 / 3 (100.00%) | 5 / 5 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hot flush | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lymphoedema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Surgical and medical procedures | | | |
| Cataract operation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General disorders and administration | | | |

| | | | |
|---------------------------------------|-----------------|----------------|----------------|
| site conditions | | | |
| Catheter site haematoma | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Asthenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 2 / 5 (40.00%) |
| occurrences (all) | 0 | 1 | 2 |
| Axillary pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Catheter site bruise | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Catheter site erythema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Catheter site pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Catheter site inflammation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypothermia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 3 / 3 (100.00%) | 2 / 3 (66.67%) | 3 / 5 (60.00%) |
| occurrences (all) | 11 | 3 | 3 |
| General physical health deterioration | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Granuloma | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Face oedema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injection site erythema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Infusion site vesicles | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injection site haemorrhage | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nodule | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Mucosal dryness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injection site rash | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oedema | | | |

| | | | |
|---|---------------------|--------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Oedema peripheral subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Xerosis subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Pyrexia subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 3 (0.00%) 0 | 1 / 5 (20.00%) 1 |
| Peripheral swelling subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Pain subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 3 (0.00%) 0 | 1 / 5 (20.00%) 1 |
| Hypersensitivity subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Social circumstances Menopause subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Reproductive system and breast disorders Intermenstrual bleeding subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Genital haemorrhage subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Breast pain | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Breast oedema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Amenorrhoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vulvovaginal pruritus | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vulvovaginal dryness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pelvic pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Menopausal symptoms | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 1 | 2 |
| Allergic sinusitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysphonia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dyspnoea | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Emphysema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 3 (33.33%) | 3 / 5 (60.00%) |
| occurrences (all) | 1 | 1 | 4 |
| Nasal dryness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal discomfort | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal obstruction | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal inflammation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sinus congestion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Pulmonary fibrosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Productive cough | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pharyngeal erythema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pharyngeal oedema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 2 / 5 (40.00%) |
| occurrences (all) | 1 | 0 | 2 |
| Tachypnoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| Abnormal dreams | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tearfulness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Anxiety | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Depression | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 3 | 0 | 1 |

| | | | |
|--|---------------------|---------------------|---------------------|
| Mood altered subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 3 (0.00%) 0 | 1 / 5 (20.00%) 1 |
| Investigations | | | |
| Alanine aminotransferase subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 1 / 5 (20.00%) 1 |
| Aspartate aminotransferase subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 1 / 5 (20.00%) 1 |
| Blood albumin decreased subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 3 (33.33%) 1 | 1 / 5 (20.00%) 1 |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Blood calcium decreased subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 2 | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Blood glucose increased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Blood magnesium decreased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Ejection fraction decreased | | | |

| | | | |
|--|----------------|----------------|---------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 1 / 3 (33.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Weight decreased | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Radiation skin injury | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Procedural pain | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Post procedural complication | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pelvic fracture | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin laceration | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Thermal burn | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 7 | 0 | 0 |
| Wound secretion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Intracardiac mass | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Ageusia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Allodynia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Headache | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 3 (33.33%) | 1 / 5 (20.00%) |
| occurrences (all) | 2 | 1 | 1 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 3 (33.33%) | 1 / 5 (20.00%) |
| occurrences (all) | 1 | 1 | 1 |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Electric shock sensation | | | |

| | | | |
|-------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Coma | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperaesthesia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Horner's syndrome | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Memory impairment | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 2 / 3 (66.67%) | 2 / 5 (40.00%) |
| occurrences (all) | 5 | 2 | 4 |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Motor dysfunction | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Migraine | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 2 / 5 (40.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Presyncope | | | |

| | | | |
|--------------------------------------|----------------|---------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Restless legs syndrome | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Taste disorder | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 0 / 3 (0.00%) | 2 / 5 (40.00%) |
| occurrences (all) | 2 | 0 | 5 |
| Sciatica | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood and lymphatic system disorders | | | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 3 |
| Anaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Splenic vein thrombosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |

| | | | |
|--------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ear disorder | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye disorders | | | |
| Conjunctival irritation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Conjunctival haemorrhage | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dry eye | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lacrimation increased | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Foreign body sensation in eyes | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eyelid oedema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Erythema of eyelid | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ocular hyperaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|-----------------------------|----------------|---------------|----------------|
| Orbital oedema | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Visual impairment | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Visual acuity reduced | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Scintillating scotoma | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Photopsia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Aerophagia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Anal fissure | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Diarrhoea | | | |

| | | | |
|----------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 2 / 3 (66.67%) | 3 / 3 (100.00%) | 3 / 5 (60.00%) |
| occurrences (all) | 15 | 5 | 4 |
| Constipation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 2 / 5 (40.00%) |
| occurrences (all) | 0 | 1 | 2 |
| Breath odour | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Aphthous ulcer | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Anal haemorrhage | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 2 / 5 (40.00%) |
| occurrences (all) | 0 | 1 | 2 |
| Dyschezia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dry mouth | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 3 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Gingival bleeding | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Gingival pain | | | |

| | | | |
|-----------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoaesthesia oral | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hiatus hernia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Haematochezia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nausea | | | |
| subjects affected / exposed | 3 / 3 (100.00%) | 2 / 3 (66.67%) | 3 / 5 (60.00%) |
| occurrences (all) | 11 | 3 | 12 |
| Mouth ulceration | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Mesenteric vein thrombosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lip pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Noninfective gingivitis | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Odynophagia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rectal haemorrhage | | | |

| | | | |
|--|-----------------|---------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oral mucosal blistering | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oral pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Periodontal disease | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 3 / 5 (60.00%) |
| occurrences (all) | 0 | 0 | 4 |
| Tongue ulceration | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Toothache | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 3 / 3 (100.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 6 | 0 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 2 / 5 (40.00%) |
| occurrences (all) | 3 | 0 | 4 |
| Drug eruption | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dermatitis allergic | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|-----------------------------|-----------------|----------------|-----------------|
| Dermatitis acneiform | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 3 | 0 | 1 |
| Blister | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Alopecia | | | |
| subjects affected / exposed | 3 / 3 (100.00%) | 2 / 3 (66.67%) | 5 / 5 (100.00%) |
| occurrences (all) | 4 | 2 | 5 |
| Acne | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Onycholysis | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 1 | 0 | 1 |
| Onychoclasia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Onychalgia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Nail toxicity | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eczema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nail disorder | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 3 (66.67%) | 1 / 5 (20.00%) |
| occurrences (all) | 1 | 3 | 1 |
| Nail ridging | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 1 | 0 | 1 |
| Erythema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |

| | | | |
|---|----------------|----------------|----------------|
| Ecchymosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Onychomadesis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rash | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 3 (66.67%) | 2 / 5 (40.00%) |
| occurrences (all) | 5 | 2 | 7 |
| Purpura | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pruritus allergic | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pain of skin | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin fissures | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin exfoliation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin disorder | | | |

| | | | |
|-----------------------------|---------------|----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Skin discolouration | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash macular | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 1 | 1 |
| Rash pruritic | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Scab | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash papular | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Xeroderma | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vascular skin disorder | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Neurogenic bladder | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 2 / 5 (40.00%) |
| occurrences (all) | 0 | 0 | 2 |

| | | | |
|---|----------------|----------------|----------------|
| Renal failure | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 3 (33.33%) | 1 / 5 (20.00%) |
| occurrences (all) | 4 | 2 | 4 |
| Arthritis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Back pain | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 2 / 3 (66.67%) | 1 / 5 (20.00%) |
| occurrences (all) | 3 | 2 | 1 |
| Bone pain | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Joint swelling | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 1 | 2 |
| Musculoskeletal discomfort | | | |

