

**Clinical trial results:****A Phase 1/2 Study of Neratinib (HKI-272) in Combination with Vinorelbine in Subjects with Solid Tumors and Metastatic Breast Cancer
Summary**

| | |
|--------------------------|-------------------|
| EudraCT number | 2007-007885-39 |
| Trial protocol | BE PL FR NL GB SE |
| Global end of trial date | 07 June 2018 |

Results information

| | |
|-----------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 06 July 2019 |
| First version publication date | 25 December 2016 |
| Version creation reason | <ul style="list-style-type: none">• New data added to full data setUpdate to reflect final study close out. |
| Summary attachment (see zip file) | 3144A1-2204 PDS (3144A1-2204 (B1891015) Public Disclosure Synopsis .doc.pdf) |

Trial information**Trial identification**

| | |
|-----------------------|----------------|
| Sponsor protocol code | 3144A1-2204-WW |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00706030 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Puma Biotechnology, Inc. |
| Sponsor organisation address | 10880 Wilshire Blvd, Suite 2150, Los Angeles, United States, 90024 |
| Public contact | Senior Director, Clinical Operations, Puma Biotechnology, Inc, 001 4242486550, clinicaltrials@pumabiotechnology.com |
| Scientific contact | Senior Director, Clinical Operations, Puma Biotechnology, Inc, 001 4242486550, clinicaltrials@pumabiotechnology.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 | 07 June 2018 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 07 June 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Part 1: The primary objectives of part 1 of the study are to assess the safety and tolerability and to define the maximum tolerated dose (MTD) of HKI-272 in combination with vinorelbine in subjects with advanced solid tumors.

Part 2: The primary objective of part 2 of the study is to estimate the ORR for subjects with ErbB-2-positive breast cancer treated at the MTD of HKI-272 in combination with vinorelbine.

Treatment Extension Period: The primary objective of the Treatment Extension Period is to provide continuous treatment to patients who continue to derive clinical benefit from study participation after the Part 2 objectives have been reached.

Protection of trial subjects:

This study was designed and monitored in accordance with Sponsor procedures, which comply with the ethical principles of the International Council for Harmonisation (ICH) Good Clinical Practice (GCP), including the Declaration of Helsinki and the applicable laws and regulations. The protocol, the investigator's brochure, and the informed consent form (ICF) for this clinical study were submitted to an institutional review board (IRB) or an independent ethics committee (IEC) for review and written approval. Any subsequent amendments to the protocol or any revisions to the ICF were submitted for IRB or IEC review and written approval. This study was conducted in accordance with the ICH Guideline for GCP and the ethical principles that have their origins in the Declaration of Helsinki. All investigators have provided written commitments to comply with GCP standards and the protocol. Clinical trial data were monitored at regular intervals by the Sponsor or their representative throughout the study to verify compliance to study protocol, completeness, accuracy and consistency of the data and adherence to local regulations on the conduct of clinical research. Patients may discontinued or were withdrawn from the study if any of the following occurred: documented disease progression; need for bisphosphonates during treatment period or palliative radiation therapy, if progressive disease was not ruled out, including whole-brain irradiation for documented central nervous system disease; required treatment with prohibited concomitant therapy; next dose was withheld for longer than 3 consecutive weeks due to test article-related toxicity; need for more than 2 dose reductions of neratinib and/or vinorelbine; any Grade 4 nonhematologic toxicity that was test article related; and pregnancy.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 29 April 2008 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Belgium: 16 |
| Country: Number of subjects enrolled | China: 16 |
| Country: Number of subjects enrolled | Spain: 11 |

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | France: 7 |
| Country: Number of subjects enrolled | United Kingdom: 4 |
| Country: Number of subjects enrolled | Hong Kong: 4 |
| Country: Number of subjects enrolled | Netherlands: 1 |
| Country: Number of subjects enrolled | Poland: 8 |
| Country: Number of subjects enrolled | Sweden: 3 |
| Country: Number of subjects enrolled | Taiwan: 3 |
| Country: Number of subjects enrolled | United States: 18 |
| Worldwide total number of subjects | 91 |
| 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) | 79 |
| From 65 to 84 years | 12 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects had to meet all inclusion criteria and not meet any exclusion criteria to participate in this study. A signed and dated informed consent was required before any screen procedures were done.

