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	• New data added to full data set Update 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 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 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	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	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	1 / 6 (16.67%)	2 / 6 (33.33%)	2 / 64 (3.13%)
occurrences (all)	1	2	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			

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

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

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			

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	0 / 15 (0.00%)		
occurrences (all)	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	0 / 15 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
White blood cell count decreased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Wound			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Wound complication			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Ageusia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Balance disorder			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Dysgeusia			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	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	0 / 15 (0.00%)		
occurrences (all)	0		
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	3		
Eye irritation			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Lacrimation increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Retinal haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Scleral haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Vision blurred			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	6		
Abdominal pain upper			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	6		
Ascites			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Constipation			

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