| | | | |
|------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 1 | 1 |
| Myalgia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 1 | 0 | 1 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Osteopenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Spinal pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pain in jaw | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 2 / 5 (40.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Systemic lupus erythematosus | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| Eye infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|-----------------------------|---------------|----------------|----------------|
| Folliculitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 2 / 5 (40.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dermatitis infected | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Infected cyst | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hordeolum | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Herpes virus infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fungal skin infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |

| | | | |
|-----------------------------------|----------------|----------------|----------------|
| Fungal foot infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Nail infection | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nail bed infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mastitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Localised infection | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 3 (33.33%) | 1 / 5 (20.00%) |
| occurrences (all) | 1 | 1 | 1 |
| Laryngitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash pustular | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| Pustule | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Paronychia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Septic rash | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Tooth abscess | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tracheitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---------------------|---------------------|---------------------|
| Vascular device infection subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 2 | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Vaginal infection subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 3 / 5 (60.00%) 3 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 3 (33.33%) 1 | 1 / 5 (20.00%) 1 |
| Vulvovaginal candidiasis subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Hyperkalaemia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Dehydration subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Decreased appetite subjects affected / exposed occurrences (all) | 2 / 3 (66.67%) 3 | 0 / 3 (0.00%) 0 | 2 / 5 (40.00%) 2 |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Hyponatraemia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Hypokalaemia | | | |

| | | | |
|-----------------------------|---------------|---------------|---------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| Non-serious adverse events | Dose Level 3 | Dose Level 4 | Dose Level 1 |
|---|-----------------|-----------------|-----------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 6 / 6 (100.00%) | 6 / 6 (100.00%) | 3 / 3 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Hot flush | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lymphoedema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Surgical and medical procedures | | | |
| Cataract operation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| General disorders and administration | | | |

| | | | |
|---------------------------------------|----------------|----------------|-----------------|
| site conditions | | | |
| Catheter site haematoma | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Asthenia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 6 (33.33%) | 1 / 3 (33.33%) |
| occurrences (all) | 2 | 4 | 7 |
| Axillary pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Catheter site bruise | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Catheter site erythema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Chest discomfort | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Catheter site pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Catheter site inflammation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypothermia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 5 / 6 (83.33%) | 3 / 6 (50.00%) | 3 / 3 (100.00%) |
| occurrences (all) | 13 | 10 | 5 |
| General physical health deterioration | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Granuloma | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Face oedema | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Injection site erythema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infusion site vesicles | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 2 / 3 (66.67%) |
| occurrences (all) | 0 | 0 | 2 |
| Injection site haemorrhage | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nodule | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Mucosal dryness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injection site rash | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oedema | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 1 / 6 (16.67%) 1 | 0 / 3 (0.00%) 0 |
| Oedema peripheral subjects affected / exposed occurrences (all) | 2 / 6 (33.33%) 2 | 1 / 6 (16.67%) 1 | 0 / 3 (0.00%) 0 |
| Xerosis subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 6 (0.00%) 0 | 1 / 3 (33.33%) 1 |
| Pyrexia subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 6 (16.67%) 2 | 1 / 3 (33.33%) 2 |
| Peripheral swelling subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 6 (0.00%) 0 | 1 / 3 (33.33%) 1 |
| Pain subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 1 / 6 (16.67%) 3 | 0 / 3 (0.00%) 0 |
| Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 0 / 6 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Hypersensitivity subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Social circumstances Menopause subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Reproductive system and breast disorders Intermenstrual bleeding subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Genital haemorrhage subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Breast pain | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Breast oedema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Amenorrhoea | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vulvovaginal pruritus | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vulvovaginal dryness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pelvic pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Menopausal symptoms | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 5 / 6 (83.33%) | 1 / 6 (16.67%) | 2 / 3 (66.67%) |
| occurrences (all) | 6 | 1 | 5 |
| Allergic sinusitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Dysphonia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dyspnoea | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 3 / 6 (50.00%) | 2 / 6 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 3 | 2 | 0 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Emphysema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 2 / 6 (33.33%) | 2 / 3 (66.67%) |
| occurrences (all) | 4 | 6 | 3 |
| Nasal dryness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Nasal discomfort | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal obstruction | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Nasal inflammation | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 6 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sinus congestion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 6 (33.33%) | 2 / 3 (66.67%) |
| occurrences (all) | 1 | 2 | 2 |
| Pulmonary fibrosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Productive cough | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pharyngeal erythema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pharyngeal oedema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 2 / 6 (33.33%) | 1 / 3 (33.33%) |
| occurrences (all) | 7 | 2 | 3 |
| Tachypnoea | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Psychiatric disorders | | | |
| Abnormal dreams | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tearfulness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Anxiety | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 1 | 2 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Depression | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 2 | 0 | 1 |

| | | | |
|--|---------------------|---------------------|---------------------|
| Mood altered subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Investigations | | | |
| Alanine aminotransferase subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 1 / 6 (16.67%) 1 | 1 / 3 (33.33%) 2 |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 2 / 6 (33.33%) 4 | 1 / 6 (16.67%) 1 | 0 / 3 (0.00%) 0 |
| Aspartate aminotransferase subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 0 / 6 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 2 / 6 (33.33%) 4 | 1 / 6 (16.67%) 1 | 0 / 3 (0.00%) 0 |
| Blood albumin decreased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 0 / 6 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 6 (16.67%) 1 | 0 / 3 (0.00%) 0 |
| Blood calcium decreased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Blood glucose increased subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 0 / 6 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Blood magnesium decreased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 6 (16.67%) 1 | 0 / 3 (0.00%) 0 |
| Ejection fraction decreased | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 2 | 1 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Radiation skin injury | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 3 / 6 (50.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Post procedural complication | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pelvic fracture | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin laceration | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Thermal burn | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Wound secretion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Intracardiac mass | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nervous system disorders | | | |
| Ageusia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Allodynia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Headache | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 2 / 6 (33.33%) | 2 / 3 (66.67%) |
| occurrences (all) | 2 | 4 | 4 |
| Dizziness | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 3 | 0 | 1 |
| Dysgeusia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 0 | 3 |
| Electric shock sensation | | | |

| | | | |
|-------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Coma | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hyperaesthesia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Horner's syndrome | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Memory impairment | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 5 / 6 (83.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 12 | 0 |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Motor dysfunction | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Migraine | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 1 | 1 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Presyncope | | | |

| | | | |
|--------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Restless legs syndrome | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Taste disorder | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 3 / 6 (50.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 5 | 0 |
| Sciatica | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Anaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Splenic vein thrombosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 3 / 3 (100.00%) |
| occurrences (all) | 1 | 0 | 8 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |

| | | | |
|--------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 6 (33.33%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 2 | 1 |
| Ear disorder | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eye disorders | | | |
| Conjunctival irritation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Conjunctival haemorrhage | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dry eye | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Lacrimation increased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 4 / 6 (66.67%) | 2 / 3 (66.67%) |
| occurrences (all) | 2 | 4 | 3 |
| Foreign body sensation in eyes | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eyelid oedema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Eye pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Erythema of eyelid | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ocular hyperaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| Orbital oedema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Visual impairment | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Visual acuity reduced | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vision blurred | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Scintillating scotoma | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Photopsia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Aerophagia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 1 / 6 (16.67%) | 1 / 3 (33.33%) |
| occurrences (all) | 4 | 2 | 1 |
| Anal fissure | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Diarrhoea | | | |

| | | | |
|----------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 5 / 6 (83.33%) | 5 / 6 (83.33%) | 3 / 3 (100.00%) |
| occurrences (all) | 27 | 33 | 16 |
| Constipation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 6 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Breath odour | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Aphthous ulcer | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Anal haemorrhage | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 1 | 1 |
| Dyspepsia | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Dyschezia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dry mouth | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastritis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 6 (33.33%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 2 | 1 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Gingival bleeding | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gingival pain | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoaesthesia oral | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hiatus hernia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 6 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Haematochezia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 5 / 6 (83.33%) | 5 / 6 (83.33%) | 2 / 3 (66.67%) |
| occurrences (all) | 8 | 14 | 12 |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mesenteric vein thrombosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lip pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Noninfective gingivitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Odynophagia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 2 | 0 | 1 |
| Rectal haemorrhage | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Oral mucosal blistering | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Oral pain | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Periodontal disease | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Stomatitis | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 1 / 6 (16.67%) | 1 / 3 (33.33%) |
| occurrences (all) | 2 | 2 | 3 |
| Tongue ulceration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Toothache | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 2 / 6 (33.33%) | 2 / 3 (66.67%) |
| occurrences (all) | 4 | 11 | 5 |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 1 / 6 (16.67%) | 2 / 3 (66.67%) |
| occurrences (all) | 9 | 7 | 2 |
| Drug eruption | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dermatitis allergic | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| Dermatitis acneiform | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blister | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Alopecia | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 4 / 6 (66.67%) | 2 / 3 (66.67%) |
| occurrences (all) | 4 | 4 | 2 |
| Acne | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Onycholysis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 2 / 3 (66.67%) |
| occurrences (all) | 0 | 1 | 2 |
| Onychoclasia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Onychalgia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Nail toxicity | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Eczema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nail disorder | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 4 / 6 (66.67%) | 2 / 3 (66.67%) |
| occurrences (all) | 3 | 9 | 2 |
| Nail ridging | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Erythema | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 6 (33.33%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 3 | 1 |

| | | | |
|---|----------------|----------------|-----------------|
| Ecchymosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Onychomadesis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 4 / 6 (66.67%) | 2 / 3 (66.67%) |
| occurrences (all) | 8 | 9 | 5 |
| Purpura | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pruritus allergic | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 1 / 6 (16.67%) | 3 / 3 (100.00%) |
| occurrences (all) | 5 | 2 | 9 |
| Pain of skin | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin fissures | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 6 (33.33%) | 2 / 3 (66.67%) |
| occurrences (all) | 0 | 2 | 2 |
| Skin exfoliation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin disorder | | | |

| | | | |
|-----------------------------|----------------|----------------|---------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin discolouration | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rash macular | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash pruritic | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Scab | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash papular | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Xeroderma | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vascular skin disorder | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neurogenic bladder | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|----------------|----------------|-----------------|
| Renal failure | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 4 / 6 (66.67%) | 1 / 3 (33.33%) |
| occurrences (all) | 3 | 9 | 1 |
| Arthritis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Back pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 3 / 3 (100.00%) |
| occurrences (all) | 2 | 1 | 4 |
| Bone pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 6 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Joint swelling | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal discomfort | | | |

| | | | |
|------------------------------|----------------|----------------|---------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neck pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 6 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Osteopenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Spinal pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pain in jaw | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 5 | 1 | 0 |
| Systemic lupus erythematosus | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infections and infestations | | | |
| Eye infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| Folliculitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Conjunctivitis | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dermatitis infected | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infected cyst | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hordeolum | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Herpes virus infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Fungal skin infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|-----------------------------------|----------------|----------------|----------------|
| Fungal foot infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 2 / 3 (66.67%) |
| occurrences (all) | 1 | 8 | 8 |
| Nail infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nail bed infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Mastitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 1 / 6 (16.67%) | 1 / 3 (33.33%) |
| occurrences (all) | 7 | 2 | 1 |
| Localised infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 6 (33.33%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 2 | 1 |
| Laryngitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Influenza | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oral herpes | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Rash pustular | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| Pustule | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Paronychia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 6 (33.33%) | 2 / 3 (66.67%) |
| occurrences (all) | 0 | 2 | 3 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 6 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Septic rash | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tooth abscess | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Tracheitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---------------------|---------------------|---------------------|
| Vascular device infection subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 6 (16.67%) 1 | 0 / 3 (0.00%) 0 |
| Vaginal infection subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 0 / 6 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 6 (0.00%) 0 | 1 / 3 (33.33%) 1 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 3 | 1 / 6 (16.67%) 2 | 0 / 3 (0.00%) 0 |
| Vulvovaginal candidiasis subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 3 | 0 / 6 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Hyperkalaemia subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 6 (16.67%) 1 | 0 / 3 (0.00%) 0 |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 6 (16.67%) 1 | 0 / 3 (0.00%) 0 |
| Dehydration subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 6 (16.67%) 1 | 0 / 3 (0.00%) 0 |
| Decreased appetite subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 1 / 6 (16.67%) 5 | 1 / 3 (33.33%) 2 |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Hyponatraemia subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 6 (16.67%) 1 | 0 / 3 (0.00%) 0 |
| Hypokalaemia | | | |