Period 1

| | |
|------------------------------|-----------------------------------|
| Period 1 title | Treatment Period (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 | Part 1 Ner160 + Vinorelbine |

Arm description:

In Part 1, subjects with advanced solid tumors were to be enrolled in the dose group Ner160mg+Vinorelbine. AEs and DLTs were assessed from the first dose of test article through Day 21. A DLT was defined as any of the following related drug:

- 1) Grade 3 or 4 nonhematologic toxicity.
- 2) Grade 3 diarrhea lasting >2 days while the subject was on optimal medical therapy or that was associated with fever or dehydration.
- 3) Grade 4 neutropenia lasting 7 or more days or Grade 4 febrile neutropenia.
- 4) Grade 4 thrombocytopenia lasting 3 or more days or complicated with bleeding.
- 5) Delayed recovery (to NCI) Grade ≤ 1 or Baseline) from 1 of the above listed toxicities related to combo and delayed next dose by more than 3 weeks.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Neratinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

4 neratinib 40-mg tables, taken with food, preferably in the morning.

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

Dosage and administration details:

25 mg/m² intravenous on day 1 and day 8 of a 21-day cycle.

| | |
|------------------|-----------------------------|
| Arm title | Part 1 Ner240 + Vinorelbine |
|------------------|-----------------------------|

Arm description:

In Part 1, subjects with advanced solid tumors were to be enrolled in the dose group Ner240mg+Vinorelbine. AEs and DLTs were assessed from the first dose of test article through Day 21. A DLT was defined as any of the following related drug:

- 1) Grade 3 or 4 nonhematologic toxicity.
- 2) Grade 3 diarrhea lasting >2 days while the subject was on optimal medical therapy or that was associated with fever or dehydration.
- 3) Grade 4 neutropenia lasting 7 or more days or Grade 4 febrile neutropenia.
- 4) Grade 4 thrombocytopenia lasting 3 or more days or complicated with bleeding.
- 5) Delayed recovery (to NCI) Grade ≤ 1 or Baseline) from 1 of the above listed toxicities related to combo and delayed next dose by more than 3 weeks.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Neratinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

1 neratinib 240-mg tables, taken with food, preferably in the morning.

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

Dosage and administration details:

25 mg/m² intravenous on day 1 and day 8 of a 21-day cycle.

| | |
|------------------|---|
| Arm title | Part 2 Ner240 + Vinorelbine, no Prior Lap |
|------------------|---|

Arm description:

Neratinib 240 mg qd + Vinorelbine 25 mg/m² IV on day 1 and 8 of a 21 day cycle; patients who had not received prior lapatinib.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Neratinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

1 neratinib 240-mg tables, taken with food, preferably in the morning.

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

Dosage and administration details:

25 mg/m² intravenous on day 1 and day 8 of a 21-day cycle.

| | |
|------------------|--|
| Arm title | Part 2 Ner240 + Vinorelbine, Prior Lap |
|------------------|--|

Arm description:

Neratinib 240 mg qd + Vinorelbine 25 mg/m² IV on day 1 and 8 of a 21 day cycle; patients who had received prior lapatinib.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Neratinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

1 neratinib 240-mg tables, taken with food, preferably in the morning.

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

Dosage and administration details:

25 mg/m² intravenous on day 1 and day 8 of a 21-day cycle.

| Number of subjects in period 1 | Part 1 Ner160 + Vinorelbine | Part 1 Ner240 + Vinorelbine | Part 2 Ner240 + Vinorelbine, no Prior Lap |
|--------------------------------|-----------------------------|-----------------------------|---|
| | | | |
| Started | 6 | 6 | 64 |
| Completed | 0 | 0 | 0 |
| Not completed | 6 | 6 | 64 |
| Adverse event, serious fatal | - | - | 1 |
| Consent withdrawn by subject | 1 | - | 5 |
| Physician decision | - | - | 3 |
| Adverse event, non-fatal | 1 | - | 4 |
| Symptomatic Deterioration | - | - | 1 |
| Lost to follow-up | - | - | 1 |
| Disease Progression | 4 | 6 | 46 |
| Study discontinued by sponsor | - | - | 1 |
| Protocol deviation | - | - | 2 |

| Number of subjects in period 1 | Part 2 Ner240 + Vinorelbine, Prior Lap |
|--------------------------------|--|
| Started | 15 |
| Completed | 0 |
| Not completed | 15 |
| Adverse event, serious fatal | - |
| Consent withdrawn by subject | - |
| Physician decision | - |
| Adverse event, non-fatal | 2 |
| Symptomatic Deterioration | - |
| Lost to follow-up | - |
| Disease Progression | 12 |
| Study discontinued by sponsor | - |
| Protocol deviation | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Treatment Period |
|-----------------------|------------------|

Reporting group description: -

| Reporting group values | Treatment Period | Total | |
|---|------------------|-------|--|
| Number of subjects | 91 | 91 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | | 0 | |
| Newborns (0-27 days) | | 0 | |
| Infants and toddlers (28 days-23 months) | | 0 | |
| Children (2-11 years) | | 0 | |
| Adolescents (12-17 years) | | 0 | |
| Adults (18-64 years) | | 0 | |
| From 65-84 years | | 0 | |
| 85 years and over | | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 51.6 | | |
| standard deviation | ± 10.8 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 89 | 89 | |
| Male | 2 | 2 | |

End points

End points reporting groups

| | |
|---|---|
| Reporting group title | Part 1 Ner160 + Vinorelbine |
| Reporting group description: In Part 1, subjects with advanced solid tumors were to be enrolled in the dose group Ner160mg+Vinorelbine. AEs and DLTs were assessed from the first dose of test article through Day 21. A DLT was defined as any of the following related drug: 1) Grade 3 or 4 nonhematologic toxicity. 2) Grade 3 diarrhea lasting >2 days while the subject was on optimal medical therapy or that was associated with fever or dehydration. 3) Grade 4 neutropenia lasting 7 or more days or Grade 4 febrile neutropenia. 4) Grade 4 thrombocytopenia lasting 3 or more days or complicated with bleeding. 5) Delayed recovery (to NCI) Grade <=1 or Baseline) from 1 of of the above listed toxicities related to combo and delayed next dose by more than 3 weeks. | |
| Reporting group title | Part 1 Ner240 + Vinorelbine |
| Reporting group description: In Part 1, subjects with advanced solid tumors were to be enrolled in the dose group Ner240mg+Vinorelbine. AEs and DLTs were assessed from the first dose of test article through Day 21. A DLT was defined as any of the following related drug: 1) Grade 3 or 4 nonhematologic toxicity. 2) Grade 3 diarrhea lasting >2 days while the subject was on optimal medical therapy or that was associated with fever or dehydration. 3) Grade 4 neutropenia lasting 7 or more days or Grade 4 febrile neutropenia. 4) Grade 4 thrombocytopenia lasting 3 or more days or complicated with bleeding. 5) Delayed recovery (to NCI) Grade <=1 or Baseline) from 1 of of the above listed toxicities related to combo and delayed next dose by more than 3 weeks. | |
| Reporting group title | Part 2 Ner240 + Vinorelbine, no Prior Lap |
| Reporting group description: Neratinib 240 mg qd + Vinorelbine 25 mg/m2 IV on day 1 and 8 of a 21 day cycle; patients who had not received prior lapatinib. | |
| Reporting group title | Part 2 Ner240 + Vinorelbine, Prior Lap |
| Reporting group description: Neratinib 240 mg qd + Vinorelbine 25 mg/m2 IV on day 1 and 8 of a 21 day cycle; patients who had received prior lapatinib. | |

Primary: Objective Response Rate - Part 2

| | |
|--|--|
| End point title | Objective Response Rate - Part 2 ^{[1][2]} |
| End point description: | |
| End point type | Primary |
| End point timeframe: hold | |
| Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No comparisons between the 2 groups in Part 2 of the study were planned for the objective response rate. [2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Efficacy assessments to derive the objective response rate were collected only for subjects in Part 2. | |

| End point values | Part 2 Ner240 + Vinorelbine, no Prior Lap | Part 2 Ner240 + Vinorelbine, Prior Lap | | |
|----------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 56 ^[3] | 12 ^[4] | | |
| Units: percentage | | | | |
| number (confidence interval 95%) | 58.9 (45.0 to 71.9) | 50 (21.1 to 78.9) | | |

Notes:

[3] - Evaluable population.

[4] - Evaluable Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of Patients with Dose Limiting Toxicities

| | |
|-----------------|--|
| End point title | Number of Patients with Dose Limiting Toxicities ^{[5][6]} |
|-----------------|--|

End point description:

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

End point timeframe:

From Day 1 of dose through Day 21

Notes:

[5] - 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: Part 1 of the study was dose escalation and there were no comparisons planned between treatment groups.

