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

Summary

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

Results information

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

Trial information

Trial identification

Sponsor protocol code	EGF100161

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland, 4002
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 June 2022
Is this the analysis of the primary completion data?	No

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

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 September 2005
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	49

From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

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

Period 1

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

Arms

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

Arm description:

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

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

Dosage and administration details:

500mg OD

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

Dosage and administration details:

60mg/m2 q3weeks

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

Dosage and administration details:

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

Arm title	Phase I: Dose Level 1

Arm description:

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

Arm type	Experimental

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

Dosage and administration details:

500mg OD

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

Dosage and administration details:

75mg/m2 q3weeks

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

Dosage and administration details:

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

Arm title	Phase I: Dose Level 1A

Arm description:

Lapatinib 750 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).

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

Dosage and administration details:

750mg OD

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

Dosage and administration details:

75mg/m2 q3weeks

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

Dosage and administration details:

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

Arm title	Phase I: Dose Level 1B

Arm description:

Lapatinib 1000 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).

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

Dosage and administration details:

1000mg OD

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

Dosage and administration details:

75mg/m2 q3weeks

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

Dosage and administration details:

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

Arm title	Phase I: Dose Level 1C

Arm description:

Lapatinib 1250 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).

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

Dosage and administration details:

1250mg OD

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

Dosage and administration details:

75mg/m2 q3weeks

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion, Powder for concentrate, Powder for

	concentrate for solution for infusion, Powder for concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

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

Arm title	Phase I: Dose Level 1D

Arm description:

Lapatinib 1500 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).

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

Dosage and administration details:

1500mg OD

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

Dosage and administration details:

75mg/m2 q3weeks

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

Dosage and administration details:

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

Arm title	Phase I: Dose Level 2

Arm description:

Lapatinib 500 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).

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

Dosage and administration details:

500mg OD

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

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

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

Dosage and administration details:

100mg/m2 q3weeks

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

Dosage and administration details:

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

Arm title	Phase I: Dose Level 5

Arm description:

Lapatinib 1250 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).

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

Dosage and administration details:

1250mg OD

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

Dosage and administration details:

100mg/m2 q3weeks

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

Dosage and administration details:

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

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

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

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

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

Baseline characteristics

Reporting groups	
Reporting group title	Phase I: Dose Level 0
Reporting group description:	
Lapatinib 500 mg once daily (OD) with Docetaxel 60 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	
Reporting group title	Phase I: Dose Level 1
Reporting group description:	
Lapatinib 500 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	
Reporting group title	Phase I: Dose Level 1A
Reporting group description:	
Lapatinib 750 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	
Reporting group title	Phase I: Dose Level 1B
Reporting group description:	
Lapatinib 1000 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	
Reporting group title	Phase I: Dose Level 1C
Reporting group description:	
Lapatinib 1250 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	
Reporting group title	Phase I: Dose Level 1D
Reporting group description:	
Lapatinib 1500 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	
Reporting group title	Phase I: Dose Level 2
Reporting group description:	
Lapatinib 500 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	
Reporting group title	Phase I: Dose Level 3
Reporting group description:	
Lapatinib 750 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	
Reporting group title	Phase I: Dose Level 4
Reporting group description:	
Lapatinib 1000 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	
Reporting group title	Phase I: Dose Level 5
Reporting group description:	
Lapatinib 1250 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	

Reporting group values	Phase I: Dose Level 0	Phase I: Dose Level 1	Phase I: Dose Level 1A
Number of subjects	6	3	12
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0

Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	6	3	11
From 65-84 years	0	0	1
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	45.2	49.7	46.2
standard deviation	± 11.92	± 7.51	± 9.43
Sex: Female, Male			
Units: Participants			
Female	6	3	12
Male	0	0	0
Race/Ethnicity, Customized			
Units: Subjects			
White	6	3	12
Asian	0	0	0

Reporting group values	Phase I: Dose Level 1B	Phase I: Dose Level 1C	Phase I: Dose Level 1D
Number of subjects	5	4	3
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	4	4	3
From 65-84 years	1	0	0
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	54.4	44.0	53.0
standard deviation	± 12.74	± 10.03	± 7.00
Sex: Female, Male			
Units: Participants			
Female	5	4	3
Male	0	0	0
Race/Ethnicity, Customized			
Units: Subjects			
White	5	4	3
Asian	0	0	0

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

Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	5	6	4
From 65-84 years	0	0	2
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	50.0	53.7	55.8
standard deviation	± 10.70	± 8.04	± 10.93
Sex: Female, Male Units: Participants			
Female	5	6	6
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
White	5	5	6
Asian	0	1	0

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

Asian	0	1	

End points

End points reporting groups

Reporting group title	Phase I: Dose Level 0
Reporting group description:	
Lapatinib 500 mg once daily (OD) with Docetaxel 60 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	
Reporting group title	Phase I: Dose Level 1
Reporting group description:	
Lapatinib 500 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	
Reporting group title	Phase I: Dose Level 1A
Reporting group description:	
Lapatinib 750 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	
Reporting group title	Phase I: Dose Level 1B
Reporting group description:	
Lapatinib 1000 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	
Reporting group title	Phase I: Dose Level 1C
Reporting group description:	
Lapatinib 1250 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	
Reporting group title	Phase I: Dose Level 1D
Reporting group description:	
Lapatinib 1500 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	
Reporting group title	Phase I: Dose Level 2
Reporting group description:	
Lapatinib 500 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	
Reporting group title	Phase I: Dose Level 3
Reporting group description:	
Lapatinib 750 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	
Reporting group title	Phase I: Dose Level 4
Reporting group description:	
Lapatinib 1000 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	
Reporting group title	Phase I: Dose Level 5
Reporting group description:	
Lapatinib 1250 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	

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

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

End point description:

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

End point type	Primary

End point timeframe:

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

Notes:

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

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

Notes:

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

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

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

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

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

Notes:

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

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

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

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

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

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I: Overall Response Rate (ORR)

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I: Duration of Response (DoR)

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

End point description:

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

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

End point type	Secondary

End point timeframe:

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

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I: Time to Response

End point title	Phase I: Time to Response

End point description:

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

End point type	Secondary

End point timeframe:
Week 8, Week 12, Week 16, Week 24, Week 32

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I: Time to Progression

End point title	Phase I: Time to Progression

End point description:

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

End point type	Secondary

End point timeframe:

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

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

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

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Dose Level 0
Reporting group description:	
Dose Level 0	
Reporting group title	Dose Level 1A
Reporting group description:	
Dose Level 1A	
Reporting group title	Dose Level 1B
Reporting group description:	
Dose Level 1B	
Reporting group title	Dose Level 5
Reporting group description:	
Dose Level 5	
Reporting group title	Dose Level 1D
Reporting group description:	
Dose Level 1D	
Reporting group title	Dose Level 2
Reporting group description:	
Dose Level 2	
Reporting group title	Dose Level 3
Reporting group description:	
Dose Level 3	
Reporting group title	Dose Level 4
Reporting group description:	
Dose Level 4	
Reporting group title	Dose Level 1
Reporting group description:	
Dose Level 1	
Reporting group title	Dose Level 1C
Reporting group description:	
Dose Level 1C	

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

subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	5 / 12 (41.67%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	10 / 12	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal inflammation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Emphysema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			

subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular device infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Vascular device infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vaginal infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	2 / 12 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Dehydration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Decreased appetite			
subjects affected / exposed	0 / 6 (0.00%)	4 / 12 (33.33%)	2 / 5 (40.00%)
occurrences (all)	0	5	2
Hyponatraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Hypoglycaemia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 12 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	2	0

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Hypocalcaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hypocalcaemia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results.

Please use https://www.novctrd.com for complete trial results.

Notes:

Online references

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