| | | | |
|-----------------------------|---------------|----------------|---------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| Non-serious adverse events | Dose Level 1C | | |
|---|-----------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 4 / 4 (100.00%) | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hot flush | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Lymphoedema | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Surgical and medical procedures | | | |
| Cataract operation | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| General disorders and administration | | | |

| | | | |
|---------------------------------------|----------------|--|--|
| site conditions | | | |
| Catheter site haematoma | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | | |
| occurrences (all) | 7 | | |
| Axillary pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Catheter site bruise | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Catheter site erythema | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Catheter site pain | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 2 | | |
| Catheter site inflammation | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypothermia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | | |
| occurrences (all) | 8 | | |
| General physical health deterioration | | | |

| | | | |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Granuloma | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Face oedema | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Injection site erythema | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infusion site vesicles | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Injection site haemorrhage | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nodule | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Mucosal dryness | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Injection site rash | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oedema | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 2 | | |
| Xerosis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | | |
| occurrences (all) | 3 | | |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pain | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Social circumstances | | | |
| Menopause | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Reproductive system and breast disorders | | | |
| Intermenstrual bleeding | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Genital haemorrhage | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Breast pain | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Breast oedema | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Amenorrhoea | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vulvovaginal pruritus | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vulvovaginal dryness | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pelvic pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Menopausal symptoms | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | | |
| occurrences (all) | 4 | | |
| Allergic sinusitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dysphonia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dyspnoea | | | |

| | | | |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 2 | | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Emphysema | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Epistaxis | | | |
| subjects affected / exposed | 3 / 4 (75.00%) | | |
| occurrences (all) | 3 | | |
| Nasal dryness | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Nasal discomfort | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Nasal obstruction | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nasal inflammation | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Sinus congestion | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | | |
| occurrences (all) | 3 | | |
| Pulmonary fibrosis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Productive cough | | | |

| | | | |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pharyngeal erythema | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pharyngeal oedema | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | | |
| occurrences (all) | 2 | | |
| Tachypnoea | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Psychiatric disorders | | | |
| Abnormal dreams | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tearfulness | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Depression | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Insomnia | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |

| | | | |
|--|---------------------|--|--|
| Mood altered subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 1 | | |
| Investigations | | | |
| Alanine aminotransferase subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | | |
| Aspartate aminotransferase subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | | |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | | |
| Blood albumin decreased subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | | |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | | |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | | |
| Blood calcium decreased subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | | |
| Blood glucose increased subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | | |
| Blood magnesium decreased subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | | |
| Ejection fraction decreased | | | |

| | | | |
|--|---------------|--|--|
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Fall | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Radiation skin injury | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Post procedural complication | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pelvic fracture | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin laceration | | | |

| | | | |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 3 | | |
| Thermal burn | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Wound secretion | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Intracardiac mass | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nervous system disorders | | | |
| Ageusia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Allodynia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Headache | | | |
| subjects affected / exposed | 3 / 4 (75.00%) | | |
| occurrences (all) | 8 | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 2 | | |
| Dysgeusia | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | | |
| occurrences (all) | 2 | | |
| Electric shock sensation | | | |

| | | | |
|-------------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Coma | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hyperaesthesia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Horner's syndrome | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Memory impairment | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Motor dysfunction | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Migraine | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | | |
| occurrences (all) | 2 | | |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Presyncope | | | |

| | | | |
|--------------------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Restless legs syndrome | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Syncope | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Taste disorder | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | | |
| occurrences (all) | 2 | | |
| Sciatica | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Seizure | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood and lymphatic system disorders | | | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Splenic vein thrombosis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |

| | | | |
|--------------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Ear disorder | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Ear pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Eye disorders | | | |
| Conjunctival irritation | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Conjunctival haemorrhage | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dry eye | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Lacrimation increased | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | | |
| occurrences (all) | 3 | | |
| Foreign body sensation in eyes | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Eyelid oedema | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Eye pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Erythema of eyelid | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Ocular hyperaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|-----------------------------|----------------|--|--|
| Orbital oedema | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Visual impairment | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Visual acuity reduced | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Scintillating scotoma | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Photopsia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Aerophagia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Anal fissure | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Diarrhoea | | | |

| | | | |
|----------------------------------|-----------------|--|--|
| subjects affected / exposed | 4 / 4 (100.00%) | | |
| occurrences (all) | 32 | | |
| Constipation | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Breath odour | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Aphthous ulcer | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Anal haemorrhage | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dyschezia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dry mouth | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastritis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gingival bleeding | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gingival pain | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypoaesthesia oral | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hiatus hernia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Haematochezia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nausea | | | |
| subjects affected / exposed | 4 / 4 (100.00%) | | |
| occurrences (all) | 14 | | |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Mesenteric vein thrombosis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Lip pain | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Noninfective gingivitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Odynophagia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rectal haemorrhage | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oral mucosal blistering | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oral pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Periodontal disease | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Stomatitis | | | |
| subjects affected / exposed | 3 / 4 (75.00%) | | |
| occurrences (all) | 7 | | |
| Tongue ulceration | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Toothache | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 3 / 4 (75.00%) | | |
| occurrences (all) | 7 | | |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | | |
| occurrences (all) | 6 | | |
| Drug eruption | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dermatitis allergic | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|-----------------------------|-----------------|--|--|
| Dermatitis acneiform | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Blister | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Alopecia | | | |
| subjects affected / exposed | 4 / 4 (100.00%) | | |
| occurrences (all) | 4 | | |
| Acne | | | |
| subjects affected / exposed | 3 / 4 (75.00%) | | |
| occurrences (all) | 3 | | |
| Onycholysis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Onychoclasia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Onychalgia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nail toxicity | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Eczema | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Nail disorder | | | |
| subjects affected / exposed | 4 / 4 (100.00%) | | |
| occurrences (all) | 10 | | |
| Nail ridging | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Erythema | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|---|-----------------|--|--|
| Ecchymosis | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Onychomadesis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rash erythematous | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Rash | | | |
| subjects affected / exposed | 4 / 4 (100.00%) | | |
| occurrences (all) | 6 | | |
| Purpura | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pruritus allergic | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pruritus | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Pain of skin | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin fissures | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 2 | | |
| Skin exfoliation | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin disorder | | | |

| | | | |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin discolouration | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rash macular | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | | |
| occurrences (all) | 4 | | |
| Rash pruritic | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Scab | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rash papular | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Xeroderma | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vascular skin disorder | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Neurogenic bladder | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|---|----------------|--|--|
| Renal failure | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | | |
| occurrences (all) | 3 | | |
| Arthritis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 2 | | |
| Bone pain | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 2 | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Joint swelling | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Musculoskeletal discomfort | | | |

| | | | |
|------------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Neck pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Myalgia | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | | |
| occurrences (all) | 4 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Osteopenia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Spinal pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pain in jaw | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Systemic lupus erythematosus | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infections and infestations | | | |
| Eye infection | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Ear infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|-----------------------------|----------------|--|--|
| Folliculitis | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 6 | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Cystitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dermatitis infected | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infected cyst | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hordeolum | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Herpes virus infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Fungal skin infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|-----------------------------------|----------------|--|--|
| Fungal foot infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | | |
| occurrences (all) | 3 | | |
| Nail infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nail bed infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Mastitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Localised infection | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 2 | | |
| Laryngitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Influenza | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rash pustular | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|-----------------------------|----------------|--|--|
| Pustule | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Paronychia | | | |
| subjects affected / exposed | 3 / 4 (75.00%) | | |
| occurrences (all) | 8 | | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Septic rash | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tooth abscess | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tracheitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|---|---------------------|--|--|
| Vascular device infection subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | | |
| Vaginal infection subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 1 | | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | | |
| Vulvovaginal candidiasis subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | | |
| Metabolism and nutrition disorders | | | |
| Hyperkalaemia subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | | |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | | |
| Dehydration subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 3 / 4 (75.00%) 3 | | |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | | |
| Hyponatraemia subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | | |
| Hypokalaemia | | | |

| | | | |
|-----------------------------|---------------|--|--|
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| occurrences (all) | 0 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 13 January 2006 | Amendment 01: The protocol was amended to include pharmacokinetic sampling in the Phase I part of the study. Inclusion/exclusion criteria were amended to facilitate recruitment. The prohibited medication list was revised. |
| 08 December 2006 | Amendment 2: The protocol was amended to include additional cohorts in Phase I to investigate doses of lapatinib (750mg, 1000mg, 1250mg, 1500mg) with 75mg/m ² once every 3 weeks docetaxel plus standard weekly doses of trastuzumab with prophylactic use of growth factors in all subjects and two further additional cohorts of subjects in the Phase I design to investigate the safety and tolerability of once every 3 weeks trastuzumab in combination with once every 3 weeks docetaxel plus lapatinib and 3- weekly trastuzumab with lapatinib as maintenance therapy. |
| 13 June 2008 | Amendment 3: The protocol was amended to include information regarding hepatotoxicity associated with lapatinib treatment, the allowance of the use of once every 3 weeks trastuzumab post completion of docetaxel, removal of cohort Z (1000mg lapatinib once daily plus 3-weekly trastuzumab after chemotherapy (docetaxel) course), and addition of a 6th optional cohort. |
| 14 July 2008 | Amendment 4: As part of the liver toxicity update of GM2003/00455/003, inclusion of pharmacokinetics sample needing to be taken has been added to the follow up criteria in Section 7.2.1.2. |
| 18 November 2008 | Amendment 5: The protocol was amended to allow more subjects to be investigated at the doses used in cohort 1D following its successful completion with the first 3 subjects with no dose limiting toxicities. Amendment to the wording regarding the use of three weekly trastuzumab post completion of docetaxel administration. Amendment to exclusion criteria 6. Allowance for investigators to perform efficacy assessments every 12 weeks once they have completed 24 weeks of treatment rather than every 6 weeks. |
| 28 August 2012 | Amendment 6: Added Long Term Follow-Up Phase. Discontinuation of many specific efficacy and safety assessments. The study was stopped for subjects in post treatment follow up. Continued access to study treatment lapatinib was permitted for subjects ongoing at the time of implementation of this amendment. Subjects on post treatment follow up were withdrawn. Changed subject visit frequency to Investigator Discretion as per institutional/local standards of medical care. |
| 20 February 2013 | Amendment 7 (country specific amendment for France): New information regarding diarrhea and dermatological (rash) management added. |
| 03 October 2016 | Amendment 8: Deleted or replaced references to GSK or its staff with that of Novartis/Novartis and its authorized agents. Administrative changes to align with Novartis processes and procedures. Replaced reference to Investigational product from non-commercial sources with that of commercial supply. |

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.

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> for complete trial results.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/23878115>