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

Justification: Dose limiting toxicities only collected in Part 1 of the study.

| End point values | Part 1 Ner160 + Vinorelbine | Part 1 Ner240 + Vinorelbine | | |
|-----------------------------|-----------------------------|-----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 | 6 | | |
| Units: Patients | 1 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: AUC at Day 21 Neratinib

| | |
|-----------------|--|
| End point title | AUC at Day 21 Neratinib ^[7] |
|-----------------|--|

End point description:

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

End point timeframe:

Day 8

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic samples were collected only for subjects in Part 2.

| End point values | Part 2 Ner240 + Vinorelbine, no Prior Lap | Part 2 Ner240 + Vinorelbine, Prior Lap | | |
|----------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 57 | 13 | | |
| Units: ng*h/mL | | | | |
| number (confidence interval 95%) | 1945 (1514 to 2374) | 2136 (794 to 3478) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

1st dose through 28 days after last dose

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | P1 N160+V25 |
|-----------------------|-------------|

Reporting group description:

Part 1 Ner160 + Vinorelbine 25 mg/m2

| | |
|-----------------------|--------------|
| Reporting group title | P1 N2400+V25 |
|-----------------------|--------------|

Reporting group description:

Part 1 Ner240 + Vinorelbine 25 mg/m2

| | |
|-----------------------|------------------|
| Reporting group title | P2 N2400+V25 NPL |
|-----------------------|------------------|

Reporting group description:

Neratinib 240 mg qd + Vinorelbine 25 mg/m2 IV on day 1 and 8 of a 21 day cycle; patients who had not received prior lapatinib

| | |
|-----------------------|-----------------|
| Reporting group title | P2 N2400+V25 PL |
|-----------------------|-----------------|

Reporting group description:

Neratinib 240 mg qd + Vinorelbine 25 mg/m2 IV on day 1 and 8 of a 21 day cycle; patients who had received prior lapatinib

| Serious adverse events | P1 N160+V25 | P1 N2400+V25 | P2 N2400+V25 NPL |
|---|----------------|----------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 3 / 6 (50.00%) | 21 / 64 (32.81%) |
| number of deaths (all causes) | 0 | 2 | 2 |
| number of deaths resulting from adverse events | 0 | 2 | 1 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer metastatic | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac myxoma | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant melanoma | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 64 (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 |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 3 / 64 (4.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-small cell lung cancer metastatic | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 64 (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 |
| Tumour associated fever | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 64 (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 |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Phlebitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 64 (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 |
| Vena cava thrombosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |

| | | | |
|--|---------------|----------------|----------------|
| Mastectomy | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Disease progression | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 64 (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 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 64 (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 |
| Reproductive system and breast disorders | | | |
| Uterine prolapse | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cough | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Amylase increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 64 (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 creatinine increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 64 (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 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 64 (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 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---------------|---------------|----------------|
| Injury, poisoning and procedural complications | | | |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Ataxia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain oedema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| 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 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 64 (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 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 4 / 64 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 3 / 64 (4.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 64 (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 |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 64 (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 |

| | | | |
|---|-----------------|---------------|----------------|
| Ureteric haemorrhage | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 64 (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 | | | |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 64 (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 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 2 / 64 (3.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Serious adverse events | | | |
| | P2 N2400+V25 PL | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 15 (33.33%) | | |
| number of deaths (all causes) | 1 | | |

| | | | |
|---|----------------|--|--|
| number of deaths resulting from adverse events | 1 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer metastatic | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac myxoma | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malignant melanoma | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Non-small cell lung cancer metastatic | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tumour associated fever | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tumour pain | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Orthostatic hypotension | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Phlebitis | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vena cava thrombosis | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Mastectomy | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Disease progression | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Uterine prolapse | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cough | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Amylase increased | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aspartate aminotransferase increased | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Ataxia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Brain oedema | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Headache | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic pain | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ureteric haemorrhage | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 15 (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 | P1 N160+V25 | P1 N2400+V25 | P2 N2400+V25 NPL |
|---|-----------------|-----------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 6 / 6 (100.00%) | 6 / 6 (100.00%) | 64 / 64 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour associated fever | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 2 / 64 (3.13%) |
| occurrences (all) | 0 | 1 | 4 |
| Hypotension | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Lymphoedema | | | |

| | | | |
|--|----------------|----------------|------------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 3 / 64 (4.69%) |
| occurrences (all) | 0 | 0 | 3 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 6 (33.33%) | 16 / 64 (25.00%) |
| occurrences (all) | 0 | 4 | 48 |
| Chest discomfort | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences (all) | 1 | 0 | 1 |
| Fatigue | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 3 / 6 (50.00%) | 24 / 64 (37.50%) |
| occurrences (all) | 3 | 4 | 72 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 5 / 64 (7.81%) |
| occurrences (all) | 0 | 0 | 9 |
| Malaise | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 4 / 64 (6.25%) |
| occurrences (all) | 0 | 0 | 6 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 12 / 64 (18.75%) |
| occurrences (all) | 1 | 0 | 26 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 7 / 64 (10.94%) |
| occurrences (all) | 0 | 1 | 10 |
| Pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 2 / 64 (3.13%) |
| occurrences (all) | 1 | 0 | 3 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 19 / 64 (29.69%) |
| occurrences (all) | 0 | 1 | 33 |
| Thrombosis in device | | | |

| | | | |
|--|--------------------|--------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Reproductive system and breast disorders | | | |
| Breast pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 2 / 64 (3.13%) |
| occurrences (all) | 0 | 1 | 2 |
| Menstruation irregular | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Vulvovaginal pruritus | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 13 / 64 (20.31%) |
| occurrences (all) | 1 | 1 | 23 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 3 / 6 (50.00%) | 7 / 64 (10.94%) |
| occurrences (all) | 0 | 3 | 8 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 3 / 6 (50.00%) | 5 / 64 (7.81%) |
| occurrences (all) | 0 | 4 | 6 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 4 / 64 (6.25%) |
| occurrences (all) | 1 | 0 | 6 |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences (all) | 2 | 0 | 1 |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 4 / 64 (6.25%) |
| occurrences (all) | 0 | 0 | 8 |
| Rhinorrhoea | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 2 / 6 (33.33%) 2 | 2 / 64 (3.13%) 2 |
| Psychiatric disorders | | | |
| Abnormal behaviour | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Anxiety | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 5 / 64 (7.81%) |
| occurrences (all) | 2 | 1 | 6 |
| Depression | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 3 / 64 (4.69%) |
| occurrences (all) | 0 | 1 | 3 |
| Insomnia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 5 / 64 (7.81%) |
| occurrences (all) | 0 | 0 | 15 |
| Investigations | | | |
| Alanine aminotransferase | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 12 / 64 (18.75%) |
| occurrences (all) | 0 | 0 | 41 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 9 / 64 (14.06%) |
| occurrences (all) | 1 | 0 | 29 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 2 / 64 (3.13%) |
| occurrences (all) | 0 | 0 | 2 |
| Blood magnesium decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 2 / 64 (3.13%) |
| occurrences (all) | 0 | 0 | 10 |
| Haemoglobin decreased | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 4 / 64 (6.25%) |
| occurrences (all) | 0 | 0 | 15 |
| High density lipoprotein decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Red blood cells urine | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 6 (33.33%) | 4 / 64 (6.25%) |
| occurrences (all) | 0 | 2 | 4 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 5 / 64 (7.81%) |
| occurrences (all) | 0 | 0 | 25 |
| Injury, poisoning and procedural complications | | | |
| Wound | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Wound complication | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 5 / 64 (7.81%) |
| occurrences (all) | 0 | 0 | 5 |
| Nervous system disorders | | | |

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|-------------------------------|----------------|----------------|------------------|
| Ageusia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Balance disorder | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 11 / 64 (17.19%) |
| occurrences (all) | 1 | 0 | 15 |
| Dysgeusia | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 1 / 6 (16.67%) | 6 / 64 (9.38%) |
| occurrences (all) | 4 | 1 | 7 |
| Headache | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 2 / 6 (33.33%) | 18 / 64 (28.13%) |
| occurrences (all) | 3 | 2 | 33 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 4 / 64 (6.25%) |
| occurrences (all) | 0 | 0 | 6 |
| Lethargy | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Migraine | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 9 / 64 (14.06%) |
| occurrences (all) | 2 | 0 | 14 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 5 / 64 (7.81%) |
| occurrences (all) | 0 | 0 | 5 |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 2 / 64 (3.13%) |
| occurrences (all) | 1 | 0 | 2 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 0 / 6 (0.00%) | 9 / 64 (14.06%) |
| occurrences (all) | 4 | 0 | 14 |

| | | | |
|---|---------------------|---------------------|-------------------------|
| Somnolence subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 6 (16.67%) 1 | 2 / 64 (3.13%) 2 |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 2 / 6 (33.33%) 3 | 2 / 6 (33.33%) 2 | 15 / 64 (23.44%) 78 |
| Leukopenia subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 6 (0.00%) 0 | 21 / 64 (32.81%) 130 |
| Neutropenia subjects affected / exposed occurrences (all) | 3 / 6 (50.00%) 5 | 1 / 6 (16.67%) 1 | 36 / 64 (56.25%) 187 |
| Ear and labyrinth disorders | | | |
| Vertigo subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 6 (0.00%) 0 | 4 / 64 (6.25%) 6 |
| Eye disorders | | | |
| Conjunctivitis subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 6 (0.00%) 0 | 3 / 64 (4.69%) 5 |
| Eye irritation subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 6 (16.67%) 1 | 1 / 64 (1.56%) 1 |
| Lacrimation increased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Retinal haemorrhage subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 6 (16.67%) 1 | 0 / 64 (0.00%) 0 |
| Scleral haemorrhage subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 6 (16.67%) 1 | 0 / 64 (0.00%) 0 |
| Vision blurred subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 6 (16.67%) 1 | 5 / 64 (7.81%) 6 |
| Gastrointestinal disorders | | | |

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|-----------------------------|-----------------|-----------------|------------------|
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 4 / 64 (6.25%) |
| occurrences (all) | 0 | 0 | 7 |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 6 (33.33%) | 22 / 64 (34.38%) |
| occurrences (all) | 1 | 2 | 35 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 8 / 64 (12.50%) |
| occurrences (all) | 0 | 0 | 9 |
| Ascites | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Constipation | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 5 / 6 (83.33%) | 10 / 64 (15.63%) |
| occurrences (all) | 5 | 6 | 19 |
| Diarrhoea | | | |
| subjects affected / exposed | 6 / 6 (100.00%) | 6 / 6 (100.00%) | 61 / 64 (95.31%) |
| occurrences (all) | 32 | 12 | 322 |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 5 / 64 (7.81%) |
| occurrences (all) | 1 | 0 | 10 |
| Gingival ulceration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 6 / 64 (9.38%) |
| occurrences (all) | 0 | 0 | 8 |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 10 / 64 (15.63%) |
| occurrences (all) | 0 | 0 | 14 |
| Nausea | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 3 / 6 (50.00%) | 35 / 64 (54.69%) |
| occurrences (all) | 7 | 3 | 87 |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 8 / 64 (12.50%) |
| occurrences (all) | 1 | 0 | 12 |

| | | | |
|--|---------------------|---------------------|------------------------|
| Tongue discolouration subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 0 / 6 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Vomiting subjects affected / exposed occurrences (all) | 2 / 6 (33.33%) 4 | 1 / 6 (16.67%) 4 | 23 / 64 (35.94%) 46 |
| Hepatobiliary disorders Jaundice subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 6 (16.67%) 1 | 0 / 64 (0.00%) 0 |
| Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 0 / 6 (0.00%) 0 | 12 / 64 (18.75%) 14 |
| Blister subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Dermatitis acneiform subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 6 (0.00%) 0 | 3 / 64 (4.69%) 3 |
| Dry skin subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 6 (16.67%) 1 | 7 / 64 (10.94%) 10 |
| Hyperhidrosis subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 6 (16.67%) 1 | 1 / 64 (1.56%) 1 |
| Nail disorder subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 0 / 6 (0.00%) 0 | 1 / 64 (1.56%) 1 |
| Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 6 (0.00%) 0 | 2 / 64 (3.13%) 2 |
| Rash subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 4 | 0 / 6 (0.00%) 0 | 10 / 64 (15.63%) 19 |
| Skin fissures | | | |

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| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 4 / 64 (6.25%) |
| occurrences (all) | 0 | 1 | 4 |
| Skin toxicity | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal and urinary disorders | | | |
| Bladder prolapse | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Chromaturia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 1 / 64 (1.56%) |
| occurrences (all) | 0 | 1 | 1 |
| Dysuria | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 4 / 64 (6.25%) |
| occurrences (all) | 0 | 0 | 6 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haemoglobinuria | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Leukocyturia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 2 / 64 (3.13%) |
| occurrences (all) | 0 | 0 | 3 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ureteric haemorrhage | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 0 / 6 (0.00%) | 6 / 64 (9.38%) |
| occurrences (all) | 4 | 0 | 6 |
| Back pain | | | |

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| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 6 (33.33%) | 7 / 64 (10.94%) |
| occurrences (all) | 1 | 3 | 10 |
| Bone pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 3 / 64 (4.69%) |
| occurrences (all) | 0 | 0 | 4 |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 12 / 64 (18.75%) |
| occurrences (all) | 1 | 1 | 19 |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 2 / 64 (3.13%) |
| occurrences (all) | 1 | 0 | 3 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 4 / 64 (6.25%) |
| occurrences (all) | 1 | 0 | 6 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 2 / 64 (3.13%) |
| occurrences (all) | 3 | 1 | 2 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 10 / 64 (15.63%) |
| occurrences (all) | 0 | 1 | 17 |
| Neck pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 2 / 64 (3.13%) |
| occurrences (all) | 1 | 0 | 2 |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 4 / 64 (6.25%) |
| occurrences (all) | 5 | 1 | 4 |
| Infections and infestations | | | |
| Device related infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 9 / 64 (14.06%) |
| occurrences (all) | 0 | 1 | 11 |

| | | | |
|------------------------------------|----------------|----------------|------------------|
| Oral herpes | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Paronychia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 3 / 64 (4.69%) |
| occurrences (all) | 0 | 0 | 3 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 7 / 64 (10.94%) |
| occurrences (all) | 0 | 1 | 8 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 7 / 64 (10.94%) |
| occurrences (all) | 0 | 0 | 8 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 6 (33.33%) | 6 / 64 (9.38%) |
| occurrences (all) | 1 | 3 | 8 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 6 (33.33%) | 20 / 64 (31.25%) |
| occurrences (all) | 2 | 4 | 33 |
| Dehydration | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 4 / 64 (6.25%) |
| occurrences (all) | 1 | 0 | 6 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences (all) | 0 | 0 | 3 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 5 / 64 (7.81%) |
| occurrences (all) | 0 | 0 | 10 |
| Hyponatraemia | | | |

| | | | |
|-----------------------------|----------------|---------------|----------------|
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences (all) | 1 | 0 | 7 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 64 (1.56%) |
| occurrences (all) | 0 | 0 | 2 |

| | | | |
|---|-------------------|--|--|
| Non-serious adverse events | P2 N2400+V25 PL | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 15 / 15 (100.00%) | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour associated fever | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tumour pain | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 3 | | |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Lymphoedema | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Thrombophlebitis | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 5 / 15 (33.33%) | | |
| occurrences (all) | 11 | | |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|--|-----------------|--|--|
| Fatigue | | | |
| subjects affected / exposed | 4 / 15 (26.67%) | | |
| occurrences (all) | 6 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Malaise | | | |
| subjects affected / exposed | 2 / 15 (13.33%) | | |
| occurrences (all) | 2 | | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 3 | | |
| Pain | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 15 (13.33%) | | |
| occurrences (all) | 3 | | |
| Thrombosis in device | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Reproductive system and breast disorders | | | |
| Breast pain | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Menstruation irregular | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 2 | | |
| Ovarian cyst | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Vulvovaginal pruritus | | | |

| | | | |
|--|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 3 / 15 (20.00%) | | |
| occurrences (all) | 3 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 3 / 15 (20.00%) | | |
| occurrences (all) | 4 | | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 2 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Psychiatric disorders | | | |
| Abnormal behaviour | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Depression | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Insomnia | | | |

| | | | |
|--------------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Investigations | | | |
| Alanine aminotransferase | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 3 / 15 (20.00%) | | |
| occurrences (all) | 7 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 4 / 15 (26.67%) | | |
| occurrences (all) | 7 | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 4 | | |
| Blood magnesium decreased | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 2 / 15 (13.33%) | | |
| occurrences (all) | 4 | | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 4 | | |
| High density lipoprotein decreased | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Red blood cells urine | | | |

| | | | |
|--|----------------------|--|--|
| subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | | |
| Weight decreased subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | | |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 3 | | |
| Injury, poisoning and procedural complications | | | |
| Wound subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | | |
| Wound complication subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | | |
| Cardiac disorders | | | |
| Palpitations subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | | |
| Tachycardia subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | | |
| Nervous system disorders | | | |
| Ageusia subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | | |
| Balance disorder subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | | |
| Dizziness subjects affected / exposed occurrences (all) | 3 / 15 (20.00%) 3 | | |
| Dysgeusia subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | | |
| Headache | | | |

| | | | |
|--------------------------------------|-----------------|--|--|
| subjects affected / exposed | 2 / 15 (13.33%) | | |
| occurrences (all) | 6 | | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Lethargy | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Migraine | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 2 / 15 (13.33%) | | |
| occurrences (all) | 4 | | |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 5 / 15 (33.33%) | | |
| occurrences (all) | 9 | | |
| Leukopenia | | | |
| subjects affected / exposed | 2 / 15 (13.33%) | | |
| occurrences (all) | 14 | | |
| Neutropenia | | | |
| subjects affected / exposed | 9 / 15 (60.00%) | | |
| occurrences (all) | 36 | | |

| | | | |
|--|--|--|--|
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | | |
| Eye disorders Conjunctivitis subjects affected / exposed occurrences (all) Eye irritation subjects affected / exposed occurrences (all) Lacrimation increased subjects affected / exposed occurrences (all) Retinal haemorrhage subjects affected / exposed occurrences (all) Scleral haemorrhage subjects affected / exposed occurrences (all) Vision blurred subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 3 0 / 15 (0.00%) 0 1 / 15 (6.67%) 1 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0 | | |
| Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Ascites subjects affected / exposed occurrences (all) Constipation | 0 / 15 (0.00%) 0 4 / 15 (26.67%) 6 3 / 15 (20.00%) 6 0 / 15 (0.00%) 0 | | |

| | | | |
|--|-------------------|--|--|
| subjects affected / exposed | 3 / 15 (20.00%) | | |
| occurrences (all) | 3 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 15 / 15 (100.00%) | | |
| occurrences (all) | 87 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gingival ulceration | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Mouth ulceration | | | |
| subjects affected / exposed | 2 / 15 (13.33%) | | |
| occurrences (all) | 3 | | |
| Nausea | | | |
| subjects affected / exposed | 7 / 15 (46.67%) | | |
| occurrences (all) | 17 | | |
| Stomatitis | | | |
| subjects affected / exposed | 2 / 15 (13.33%) | | |
| occurrences (all) | 4 | | |
| Tongue discolouration | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 10 / 15 (66.67%) | | |
| occurrences (all) | 16 | | |
| Hepatobiliary disorders | | | |
| Jaundice | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Blister | | | |
| subjects affected / exposed | 2 / 15 (13.33%) | | |
| occurrences (all) | 2 | | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Dry skin | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nail disorder | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 5 | | |
| Rash | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin fissures | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 2 | | |
| Skin toxicity | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Renal and urinary disorders | | | |
| Bladder prolapse | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Chromaturia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dysuria | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Haemoglobinuria | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Leukocyturia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 3 | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Ureteric haemorrhage | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 15 (13.33%) | | |
| occurrences (all) | 7 | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Bone pain | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Muscular weakness | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Myalgia | | | |
| subjects affected / exposed | 3 / 15 (20.00%) | | |
| occurrences (all) | 8 | | |
| Neck pain | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infections and infestations | | | |
| Device related infection | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 15 (13.33%) | | |
| occurrences (all) | 2 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Paronychia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 3 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|------------------------------------|-----------------|--|--|
| Sinusitis | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 2 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 15 (20.00%) | | |
| occurrences (all) | 3 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 7 / 15 (46.67%) | | |
| occurrences (all) | 12 | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 5 / 15 (33.33%) | | |
| occurrences (all) | 7 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 16 May 2008 | Amendment 1: Updated inclusion and exclusion criteria, dose limiting toxicity rules, dose adjustment rules, and the definition of the evaluable population. |
| 09 December 2008 | Amendment 2: Allowed enrollment of subjects who had relapsed under adjuvant treatment and those subjects who had skin disease (ie, as long as the skin lesions were measurable by CT/MRI). It was also amended to add CISH as an ErbB-2 testing method, extend the window for performing testing, to harmonize the reporting of medication errors, and to allow the use of neratinib 240 mg tablets. Conditions for destruction of test article on site were also revised. |
| 27 January 2010 | Amendment 3: Included additional unscheduled PK, chemistry, and coagulation testing for subjects with signs or symptoms of drug induced hepatic injury; to provide clarification regarding criteria for prior trastuzumab use; to provide clarification for the definition of evaluable population; to update the study contact information; and to remove the immunohistochemistry (IHC) testing methods specific to Part 1 of the protocol. |
| 22 March 2012 | Amendment 4: Updated the Sponsor to Puma and added a treatment extension period in order to allow subjects who continued to derive benefit from study participation to continue to receive test article with a reduced number of protocol required assessments. Amendment 4 enabled the Sponsor to continue to provide investigational product (IP) to these patients until disease progression, death or withdrawal from the study. During the treatment extension period, subject safety continued to be monitored through reporting of all adverse events (AEs), serious adverse events (SAEs), IP administration, and reasons for study withdrawal. Decision regarding laboratory assessments, monitoring for prohibited concomitant medications, and follow-up of disease progression were left to the investigators discretion to be performed as clinically indicated. No efficacy data were collected during the treatment extension period. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported