Clinical trial results:
A Phase 1/2, Open-Label Study of Neratinib (HKI-272) in Combination with Capecitabine in Subjects with Solid Tumors and ERBB2-Positive Metastatic or Locally Advanced Breast Cancer

Summary

EudraCT number	2008-001662-85
Trial protocol	ES HU
Global end of trial date	01 June 2018

Results information

Result version number	v2 (current)
This version publication date	06 July 2019
First version publication date	31 December 2016
Version creation reason	
Summary attachment (see zip file)	3144A1-2206 PDS (3144A1-2206 (B1891017) Public Disclosure Synopsis .doc.pdf)

Trial information

Trial identification

Sponsor protocol code	3144A1-2206-WW

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00741260
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., 1 4242486500, clinicaltrials@pumabiotechnology.com
Scientific contact	Senior Director, Clinical Operations, Puma Biotechnology, Inc., 1 4242486500, 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	01 June 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Objectives
Part 1: The primary objectives of Part 1 were to assess the safety and tolerability, and to define the MTD of neratinib in combination with capecitabine in subjects with advanced solid tumors.
Part 2: The primary objectives of Part 2 of this study were to confirm the MTD identified in Part 1 by collecting further data on the safety and tolerability of the combination of neratinib and capecitabine at the MTD in subjects with erbB-2 positive breast cancer.

Secondary Objectives
Part 1: The secondary objective of Part 1 was to obtain preliminary anti-tumor activity for neratinib in combination with capecitabine.
Part 2: The secondary objectives of Part 2 were to obtain pharmacokinetic (PK) information, and to assess additional efficacy parameters including objective response rate (ORR = complete response [CR] +partial response [PR]), progression-free survival (PFS), clinical benefit rate (CR + PR + stable disease [SD] ≥24 weeks), and duration of response fo

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 (IB), 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 International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (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 were discontinued from the study if any of the following occurred: documented disease progression as determined by the investigator (following the definitions provided in the Response Criteria section), patients requiring initiation of bisphosphonate treatment, during the course of the study, were to be discontinued due to progressive disease unless disease progression could be completely ruled out and was clearly documented in the patient's source documentation, adverse event (AE), symptomatic deterioration, investigator request (with detailed documentation of reasoning), protocol deviation, discontinuation of the study by the sponsor, lost to follow-up, or death.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 December 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	Australia: 7
Country: Number of subjects enrolled	Brazil: 1
Country: Number of subjects enrolled	China: 13
Country: Number of subjects enrolled	Spain: 27
Country: Number of subjects enrolled	Hong Kong: 1
Country: Number of subjects enrolled	Croatia: 4
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Korea, Republic of: 14
Country: Number of subjects enrolled	Russian Federation: 8
Country: Number of subjects enrolled	United States: 27
Worldwide total number of subjects	105
EEA total number of subjects	34

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)	91
From 65 to 84 years	14
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.

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	N160+C1500

Arm description:

Part 1 of the study. Neratinib 160 mg / day in combination with Capecitabine 1500 mg/m2/day (750 mg/m2 bid)

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

Dosage and administration details:

750 mg/m2 bid, for a total of 1500 mg/m2 daily, on days 1-14 of each 21 day cycle.

Investigational medicinal product name	Neratinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Neratinib 4 40-mg tablets, qd, p.o., preferably with food in the morning.

Arm title	N240+C1500

Arm description:

Part 1 of the study. Neratinib 240 mg / day in combination with Capecitabine 1500 mg/m2/day (750 mg/m2 bid)

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:

Neratinib 240 mg qd po, preferably with food in the morning.

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet

Routes of administration	Oral use

Dosage and administration details:

750 mg/m2 bid, for a total of 1500 mg/m2 daily, on days 1-14 of each 21 day cycle.

Arm title	N240+C2000

Arm description:

Part 1 of the study. Neratinib 240 mg / day in combination with Capecitabine 2000 mg/m2/day (1000 mg/m2 bid)

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:

Neratinib 240 mg qd po, preferably with food in the morning.

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1000 mg/m2 bid, for a total of 2000 mg/m2 daily, on days 1-14 of each 21 day cycle.

Arm title	N200+C2000

Arm description:

Part 1 of the study. Neratinib 200 mg / day in combination with Capecitabine 2000 mg/m2/day (1000 mg/m2 bid)

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:

5 neratinib 40 mg tablets qd, preferably with food, in morning.

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine 1000 (mg/m2) BID (2000 mg/m2/day) on days 1 – 14 of each 21-day cycle

Arm title	N160+C2000

Arm description:

Part 1 of the study. Neratinib 160 mg / day in combination with Capecitabine 2000 mg/m2/day (1000 mg/m2 bid)

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:

Neratinib 4 40-mg tablets, qd, p.o., preferably with food in the morning.

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine 1000 mg/m2/day BID (2000 mg/m2/day) on days 1-14 of each 21 day cycle.

Arm title	P2 N240+C1500 NPL

Arm description:

Part 2 of the study. Neratinib 240 mg / day in combination with Capecitabine 1500mg/m2/day (750mg/m2 bid), for subjects who have 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:

Neratinib 240 mg qd po, preferably with food in the morning.

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

750 mg/m2 bid, for a total of 1500 mg/m2 daily, on days 1-14 of each 21 day cycle.

Arm title	P2 N240+C1500 PL

Arm description:

Part 2 of the study. Neratinib 240 mg / day in combination with Capecitabine 1500mg/m2/day (750mg/m2 bid), for subjects who have 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:

Neratinib 240 mg qd po, preferably with food in the morning.

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

750 mg/m2 bid, for a total of 1500 mg/m2 daily, on days 1-14 of each 21 day cycle.

Number of subjects in period 1	N160+C1500	N240+C1500	N240+C2000
Started	6	8	4
Completed	0	0	0
Not completed	6	8	4
Started new anti-cancer medication	-	-	-
Physician decision	1	2	-
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	1	-	1
Death	-	1	-
Discontinuation of study by sponsor	-	-	-
Disease Progression	4	5	3

Number of subjects in period 1	N200+C2000	N160+C2000	P2 N240+C1500 NPL
Started	6	9	65
Completed	0	0	0
Not completed	6	9	65
Started new anti-cancer medication	1	1	-
Physician decision	-	-	2
Consent withdrawn by subject	-	1	4
Adverse event, non-fatal	1	-	2
Death	1	2	4
Discontinuation of study by sponsor	-	-	4
Disease Progression	3	5	49

Number of subjects in period 1	P2 N240+C1500 PL
Started	7
Completed	0
Not completed	7
Started new anti-cancer medication	-
Physician decision	-
Consent withdrawn by subject	1
Adverse event, non-fatal	-
Death	-
Discontinuation of study by sponsor	-
Disease Progression	6

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Period

Reporting group description: -

Reporting group values	Treatment Period	Total	
Number of subjects	105	105	
Age categorical Units: Subjects			
Adults (18-64 years)	91	91	
From 65-84 years	14	14	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	52.4		
standard deviation	± 10.8	-	
Gender categorical Units: Subjects			
Female	93	93	
Male	12	12	

End points

End points reporting groups

Reporting group title	N160+C1500
Reporting group description:	
Part 1 of the study. Neratinib 160 mg / day in combination with Capecitabine 1500 mg/m2/day (750 mg/m2 bid)	
Reporting group title	N240+C1500
Reporting group description:	
Part 1 of the study. Neratinib 240 mg / day in combination with Capecitabine 1500 mg/m2/day (750 mg/m2 bid)	
Reporting group title	N240+C2000
Reporting group description:	
Part 1 of the study. Neratinib 240 mg / day in combination with Capecitabine 2000 mg/m2/day (1000 mg/m2 bid)	
Reporting group title	N200+C2000
Reporting group description:	
Part 1 of the study. Neratinib 200 mg / day in combination with Capecitabine 2000 mg/m2/day (1000 mg/m2 bid)	
Reporting group title	N160+C2000
Reporting group description:	
Part 1 of the study. Neratinib 160 mg / day in combination with Capecitabine 2000 mg/m2/day (1000 mg/m2 bid)	
Reporting group title	P2 N240+C1500 NPL
Reporting group description:	
Part 2 of the study. Neratinib 240 mg / day in combination with Capecitabine 1500mg/m2/day (750mg/m2 bid), for subjects who have not received prior lapatinib.	
Reporting group title	P2 N240+C1500 PL
Reporting group description:	
Part 2 of the study. Neratinib 240 mg / day in combination with Capecitabine 1500mg/m2/day (750mg/m2 bid), for subjects who have received prior lapatinib.	

Primary: Objective Response Rate

End point title	Objective Response Rate[1][2]
End point description:	
Objective response rate was defined as the proportion of subjects archiving a confirmed complete response (CR) or partial response (PR), according to RECIST. To be assigned a status of PR or CR, changes in tumor measurements were confirmed by repeat assessments that were performed no less than 4 weeks after the criteria for response were first met.	
End point type	Primary
End point timeframe:	
From first dose through last tumor assessment.	

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: The Objective Response Rate was computed for Part 2 of the study and there were no comparisons to be made. The rate and the corresponding 95% CI were estimated using the Kaplan-Meier method.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was considered for only part 2 of the study.

End point values	P2 N240+C1500 NPL	P2 N240+C1500 PL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	7		
Units: Percentage				
number (confidence interval 95%)	63.1 (50.2 to 74.7)	57.1 (18.4 to 90.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Response Rate

End point title	Clinical Benefit Response Rate[3]

End point description:

Subjects are considered a responder if their best response is either a complete or partial response. A complete or partial response must be confirmed no less than 4-weeks after the criteria for response are initially met per RECIST. A subject is deemed to have a clinical benefit if the patient is a responder or if stable disease lasted longer than 24 weeks.

End point type	Secondary

End point timeframe:

From first dose through the last tumor assessment

Notes:

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

End point values	P2 N240+C1500 NPL	P2 N240+C1500 PL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	7		
Units: Percentage				
number (confidence interval 95%)	70.8 (58.2 to 81.4)	57.1 (18.4 to 90.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival

End point title	Progression Free Survival[4]

End point description:

PFS is defined as the interval from the date of randomization until the earliest date of disease recurrence, progression (per RECIST criteria) or death due to any cause. Symptomatic deterioration is considered as progressive disease (PD). Subjects without documented progression or death will be censored at the date of last valid tumor assessment.

End point type	Secondary

End point timeframe:

From date of randomization through earliest of disease recurrence, progression, or death.

Notes:

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

End point values	P2 N240+C1500 NPL	P2 N240+C1500 PL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	7		
Units: Months				
median (confidence interval 95%)	9.03 (6.87 to 11.1)	8.28 (4.14 to 15.2)		

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	20.0
Reporting groups	
Reporting group title	N160+C1500
Reporting group description: Part 1: Neratinib 160 mg qd + Capecitabine 1500 mg	
Reporting group title	N240+C2000
Reporting group description: Part 1: Neratinib 240 mg qd + Capecitabine 2000 mg	
Reporting group title	N240+C1500
Reporting group description: Part 1: Neratinib 240 mg qd + Capecitabine 1500 mg	
Reporting group title	N200+C2000
Reporting group description: Part 1: Neratinib 200 mg qd + Capecitabine 2000 mg	
Reporting group title	N160+C2000
Reporting group description: Part 1: Neratinib 160 mg qd + Capecitabine 2000 mg	
Reporting group title	P2 N240+C1500 NPL
Reporting group description: Part 2: Neratinib 240 mg qd + Capecitabine 1500 mg No Prior Lapatinib	
Reporting group title	P2 N240+C1500 PL
Reporting group description: Part 2: Neratinib 240 mg qd + Capecitabine 1500 mg Prior Lapatinb	

Serious adverse events	N160+C1500	N240+C2000	N240+C1500
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 6 (83.33%)	2 / 4 (50.00%)	4 / 8 (50.00%)
number of deaths (all causes)	0	0	3
number of deaths resulting from adverse events	0	0	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast neoplasm			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

Hypotension			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
General physical health deterioration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	2 / 6 (33.33%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase abnormal			

subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 8 (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
Femur fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar infarction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nerve root compression			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Seizure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			

subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 8 (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
Melaena			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biloma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric stenosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Acarodermatitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cystitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	N200+C2000	N160+C2000	P2 N240+C1500 NPL
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)	3 / 9 (33.33%)	19 / 65 (29.23%)
number of deaths (all causes)	2	2	7
number of deaths resulting from adverse events	2	1	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast neoplasm			

subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (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
Shock haemorrhagic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
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			
Chills			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (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
Disease progression			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	2 / 65 (3.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 2
General physical health deterioration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	0 / 65 (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
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hypoxia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase abnormal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
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			
Accidental overdose			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (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
Femur fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
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			
Pericardial effusion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	0 / 65 (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
Tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar infarction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (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

Nerve root compression			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Spinal cord compression			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	0 / 65 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	0 / 65 (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
Thrombocytopenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (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
Ascites			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biloma			

subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric stenosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (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
Back pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Acarodermatitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	0 / 65 (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
Herpes zoster			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (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
Hypokalaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	P2 N240+C1500 PL		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 7 (28.57%)		
number of deaths (all causes)	1		

number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast neoplasm			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Shock haemorrhagic			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombosis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Disease progression			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pain			

subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Hypersensitivity				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Breast pain				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				

subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood alkaline phosphatase abnormal			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	0 / 7 (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 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lacunar infarction				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nerve root compression				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal cord compression				
subjects affected / exposed	0 / 7 (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	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				

Vertigo				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	2 / 7 (28.57%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Proctitis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				

subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Biloma			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperbilirubinaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ureteric stenosis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ureterolithiasis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Back pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Acarodermatitis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin infection			
subjects affected / exposed	0 / 7 (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 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	N160+C1500	N240+C2000	N240+C1500
Total subjects affected by non-serious adverse events subjects affected / exposed	6 / 6 (100.00%)	4 / 4 (100.00%)	8 / 8 (100.00%)
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hot flush			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Lymphoedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 6 (33.33%)	2 / 4 (50.00%)	4 / 8 (50.00%)
occurrences (all)	4	3	14
Chills			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Early satiety			

subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	1 / 6 (16.67%)	1 / 4 (25.00%)	3 / 8 (37.50%)
occurrences (all)	1	4	3
Impaired healing			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Implant site pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Inflammation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Injection site extravasation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Mucosal inflammation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	3 / 8 (37.50%)
occurrences (all)	0	1	5
Oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	1 / 6 (16.67%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	2 / 6 (33.33%)	1 / 4 (25.00%)	2 / 8 (25.00%)
occurrences (all)	3	1	2
Xerosis			

subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Seasonal allergy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Breast swelling			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Metrorrhagia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 6 (33.33%)	1 / 4 (25.00%)	1 / 8 (12.50%)
occurrences (all)	2	1	2
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Productive cough			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Rhinorrhoea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Sinus congestion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			

Anxiety			
subjects affected / exposed	1 / 6 (16.67%)	1 / 4 (25.00%)	1 / 8 (12.50%)
occurrences (all)	1	1	1
Depression			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	4 / 8 (50.00%)
occurrences (all)	0	0	4
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	1 / 8 (12.50%)
occurrences (all)	0	2	1
Alanine aminotransferase increased			
subjects affected / exposed	2 / 6 (33.33%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	4	7	0
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 6 (33.33%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	4	4	0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Blood bilirubin increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood glucose increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			

subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Haemoglobin decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
International normalised ratio increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Liver function test increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Weight decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Weight increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Eye contusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Ligament sprain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nasal injury			

subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Radius fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Balance disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	3 / 8 (37.50%)
occurrences (all)	1	0	3
Dysarthria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Monoparesis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nervous system disorder			

subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Neuralgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	4
Neuropathy peripheral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Neurotoxicity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	3	0	5
Leukopenia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Lymphopenia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	1 / 8 (12.50%)
occurrences (all)	0	2	1
Neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Lacrimation increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Abdominal distension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	5
Abdominal pain upper			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Cheilitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	4
Dental caries			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Diarrhoea			
subjects affected / exposed	5 / 6 (83.33%)	4 / 4 (100.00%)	7 / 8 (87.50%)
occurrences (all)	10	25	26
Dry mouth			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Dyspepsia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	3
Faeces soft			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Haematemesis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Intestinal obstruction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Lip dry			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Mouth ulceration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	2 / 6 (33.33%)	2 / 4 (50.00%)	4 / 8 (50.00%)
occurrences (all)	4	3	5
Stomatitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	1 / 6 (16.67%)	2 / 4 (50.00%)	6 / 8 (75.00%)
occurrences (all)	3	5	7
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Alopecia			

subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Dermatitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2
Hyperhidrosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nail disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nail dystrophy			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Night sweats			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Onychoclasis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2
Onycholysis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	2 / 6 (33.33%)	3 / 4 (75.00%)	2 / 8 (25.00%)
occurrences (all)	3	6	8
Pigmentation disorder			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	2 / 8 (25.00%)
occurrences (all)	0	3	2
Rash			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1

Skin fissures			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Skin lesion			
subjects affected / exposed	1 / 6 (16.67%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	3	0	0
Back pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	3 / 8 (37.50%)
occurrences (all)	0	0	3
Muscle spasms			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Muscular weakness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	1 / 8 (12.50%)
occurrences (all)	0	2	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Myalgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Posture abnormal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Candida infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Gastroenteritis viral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nail infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Paronychia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Rhinitis			

subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Skin infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Wound infection pseudomonas			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 6 (0.00%)	3 / 4 (75.00%)	2 / 8 (25.00%)
occurrences (all)	0	3	4
Dehydration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	3 / 8 (37.50%)
occurrences (all)	0	0	7
Hypercholesterolaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Hyperphosphataemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hypoglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1

Hypokalaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hypomagnesaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Hyponatraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	N200+C2000	N160+C2000	P2 N240+C1500 NPL
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	9 / 9 (100.00%)	62 / 65 (95.38%)
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	0	0	0
Haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	0	0	0
Hot flush			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	4 / 65 (6.15%)
occurrences (all)	0	0	6
Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	2 / 9 (22.22%)	3 / 65 (4.62%)
occurrences (all)	0	2	8
Hypotension			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences (all)	4	0	1
Lymphoedema			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	5 / 65 (7.69%)
occurrences (all)	1	0	5
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 6 (33.33%)	5 / 9 (55.56%)	12 / 65 (18.46%)
occurrences (all)	6	6	23

Chills			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	0	0	0
Early satiety			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	1 / 6 (16.67%)	4 / 9 (44.44%)	15 / 65 (23.08%)
occurrences (all)	1	8	27
Impaired healing			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	0	0	0
Implant site pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Inflammation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	1 / 65 (1.54%)
occurrences (all)	0	1	1
Influenza like illness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	6 / 65 (9.23%)
occurrences (all)	0	0	9
Injection site extravasation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	0	0	0
Mucosal inflammation			
subjects affected / exposed	2 / 6 (33.33%)	0 / 9 (0.00%)	9 / 65 (13.85%)
occurrences (all)	6	0	32
Oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	2 / 65 (3.08%)
occurrences (all)	0	0	3
Oedema peripheral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	2 / 65 (3.08%)
occurrences (all)	0	0	2
Pain			
subjects affected / exposed	0 / 6 (0.00%)	2 / 9 (22.22%)	3 / 65 (4.62%)
occurrences (all)	0	3	3

Pyrexia			
subjects affected / exposed	1 / 6 (16.67%)	2 / 9 (22.22%)	6 / 65 (9.23%)
occurrences (all)	1	2	8
Xerosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Seasonal allergy			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Breast swelling			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	0	0	0
Metrorrhagia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	4 / 65 (6.15%)
occurrences (all)	0	1	5
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	3 / 9 (33.33%)	10 / 65 (15.38%)
occurrences (all)	0	6	15
Epistaxis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	5 / 65 (7.69%)
occurrences (all)	0	0	8
Productive cough			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	2 / 65 (3.08%)
occurrences (all)	0	0	3
Rhinorrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1

Sinus congestion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	3 / 65 (4.62%)
occurrences (all)	2	0	3
Depression			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	3	0	0
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	9 / 65 (13.85%)
occurrences (all)	0	0	12
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	2 / 6 (33.33%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences (all)	4	0	7
Alanine aminotransferase increased			
subjects affected / exposed	1 / 6 (16.67%)	2 / 9 (22.22%)	11 / 65 (16.92%)
occurrences (all)	1	2	19
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 6 (16.67%)	2 / 9 (22.22%)	10 / 65 (15.38%)
occurrences (all)	1	2	17
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 6 (0.00%)	3 / 9 (33.33%)	3 / 65 (4.62%)
occurrences (all)	0	4	5
Blood bilirubin increased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 9 (11.11%)	6 / 65 (9.23%)
occurrences (all)	1	2	14
Blood creatinine increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	2 / 65 (3.08%)
occurrences (all)	1	0	9
Blood glucose increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Blood lactate dehydrogenase			

increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	3 / 65 (4.62%)
occurrences (all)	0	1	4
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	6 / 65 (9.23%)
occurrences (all)	0	0	13
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 9 (22.22%)	1 / 65 (1.54%)
occurrences (all)	0	4	1
Haemoglobin decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	3 / 65 (4.62%)
occurrences (all)	0	2	12
International normalised ratio increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	1 / 65 (1.54%)
occurrences (all)	0	1	1
Liver function test increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Weight decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	7 / 65 (10.77%)
occurrences (all)	0	1	14
Weight increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	4
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Eye contusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Ligament sprain			

subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Nasal injury			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	0	0	0
Radius fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	1 / 65 (1.54%)
occurrences (all)	0	2	1
Balance disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	7 / 65 (10.77%)
occurrences (all)	0	0	14
Dysarthria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	4 / 65 (6.15%)
occurrences (all)	2	0	6
Headache			
subjects affected / exposed	0 / 6 (0.00%)	2 / 9 (22.22%)	12 / 65 (18.46%)
occurrences (all)	0	3	28
Hypoaesthesia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Monoparesis			

subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Nervous system disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	0	0	0
Neuralgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	5 / 65 (7.69%)
occurrences (all)	0	0	9
Neurotoxicity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	6 / 65 (9.23%)
occurrences (all)	0	0	11
Somnolence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	2 / 65 (3.08%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	6 / 65 (9.23%)
occurrences (all)	0	3	36
Leukopenia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 9 (11.11%)	4 / 65 (6.15%)
occurrences (all)	1	1	15
Lymphopenia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	2 / 65 (3.08%)
occurrences (all)	1	0	2
Neutropenia			
subjects affected / exposed	1 / 6 (16.67%)	2 / 9 (22.22%)	11 / 65 (16.92%)
occurrences (all)	6	2	31
Thrombocytopenia			
subjects affected / exposed	2 / 6 (33.33%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences (all)	3	0	9

Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	4 / 65 (6.15%)
occurrences (all)	0	0	6
Eye disorders			
Lacrimation increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	2 / 65 (3.08%)
occurrences (all)	0	0	2
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Abdominal distension			
subjects affected / exposed	2 / 6 (33.33%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences (all)	2	0	1
Abdominal pain			
subjects affected / exposed	2 / 6 (33.33%)	0 / 9 (0.00%)	8 / 65 (12.31%)
occurrences (all)	4	0	12
Abdominal pain upper			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	6 / 65 (9.23%)
occurrences (all)	1	0	11
Cheilitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	2 / 65 (3.08%)
occurrences (all)	2	0	2
Constipation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	8 / 65 (12.31%)
occurrences (all)	1	0	11
Dental caries			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	6 / 6 (100.00%)	8 / 9 (88.89%)	59 / 65 (90.77%)
occurrences (all)	25	27	651
Dry mouth			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	3 / 65 (4.62%)
occurrences (all)	1	0	4
Dyspepsia			

subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	11 / 65 (16.92%)
occurrences (all)	0	1	14
Faeces soft			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	0	0	0
Haematemesis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Intestinal obstruction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	0	0	0
Lip dry			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	2 / 65 (3.08%)
occurrences (all)	0	0	2
Nausea			
subjects affected / exposed	3 / 6 (50.00%)	3 / 9 (33.33%)	25 / 65 (38.46%)
occurrences (all)	6	9	50
Stomatitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	12 / 65 (18.46%)
occurrences (all)	1	0	20
Vomiting			
subjects affected / exposed	1 / 6 (16.67%)	3 / 9 (33.33%)	21 / 65 (32.31%)
occurrences (all)	4	11	42
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	2 / 65 (3.08%)
occurrences (all)	0	1	3
Skin and subcutaneous tissue disorders			
Alopecia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Dermatitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	2 / 6 (33.33%)	0 / 9 (0.00%)	7 / 65 (10.77%)
occurrences (all)	3	0	7
Hyperhidrosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	2 / 65 (3.08%)
occurrences (all)	0	1	2
Nail disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	4 / 65 (6.15%)
occurrences (all)	0	0	5
Nail dystrophy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	0	0	0
Onychoclasis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Onycholysis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	3 / 65 (4.62%)
occurrences (all)	0	0	3
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 6 (16.67%)	4 / 9 (44.44%)	41 / 65 (63.08%)
occurrences (all)	3	13	107
Pigmentation disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	13 / 65 (20.00%)
occurrences (all)	1	0	27

Skin fissures			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Skin lesion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	4 / 65 (6.15%)
occurrences (all)	0	0	5
Haematuria			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	3 / 65 (4.62%)
occurrences (all)	1	0	3
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	5 / 65 (7.69%)
occurrences (all)	0	0	7
Back pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	7 / 65 (10.77%)
occurrences (all)	4	0	10
Muscle spasms			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	5 / 65 (7.69%)
occurrences (all)	0	0	9
Muscular weakness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 6 (16.67%)	1 / 9 (11.11%)	1 / 65 (1.54%)
occurrences (all)	1	1	2
Musculoskeletal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	7 / 65 (10.77%)
occurrences (all)	0	0	8

Myalgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	4 / 65 (6.15%)
occurrences (all)	0	0	4
Neck pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	2 / 65 (3.08%)
occurrences (all)	0	0	3
Pain in extremity			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	8 / 65 (12.31%)
occurrences (all)	1	0	10
Posture abnormal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Candida infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis viral			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Nail infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	3 / 65 (4.62%)
occurrences (all)	0	0	4
Paronychia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	8 / 65 (12.31%)
occurrences (all)	0	1	17
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	2 / 65 (3.08%)
occurrences (all)	0	1	2
Rhinitis			

subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	4 / 65 (6.15%)
occurrences (all)	0	0	4
Skin infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	2 / 9 (22.22%)	10 / 65 (15.38%)
occurrences (all)	0	2	16
Urinary tract infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	4 / 65 (6.15%)
occurrences (all)	1	0	6
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	5 / 65 (7.69%)
occurrences (all)	0	0	6
Wound infection pseudomonas			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 6 (66.67%)	2 / 9 (22.22%)	19 / 65 (29.23%)
occurrences (all)	6	4	24
Dehydration			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	3 / 65 (4.62%)
occurrences (all)	0	1	3
Hypercholesterolaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Hyperglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	5 / 65 (7.69%)
occurrences (all)	0	0	11
Hyperphosphataemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Hypoglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 65 (0.00%)
occurrences (all)	0	0	0

Hypokalaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	3 / 65 (4.62%)
occurrences (all)	0	1	3
Hypomagnesaemia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 9 (11.11%)	1 / 65 (1.54%)
occurrences (all)	3	1	21
Hyponatraemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	1 / 65 (1.54%)
occurrences (all)	5	0	2

Non-serious adverse events	P2 N240+C1500 PL		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)		
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Haemorrhage			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Hot flush			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypotension			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Lymphoedema			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Chills			

subjects affected / exposed	1 / 7 (14.29%)			
occurrences (all)	2			
Early satiety				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences (all)	1			
Fatigue				
subjects affected / exposed	2 / 7 (28.57%)			
occurrences (all)	3			
Impaired healing				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Implant site pain				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Inflammation				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Influenza like illness				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Injection site extravasation				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Mucosal inflammation				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Oedema				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences (all)	1			
Oedema peripheral				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Pain				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Pyrexia				

subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Xerosis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Seasonal allergy			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Breast swelling			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Metrorrhagia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
Productive cough			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Sinus congestion			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Alanine aminotransferase increased			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Blood bilirubin increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Blood creatinine increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Blood glucose increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Blood lactate dehydrogenase increased			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	3		
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Haemoglobin decreased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
International normalised ratio increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Liver function test increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Weight increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Eye contusion			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Ligament sprain			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Nasal injury			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Radius fracture			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Balance disorder			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	3		
Dizziness			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	3		
Dysarthria			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Dysgeusia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypoaesthesia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Monoparesis			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Nervous system disorder			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Neuralgia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Neuropathy peripheral			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Neurotoxicity			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Leukopenia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
Lymphopenia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Neutropenia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
Thrombocytopenia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		

Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Eye disorders			
Lacrimation increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Abdominal distension			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Cheilitis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	3		
Dental caries			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	7 / 7 (100.00%)		
occurrences (all)	29		
Dry mouth			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Dyspepsia			

subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Faeces soft			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorder			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Haematemesis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Intestinal obstruction			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Lip dry			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Mouth ulceration			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	4 / 7 (57.14%)		
occurrences (all)	6		
Stomatitis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	3 / 7 (42.86%)		
occurrences (all)	3		
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Alopecia			

subjects affected / exposed	1 / 7 (14.29%)			
occurrences (all)	1			
Dermatitis				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences (all)	2			
Dry skin				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Hyperhidrosis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Nail disorder				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Nail dystrophy				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Night sweats				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Onychoclasis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Onycholysis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Palmar-plantar erythrodysaesthesia syndrome				
subjects affected / exposed	5 / 7 (71.43%)			
occurrences (all)	14			
Pigmentation disorder				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Rash				
subjects affected / exposed	2 / 7 (28.57%)			
occurrences (all)	5			

Skin fissures			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Skin lesion			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Haematuria			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Muscular weakness			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Musculoskeletal pain			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		

Myalgia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Neck pain				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences (all)	1			
Pain in extremity				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Posture abnormal				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences (all)	2			
Infections and infestations				
Candida infection				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Gastroenteritis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Gastroenteritis viral				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Nail infection				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Paronychia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Pneumonia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Respiratory tract infection				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Rhinitis				

subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Skin infection			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Wound infection pseudomonas			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	3		
Dehydration			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypercholesterolaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hyperglycaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hyperphosphataemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypoglycaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		

Hypokalaemia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Hypomagnesaemia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Hyponatraemia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 August 2008	Revised Part 2 of the study from a 3 treatment arm comparison to a single treatment arm study; Removed the following treatment arms: ARM A: neratinib (240 mg), and ARM C: lapatinib (1250 mg) + capecitabine (2000 mg/m2). The remaining study arm (neratinib and capecitabine at administered as determined in Part 1 [MTD]) was retained as a single arm. Consistent with the removal of Part 2 treatment arms A and C, the procedure for assignment to treatment group was clarified to indicate that subjects would not be randomized to treatment in Part 1 or Part 2. In Part 1, subjects were enrolled in a non-random manner according to a pre-specified dose escalation scheme. In Part 2, subjects were enrolled at the MTD established in Part 1; hence, randomization to treatment was not required. The major inclusion criterion specifying prior treatment with a both a taxane and an anthracycline was changed from a requirement of a specific number of cycles (at least 4 cycles in the absence of disease progression and a least 2 cycles if disease progresses during treatment) to a requirement of prior treatment only. Additionally, the locally advanced disease treatment setting was added to the list of treatment settings for inclusion. Consistent with the removal of Part 2 treatment arms A and C, the specification that the study would continue without the neratinib + capecitabine (MTD) treatment arm if dose level 1 was not tolerated was removed from the dose escalation scheme discussion. The secondary endpoint of overall survival (OS) was removed. The involvement of an independent radiology vendor for primary analysis was cancelled. The plasma collection for capecitabine metabolites PK dosing was removed.
03 March 2009	Added LVEF monitoring time points to the active study period; data were to be collected for any stool culture that was performed to exclude infectious etiologies; subject exposure to unnecessary exposure to radiographic materials was reduced; allowance of radiotherapy was removed; clarification regarding subjects who were not able to give consent for themselves but needed a legally authorized representative; a 2-week washout period between trastuzumab treatment and first dose of the test article was added; anthracycline requirement was removed; skin lesions could be measurable lesions (per RECIST) on CT/MRI scan, and therefore, could be included as long as skin lesions were measurable by CT/MRI scan; definition of modest elevated total bilirubin (≤1.5 × ULN) was amended; the number of subjects in Part 2 was increased to include a subgroup of subjects with prior lapatinib exposure; washout period was shortened to allow subjects with CNS metastases who had been shown to be stable off of steroids and anticonvulsants for 4 weeks; clarified requirements for birth control during the study and exclusion criteria related to pregnant; breast-feeding or women of childbearing potential who were not using effective contraception; amended permitted bisphosphonate use for subjects with bone lesions present at screening that required bisphosphonate therapy, neratinib administration instructions, diarrhea management instructions, dose adjustment guidelines; Neratinib dose re-escalation was removed; use of diary cards was deleted; clarification of lymph nodes as a new site of disease was added to the evaluation of overall response; overdose definitions were revised.

03 December 2009	Added radiation therapy for palliative use; explored two additional dosing cohorts (Dose level 4: neratinib 200 mg/capecitabine 2000 mg/m2 and Dose level 5: neratinib 160 mg/capecitabine 2000 mg/m2); updated PK monitoring, review of laboratory values at the beginning of each cycle, ECHO and MUGA assessment schedule, inclusion criteria regarding gender of subjects; exclusion of prior erbB-2 targeted agents; clarified use of concomitant steroids for subjects with CNS metastases, added additional dose reductions to the table for Part 1, cohort 4 subjects (neratinib starting dose 200 mg [Dose level -1: 160 mg and Dose level -2: 120 mg]); added guidelines for potential liver toxicity; corrected a typographical error to accurately reflect that LVEF monitoring was to occur every 12 weeks instead of every 9 weeks; removed allowance of neratinib re-escalation to the previous dose in case of certain events.
05 September 2017	Added guidance to monitor for the signs and symptoms of pancreatitis to the dose adjustment guidelines and minor corrections and clarifications.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported