Clinical trial results:
A phase Ib, multi-center, open-label, dose-escalation study of oral panobinostat (PAN) when administered in combination with oral lenalidomide and dexamethasone in adult patients with multiple myeloma

Summary

EudraCT number	2006-007030-35
Trial protocol	IT
Global end of trial date	08 November 2017

Results information

Result version number	v1 (current)
This version publication date	24 November 2018
First version publication date	24 November 2018

Trial information

Trial identification

Sponsor protocol code	CLBH589B2206

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00532675
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	08 November 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the maximum tolerated dose (MTD) of panobinostat (PAN) when used in combination with a fixed dose of lenalidomide (Revlimid®) and dexamethasone

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	22 August 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 18
Country: Number of subjects enrolled	United States: 7
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Spain: 16
Worldwide total number of subjects	46
EEA total number of subjects	21

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)	32
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

46 patients were enrolled in this study and were assigned treatment.

Period 1

Period 1 title	Core 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	PAN 5 mg

Arm description:

PAN 5 mg in combination with lenalidomide and dexamethasone

Arm type	Experimental
Investigational medicinal product name	Panobinostat
Investigational medicinal product code	LBH589
Other name	LBH589
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Panobinostat hard gelatin capsules 5 mg or 20 mg and administered orally at escalating dose for three days per week (i.e., Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24 and 26 in a 28-day cycle).

Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	Revlamid
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Lenalidomide was supplied as 5 mg and 25 mg capsules which was administered at a dose of 25 mg orally once daily on Days 1 to 21 of repeated 28-day cycles.

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

Dosage and administration details:

Dexamethasone tablets was supplied locally by each study site and administered at a dose of 40 mg orally once daily on Days 1-4, 9-12, and 17-20 for the first 4 cycles, then once daily on Days 1-4 every 28 days thereafter.

Arm title	PAN 10 mg

Arm description:

Pan 10 mg in combination with lenalidomide and dexamethasone

Arm type	Experimental

Investigational medicinal product name	Panobinostat
Investigational medicinal product code	LBH589
Other name	LBH589
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Panobinostat hard gelatin capsules 5 mg or 20 mg and administered orally at escalating dose for three days per week (i.e., Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24 and 26 in a 28-day cycle).

Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	Revlamid
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Lenalidomide was supplied as 5 mg and 25 mg capsules which was administered at a dose of 25 mg orally once daily on Days 1 to 21 of repeated 28-day cycles.

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

Dosage and administration details:

Dexamethasone tablets was supplied locally by each study site and administered at a dose of 40 mg orally once daily on Days 1-4, 9-12, and 17-20 for the first 4 cycles, then once daily on Days 1-4 every 28 days thereafter.

Arm title	PAN 20 mg

Arm description:

PAN 20 mg in combination with lenalidomide and dexamethasone

Arm type	Experimental
Investigational medicinal product name	Panobinostat
Investigational medicinal product code	LBH589
Other name	LBH589
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Panobinostat hard gelatin capsules 5 mg or 20 mg and administered orally at escalating dose for three days per week (i.e., Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24 and 26 in a 28-day cycle).

Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	Revlamid
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Lenalidomide was supplied as 5 mg and 25 mg capsules which was administered at a dose of 25 mg orally once daily on Days 1 to 21 of repeated 28-day cycles.

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

Dosage and administration details:

Dexamethasone tablets was supplied locally by each study site and administered at a dose of 40 mg orally once daily on Days 1-4, 9-12, and 17-20 for the first 4 cycles, then once daily on Days 1-4 every 28 days thereafter.

Arm title	Pan 25 mg

Arm description:

PAN 25 mg in combination with lenalidomide and dexamethasone

Arm type	Experimental
Investigational medicinal product name	Panobinostat
Investigational medicinal product code	LBH589
Other name	LBH589
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Panobinostat hard gelatin capsules 5 mg or 20 mg and administered orally at escalating dose for three days per week (i.e., Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24 and 26 in a 28-day cycle).

Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	Revlamid
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Lenalidomide was supplied as 5 mg and 25 mg capsules which was administered at a dose of 25 mg orally once daily on Days 1 to 21 of repeated 28-day cycles.

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

Dosage and administration details:

Dexamethasone tablets was supplied locally by each study site and administered at a dose of 40 mg orally once daily on Days 1-4, 9-12, and 17-20 for the first 4 cycles, then once daily on Days 1-4 every 28 days thereafter.

Number of subjects in period 1	PAN 5 mg	PAN 10 mg	PAN 20 mg
Started	8	8	21
Completed	0	0	0
Not completed	8	8	21
Abnormal laboratory value(s)	-	1	-
Consent withdrawn by subject	2	1	3
Adverse event, non-fatal	3	3	8
Death	-	-	4
Disease Progression	3	3	5
Protocol deviation	-	-	1

Number of subjects in period 1	Pan 25 mg
Started	9
Completed	0
Not completed	9
Abnormal laboratory value(s)	-

Consent withdrawn by subject	1
Adverse event, non-fatal	4
Death	-
Disease Progression	4
Protocol deviation	-

Baseline characteristics

Reporting groups	
Reporting group title	PAN 5 mg
Reporting group description:	
PAN 5 mg in combination with lenalidomide and dexamethasone	
Reporting group title	PAN 10 mg
Reporting group description:	
Pan 10 mg in combination with lenalidomide and dexamethasone	
Reporting group title	PAN 20 mg
Reporting group description:	
PAN 20 mg in combination with lenalidomide and dexamethasone	
Reporting group title	Pan 25 mg
Reporting group description:	
PAN 25 mg in combination with lenalidomide and dexamethasone	

Reporting group values	PAN 5 mg	PAN 10 mg	PAN 20 mg
Number of subjects	8	8	21
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	64.9	60.6	59.1
standard deviation	± 8.54	± 5.66	± 10.56
Gender categorical Units: Subjects			
Female	1	2	9
Male	7	6	12

Reporting group values	Pan 25 mg	Total	
Number of subjects	9	46	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	

Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	56.1		
standard deviation	± 10.84	-	
Gender categorical			
Units: Subjects			
Female	5	17	
Male	4	29	

End points

End points reporting groups

Reporting group title	PAN 5 mg
Reporting group description: PAN 5 mg in combination with lenalidomide and dexamethasone	
Reporting group title	PAN 10 mg
Reporting group description: Pan 10 mg in combination with lenalidomide and dexamethasone	
Reporting group title	PAN 20 mg
Reporting group description: PAN 20 mg in combination with lenalidomide and dexamethasone	
Reporting group title	Pan 25 mg
Reporting group description: PAN 25 mg in combination with lenalidomide and dexamethasone	

Primary: Maximum Therapeutic Dose (MTD) of Panobinostat in combination with a fixed dose of lenalidomide and dexamethasone

End point title	Maximum Therapeutic Dose (MTD) of Panobinostat in combination with a fixed dose of lenalidomide and dexamethasone[1]

End point description:

After a total of 46 patients had been enrolled into the dose escalation phase, it was concluded that the dosing regimen and schedule needed to be changed for the combination used in this study, based on a review of the accrued safety data and evolution of medical practice on usage of dexamethasone. It was decided that recommended dosing regimen and schedule for this combination would be better implemented in a new study, rather than in a complex protocol amendment. Hence, this study was stopped without determining the MTD, and the dose expansion phase of the study was not initiated.

End point type	Primary

End point timeframe:

24 weeks

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: After a total of 46 subjects had been enrolled into the dose escalation phase, it was concluded that the dosing regimen and schedule needed to be changed for the combination used in this study, based on a review of the accrued safety data and evolution of medical practice on usage of dexamethasone. It was decided that recommended dosing regimen and schedule for this combination would be better implemented in a new study, rather than in a complex protocol amendment. The study stopped enrollment.

End point values	PAN 5 mg	PAN 10 mg	PAN 20 mg	Pan 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[2]	0[3]	0[4]	0[5]
Units: patients				

Notes:

[2] - Study enrolment stopped without determining the MTD, & the dose expansion phase was not initiated
[3] - Study enrolment stopped without determining the MTD, & the dose expansion phase was not initiated
[4] - Study enrolment stopped without determining the MTD, & the dose expansion phase was not initiated

[5] - Study enrolment stopped without determining the MTD, & the dose expansion phase was not initiated

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response (OR) per investigator's assessment by dose level of Panobinostat

End point title	Overall Response (OR) per investigator's assessment by dose level of Panobinostat

End point description:

Patients with confirmed best overall response = Stringent Complete Response (sCR) + Complete Response (CR) + Very Good Partial Response (VGPR)+ Partial
Response (PR) were summarized on the Full Analysis Set (FAS). All 46 enrolled patients received at least one dose of study treatment; they were therefore
included in the FAS.

End point type	Secondary

End point timeframe:

24 weeks

End point values	PAN 5 mg	PAN 10 mg	PAN 20 mg	Pan 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	21	9
Units: patients	6	1	8	4

Statistical analyses

No statistical analyses for this end point

Secondary: OR as per investigator’s assessment for patients with measurable disease at baseline by dose level of Panobinostat

End point title	OR as per investigator’s assessment for patients with measurable disease at baseline by dose level of Panobinostat

End point description:

Patients with confirmed best overall response as per investigator's assessment for patients with measurable disease = Stringent Complete Response (sCR) + Complete Response (CR) + Very Good Partial Response (VGPR)+ Partial Response (PR) were summarized on the Full Analysis Set (FAS). Best confirmed overall response was analyzed by patients with measurable disease at baseline as per the International Myeloma Working Group criteria (IMWG)specified for serum M protein, urine M protein, FLC level and bone marrow plasma cell percentage. All 46 enrolled patients received at least one dose of study treatment; they were therefore included in the FAS.

End point type	Secondary

End point timeframe:

24 weeks

End point values	PAN 5 mg	PAN 10 mg	PAN 20 mg	Pan 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	8	19	8
Units: patients	5	1	7	4

Statistical analyses

No statistical analyses for this end point

Secondary: OR as per investigator’s assessment for relapsed-and-refractory patients by dose level of Panobinostat

End point title	OR as per investigator’s assessment for relapsed-and-refractory patients by dose level of Panobinostat

End point description:

Patients with confirmed best overall response (OR) as per investigator's assessment for relapsed and refractory patients = Stringent Complete Response (sCR) + Complete Response (CR) + Very Good Partial Response (VGPR)+ Partial Response (PR) were summarized on the Full Analysis Set (FAS). All 46 enrolled patients received at least one dose of study treatment; they were therefore included in the FAS.

End point type	Secondary

End point timeframe:

24 weeks

End point values	PAN 5 mg	PAN 10 mg	PAN 20 mg	Pan 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	13	6
Units: patients	4	0	4	2

Statistical analyses

No statistical analyses for this end point

Secondary: Summary statistics of AUCinf for Panobinostat on Day 1

End point title	Summary statistics of AUCinf for Panobinostat on Day 1

End point description:

Area Under the Curve from 0 to infinity (AUCinf) for Panobinostat on Day 1
Pharmacokinetics (PK) set: consisted of all patients with evaluable PK profile on Day 1 and/or steady state PK concentrations.

End point type	Secondary

End point timeframe:

Day 1

End point values	PAN 5 mg	PAN 10 mg	PAN 20 mg	Pan 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	21	9
Units: ng·h/mL				
arithmetic mean (standard deviation)	22.79 (± 25.1)	37.52 (± 34.1)	90.85 (± 44.4)	117.55 (± 43.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Summary statistics of AUClast for Panobinostat on Day 1

End point title	Summary statistics of AUClast for Panobinostat on Day 1

End point description:

Area Under the Curve from 0 to the time of the last quantifiable concentration; Pharmacokinetics (PK) set: consisted of all patients with evaluable PK profile on Day 1 and/or steady state PK concentrations.

End point type	Secondary

End point timeframe:

Day 1

End point values	PAN 5 mg	PAN 10 mg	PAN 20 mg	Pan 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	21	9
Units: ng·h/mL				
arithmetic mean (standard deviation)	10.14 (± 8.6)	31.38 (± 31.2)	75.93 (± 41.9)	102.53 (± 38.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Summary statistics of Cmax for Panobinostat on Day 1

End point title	Summary statistics of Cmax for Panobinostat on Day 1

End point description:

Maximum observed concentration (Cmax) is the peak serum concentration of a therapeutic drug after administration; and is used to determine the rate and extent of drug absorption; Pharmacokinetics (PK) set: consisted of all patients with evaluable PK profile on Day 1 and/or steady state PK concentrations.

End point type	Secondary

End point timeframe:

Day 1

End point values	PAN 5 mg	PAN 10 mg	PAN 20 mg	Pan 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	21	9
Units: ng/mL				
arithmetic mean (standard deviation)	1.87 (± 0.8)	7.89 (± 5.8)	13.91 (± 9.2)	20.03 (± 10.09)

Statistical analyses

No statistical analyses for this end point

Secondary: Summary statistics of Tmax for Panobinostat on Day 1

End point title	Summary statistics of Tmax for Panobinostat on Day 1

End point description:

Tmax = Time of occurrence of Cmax, Cmax is the peak serum concentration of a therapeutic drug after administration; and is used to determine the rate and extent of drug absorption; Pharmacokinetics (PK) set: consisted of all patients with evaluable PK profile on Day 1 and/or steady state PK concentrations.

End point type	Secondary

End point timeframe:

Day 1

End point values	PAN 5 mg	PAN 10 mg	PAN 20 mg	Pan 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	21	9
Units: hours				
median (full range (min-max))	1.26 (0.75 to 4.00)	1.25 (0.50 to 3.00)	1.00 (0.42 to 2.50)	1.00 (0.50 to 3.00)

Statistical analyses

No statistical analyses for this end point

Secondary: Summary statistics of T1/2 for Panobinostat on Day 1

End point title	Summary statistics of T1/2 for Panobinostat on Day 1

End point description:

t 1/2 = Terminal elimination half-life; Pharmacokinetics (PK) set: consisted of all patients with evaluable PK profile on Day 1 and/or steady state PK concentrations.

End point type	Secondary

End point timeframe:

Day 1

End point values	PAN 5 mg	PAN 10 mg	PAN 20 mg	Pan 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	21	9
Units: hours				
arithmetic mean (standard deviation)	15.35 (± 27.3)	4.40 (± 2.5)	11.51 (± 4.7)	13.57 (± 5.4)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Timeframe for AE	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	PAN 5 mg
Reporting group description:	
PAN 5 mg	
Reporting group title	PAN 10 mg
Reporting group description:	
PAN 10 mg	
Reporting group title	PAN 20 mg
Reporting group description:	
PAN 20 mg	
Reporting group title	PAN 25 mg
Reporting group description:	
PAN 25 mg	

Serious adverse events	PAN 5 mg	PAN 10 mg	PAN 20 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 8 (37.50%)	5 / 8 (62.50%)	18 / 21 (85.71%)
number of deaths (all causes)	0	0	6
number of deaths resulting from adverse events	0	0	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to soft tissue			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

Deep vein thrombosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (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
Orthostatic hypotension			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (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
Phlebitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis superficial			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 21 (9.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1

Non-cardiac chest pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	2 / 21 (9.52%)
occurrences causally related to treatment / all	2 / 2	0 / 8	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (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
Dyspnoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea exertional			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory failure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	4 / 21 (19.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 3
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 21 (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
Mania			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 21 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Laceration			

subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 21 (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
Rib fracture			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 21 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 4	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhythm idioventricular			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular extrasystoles			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Presyncope			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (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 / 8 (0.00%)	3 / 8 (37.50%)	4 / 21 (19.05%)
occurrences causally related to treatment / all	0 / 0	2 / 6	6 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (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
Haematemesis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumatosis intestinalis			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Anuria			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oliguria			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal suppression			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Osteolysis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacterial infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal candidiasis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (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
H1N1 influenza			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis B			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Listeria sepsis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (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
Lower respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection fungal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (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
Pneumococcal infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	3 / 21 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 8	4 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis syndrome			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (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
Septic embolus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (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
Staphylococcal infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 21 (9.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	PAN 25 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 9 (77.78%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to soft tissue			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Orthostatic hypotension			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Phlebitis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombophlebitis superficial			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fatigue			

subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Multiple organ dysfunction syndrome				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Non-cardiac chest pain				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	4 / 9 (44.44%)			
occurrences causally related to treatment / all	4 / 10			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Aspiration				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cough				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea exertional				

subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary haemorrhage				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Depression				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mania				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Electrocardiogram QT prolonged				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Weight decreased				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Laceration				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bradycardia				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rhythm idioventricular				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Ventricular extrasystoles			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Presyncope			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences causally related to treatment / all	6 / 8		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences causally related to treatment / all	6 / 8		
deaths causally related to treatment / all	0 / 0		
Haematemesis			

subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal perforation				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Nausea				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumatosis intestinalis				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Drug eruption				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Anuria				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oliguria				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal failure				

subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal impairment				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endocrine disorders				
Adrenal suppression				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Osteolysis				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bacterial infection				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Escherichia sepsis				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal candidiasis				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

H1N1 influenza			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatitis B			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Listeria sepsis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection fungal			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumococcal infection			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Sepsis syndrome			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Septic embolus			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Staphylococcal infection			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tooth infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 9 (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	PAN 5 mg	PAN 10 mg	PAN 20 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	8 / 8 (100.00%)	21 / 21 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Haematoma			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Hot flush			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Hypotension			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	2 / 21 (9.52%)
occurrences (all)	0	2	4
Orthostatic hypotension			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	3 / 21 (14.29%)
occurrences (all)	0	0	6
Phlebitis			

subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 8 (12.50%)	3 / 8 (37.50%)	7 / 21 (33.33%)
occurrences (all)	2	6	26
Chest discomfort			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	2	4	0
Chills			
subjects affected / exposed	2 / 8 (25.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences (all)	4	0	2
Discomfort			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Fatigue			
subjects affected / exposed	6 / 8 (75.00%)	3 / 8 (37.50%)	7 / 21 (33.33%)
occurrences (all)	14	8	14
Feeling abnormal			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Influenza like illness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Malaise			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences (all)	2	0	4
Non-cardiac chest pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Oedema peripheral			
subjects affected / exposed	0 / 8 (0.00%)	2 / 8 (25.00%)	4 / 21 (19.05%)
occurrences (all)	0	4	12
Pyrexia			

subjects affected / exposed	5 / 8 (62.50%)	2 / 8 (25.00%)	7 / 21 (33.33%)
occurrences (all)	10	8	30
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	2
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Bronchial obstruction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Catarrh			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	12
Cough			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	3 / 21 (14.29%)
occurrences (all)	4	2	6
Dysphonia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	3 / 8 (37.50%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences (all)	6	0	2
Dyspnoea exertional			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	2 / 21 (9.52%)
occurrences (all)	0	2	4
Epistaxis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	3 / 21 (14.29%)
occurrences (all)	0	2	6
Hiccups			

subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Oropharyngeal pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	4	0	0
Pleuritic pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Productive cough			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	4	2	0
Respiratory depression			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 21 (4.76%)
occurrences (all)	0	2	2
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 21 (4.76%)
occurrences (all)	0	2	2
Anxiety			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	4
Depressed mood			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Depression			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 21 (4.76%)
occurrences (all)	0	2	2
Insomnia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	7 / 21 (33.33%)
occurrences (all)	2	2	14
Libido decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	2	0

Mania			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Mood altered			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	2
Stress			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	2 / 21 (9.52%)
occurrences (all)	2	0	4
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	2 / 21 (9.52%)
occurrences (all)	2	0	8
Ejection fraction decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	4	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	3 / 21 (14.29%)
occurrences (all)	0	0	6
Oxygen saturation decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Weight decreased			
subjects affected / exposed	2 / 8 (25.00%)	3 / 8 (37.50%)	5 / 21 (23.81%)
occurrences (all)	6	6	10
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	4	2	0

Excoriation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Fall			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	2
Femur fracture			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Foreign body in eye			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Pelvic fracture			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	6	2	0
Cardiotoxicity			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 21 (4.76%)
occurrences (all)	0	2	2
Coronary artery disease			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Palpitations			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	4
Tachycardia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Ageusia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 21 (4.76%)
occurrences (all)	0	2	2
Coordination abnormal			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	5 / 21 (23.81%)
occurrences (all)	2	2	18
Dizziness postural			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	1 / 21 (4.76%)
occurrences (all)	2	2	2
Dysgeusia			
subjects affected / exposed	1 / 8 (12.50%)	2 / 8 (25.00%)	3 / 21 (14.29%)
occurrences (all)	2	4	6
Essential tremor			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Head discomfort			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Headache			
subjects affected / exposed	2 / 8 (25.00%)	2 / 8 (25.00%)	3 / 21 (14.29%)
occurrences (all)	6	4	8
Loss of consciousness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 21 (4.76%)
occurrences (all)	0	2	2
Neuralgia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Neuropathy peripheral			
subjects affected / exposed	3 / 8 (37.50%)	1 / 8 (12.50%)	2 / 21 (9.52%)
occurrences (all)	6	2	4
Paraesthesia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 21 (4.76%)
occurrences (all)	0	2	2
Sciatica			

subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Somnolence			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Syncope			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences (all)	2	0	2
Tremor			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	2	2	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 8 (25.00%)	3 / 8 (37.50%)	13 / 21 (61.90%)
occurrences (all)	10	18	126
Febrile neutropenia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	2 / 21 (9.52%)
occurrences (all)	0	2	4
Leukopenia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	3 / 21 (14.29%)
occurrences (all)	0	2	14
Lymphopenia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences (all)	2	0	2
Neutropenia			
subjects affected / exposed	2 / 8 (25.00%)	4 / 8 (50.00%)	13 / 21 (61.90%)
occurrences (all)	14	30	256
Thrombocytopenia			
subjects affected / exposed	1 / 8 (12.50%)	3 / 8 (37.50%)	13 / 21 (61.90%)
occurrences (all)	4	16	162
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Eye disorders			

Cataract			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	4	0	0
Conjunctival haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	4
Vision blurred			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	2	2	0
Vitreous floaters			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 8 (12.50%)	2 / 8 (25.00%)	2 / 21 (9.52%)
occurrences (all)	2	4	6
Abdominal pain upper			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	8
Aphthous ulcer			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Constipation			
subjects affected / exposed	4 / 8 (50.00%)	1 / 8 (12.50%)	10 / 21 (47.62%)
occurrences (all)	8	2	24
Diarrhoea			
subjects affected / exposed	2 / 8 (25.00%)	3 / 8 (37.50%)	13 / 21 (61.90%)
occurrences (all)	12	12	66
Dry mouth			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Dyspepsia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	1 / 21 (4.76%)
occurrences (all)	2	2	2
Dysphagia			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	2
Flatulence			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	1 / 21 (4.76%)
occurrences (all)	2	2	2
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	2 / 21 (9.52%)
occurrences (all)	2	0	4
Gingival bleeding			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Mouth ulceration			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 21 (4.76%)
occurrences (all)	0	2	6
Nausea			
subjects affected / exposed	2 / 8 (25.00%)	4 / 8 (50.00%)	11 / 21 (52.38%)
occurrences (all)	4	8	28
Oesophagitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 21 (4.76%)
occurrences (all)	0	2	2
Oral pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	2
Retching			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Stomatitis			
subjects affected / exposed	1 / 8 (12.50%)	2 / 8 (25.00%)	1 / 21 (4.76%)
occurrences (all)	2	4	2
Tooth disorder			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Toothache			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 21 (4.76%)
occurrences (all)	0	2	2
Vomiting			

subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	6 / 21 (28.57%)
occurrences (all)	0	2	20
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 21 (4.76%)
occurrences (all)	0	2	2
Hyperbilirubinaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	6
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Dermal cyst			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Dry skin			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	2	2	0
Erythema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	2
Hyperhidrosis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	2	2	0
Ingrowing nail			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Precancerous skin lesion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Pruritus			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences (all)	2	0	2
Rash			

subjects affected / exposed	3 / 8 (37.50%)	2 / 8 (25.00%)	2 / 21 (9.52%)
occurrences (all)	6	6	4
Urticaria			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences (all)	2	0	4
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Micturition disorder			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Nephrolithiasis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Pollakiuria			
subjects affected / exposed	2 / 8 (25.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	4	2	0
Renal impairment			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Hypothyroidism			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 21 (4.76%)
occurrences (all)	0	2	2
Steroid withdrawal syndrome			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	6
Back pain			

subjects affected / exposed	3 / 8 (37.50%)	1 / 8 (12.50%)	3 / 21 (14.29%)
occurrences (all)	8	2	10
Bone pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Joint swelling			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Muscle spasms			
subjects affected / exposed	6 / 8 (75.00%)	2 / 8 (25.00%)	3 / 21 (14.29%)
occurrences (all)	20	4	6
Muscular weakness			
subjects affected / exposed	3 / 8 (37.50%)	2 / 8 (25.00%)	2 / 21 (9.52%)
occurrences (all)	6	4	4
Musculoskeletal chest pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Osteoarthritis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Pain in extremity			
subjects affected / exposed	3 / 8 (37.50%)	1 / 8 (12.50%)	2 / 21 (9.52%)
occurrences (all)	6	2	6
Infections and infestations			
Campylobacter infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 21 (4.76%)
occurrences (all)	0	2	2
Laryngitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Localised infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences (all)	2	0	2

Lower respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	1 / 21 (4.76%)
occurrences (all)	4	4	2
Nasopharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	4
Oral herpes			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 21 (4.76%)
occurrences (all)	0	4	2
Pharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences (all)	2	0	2
Respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	3 / 21 (14.29%)
occurrences (all)	0	8	10
Sinusitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Subcutaneous abscess			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Tooth infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	4 / 8 (50.00%)	2 / 8 (25.00%)	4 / 21 (19.05%)
occurrences (all)	28	28	8
Urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	4

Vulvitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 8 (25.00%)	2 / 8 (25.00%)	5 / 21 (23.81%)
occurrences (all)	6	4	18
Dehydration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	4
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 8 (0.00%)	3 / 8 (37.50%)	7 / 21 (33.33%)
occurrences (all)	0	12	24
Hypermagnesaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	4
Hypocalcaemia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 8 (25.00%)	7 / 21 (33.33%)
occurrences (all)	0	12	30
Hypokalaemia			
subjects affected / exposed	2 / 8 (25.00%)	5 / 8 (62.50%)	10 / 21 (47.62%)
occurrences (all)	6	24	38
Hypomagnesaemia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 8 (25.00%)	3 / 21 (14.29%)
occurrences (all)	0	14	10
Hyponatraemia			

subjects affected / exposed	2 / 8 (25.00%)	0 / 8 (0.00%)	3 / 21 (14.29%)
occurrences (all)	6	0	8
Hypophosphataemia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	4 / 21 (19.05%)
occurrences (all)	2	4	8
Hypoproteinaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	2

Non-serious adverse events	PAN 25 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Haematoma			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Hot flush			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Hypotension			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	4		
Orthostatic hypotension			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	12		
Phlebitis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	6 / 9 (66.67%)		
occurrences (all)	20		
Chest discomfort			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Chills			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Discomfort			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	12		
Feeling abnormal			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Influenza like illness			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Malaise			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	4		
Non-cardiac chest pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	5 / 9 (55.56%)		
occurrences (all)	10		
Pyrexia			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	10		
Immune system disorders			
Seasonal allergy			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Bronchial obstruction			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Catarrh			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Cough			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	4		
Dysphonia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Dyspnoea			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Dyspnoea exertional			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	4		
Epistaxis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	4		
Hiccups			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			

subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	4		
Pleuritic pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Productive cough			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Respiratory depression			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Rhinorrhoea			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Anxiety			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Depressed mood			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Libido decreased			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Mania			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		

Mood altered			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	4		
Stress			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Ejection fraction decreased			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Oxygen saturation decreased			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Excoriation			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		

Fall			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Femur fracture			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Foreign body in eye			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Pelvic fracture			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Cardiotoxicity			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Coronary artery disease			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Palpitations			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Tachycardia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Ageusia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Coordination abnormal			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Dizziness			

subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Dizziness postural				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Dysgeusia				
subjects affected / exposed	3 / 9 (33.33%)			
occurrences (all)	6			
Essential tremor				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Head discomfort				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Headache				
subjects affected / exposed	2 / 9 (22.22%)			
occurrences (all)	4			
Loss of consciousness				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Neuralgia				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Neuropathy peripheral				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	2			
Paraesthesia				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	2			
Peripheral sensory neuropathy				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Sciatica				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Somnolence				

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Syncope			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Tremor			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 9 (66.67%)		
occurrences (all)	36		
Febrile neutropenia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Leukopenia			
subjects affected / exposed	4 / 9 (44.44%)		
occurrences (all)	26		
Lymphopenia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	4		
Neutropenia			
subjects affected / exposed	8 / 9 (88.89%)		
occurrences (all)	58		
Thrombocytopenia			
subjects affected / exposed	8 / 9 (88.89%)		
occurrences (all)	52		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Eye disorders			
Cataract			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Conjunctival haemorrhage			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	4		
Vision blurred			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Vitreous floaters			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	4		
Aphthous ulcer			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	6		
Diarrhoea			
subjects affected / exposed	6 / 9 (66.67%)		
occurrences (all)	36		
Dry mouth			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Dysphagia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Flatulence			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		

Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Gingival bleeding			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Mouth ulceration			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	5 / 9 (55.56%)		
occurrences (all)	12		
Oesophagitis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Oral pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Retching			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Stomatitis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Tooth disorder			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Toothache			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	4		
Hepatobiliary disorders			
Hepatotoxicity			

subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Hyperbilirubinaemia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	8		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Dermal cyst			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Dry skin			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Erythema			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Hyperhidrosis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Ingrowing nail			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Precancerous skin lesion			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	4		
Urticaria			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		

Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Micturition disorder			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Nephrolithiasis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Pollakiuria			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Renal impairment			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Hypothyroidism			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Steroid withdrawal syndrome			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	4		
Back pain			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	6		
Bone pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		

Joint swelling				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Muscle spasms				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	4			
Muscular weakness				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Musculoskeletal chest pain				
subjects affected / exposed	2 / 9 (22.22%)			
occurrences (all)	4			
Osteoarthritis				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Pain in extremity				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	2			
Infections and infestations				
Campylobacter infection				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	4			
Gastroenteritis				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Laryngitis				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Localised infection				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Lower respiratory tract infection				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Nasopharyngitis				

subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Oral herpes			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Pharyngitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Pneumonia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Respiratory tract infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Sinusitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Subcutaneous abscess			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Tonsillitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Tooth infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	4		
Upper respiratory tract infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Vulvitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Metabolism and nutrition disorders			

Decreased appetite				
subjects affected / exposed	6 / 9 (66.67%)			
occurrences (all)	14			
Dehydration				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Diabetes mellitus inadequate control				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	2			
Hyperglycaemia				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Hypermagnesaemia				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Hypertriglyceridaemia				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Hypoalbuminaemia				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	2			
Hypocalcaemia				
subjects affected / exposed	4 / 9 (44.44%)			
occurrences (all)	24			
Hypokalaemia				
subjects affected / exposed	3 / 9 (33.33%)			
occurrences (all)	28			
Hypomagnesaemia				
subjects affected / exposed	2 / 9 (22.22%)			
occurrences (all)	10			
Hyponatraemia				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	2			
Hypophosphataemia				
subjects affected / exposed	4 / 9 (44.44%)			
occurrences (all)	20			

Hypoproteinaemia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 February 2008	Protocol Amendment 1: Lenalididomide (Revlimid®) is a highly-regulated drug that has been recently approved by only a small number of health authorities around the world. In order for Novartis to use Revlimid® as a combination partner with LBH589 in the CLBH589B2206 trial, the company has entered into a Collaboration Agreement with Celgene Corporation, the manufacturers of Revlimid®. Celgene has agreed to provide Novartis with sufficient supplies of Revlimid® at no cost in exchange for the final study report. However, one of Novartis' key contractual obligations is to allow Celgene to review and comment on the original CLBH589B2206 Protocol Version 00, dated 18 April 2007. Celgene has completed their review, and the primary purpose of this amendment is to incorporate their comments into a new version of the document. In addition, there have been some adjustments made to the Bayesian statistical model being used in the trial. The details of these changes together with the correction of minor inconsistencies are described below.
16 May 2011	Amendment 2 Summary of changes: • Reduce the number of visits and assessments for the ongoing patients: • Reduce from weekly to biweekly the frequency for non labs AE assessments • Reduce ECG monitoring schedule frequency following program wide change • Points updated and / or clarified: • Clarification on the timing and wording for re-assessment of bone lesions • Update of the disease status categories for Investigator's assessment, introducing the category of Minimal Response (MR) in accordance with the update of IMWG response criteria. • Add definition for "clinical relapse" criterion. • Update the Safety Set definition and define the Fully Analysis set as per updated Novartis standard definitions. • Update to the safety section of the combination partner drug

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.

Novartis decided to terminate study enrollment on 08 Sep 2010 as there were complex changes in the dosing schedule required from safety perspective after a protocol defined routine review of safety data.

Notes: