



Clinical trial results:

A phase Ib, multi-center, open-label, dose-escalation study of oral LBH589 and IV bortezomib in adult patients with multiple myeloma

Summary

EudraCT number	2006-006638-16
Trial protocol	IT
Global end of trial date	07 October 2013

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	13 August 2015

Trial information

Trial identification

Sponsor protocol code	CLBH589B2207
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00532389
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	07 October 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	07 October 2013
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) and bortezomib (BTZ) when administered in combination.

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.

In the dose escalation phase of the study, Investigators could use their discretion to add Dexamethasone to the study treatment of subjects who in their opinion could benefit from its addition after the completion of Cycle 1.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 October 2007
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	United States: 14
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Italy: 3
Worldwide total number of subjects	62
EEA total number of subjects	39

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)	44
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were screened for eligibility over a period of 2 weeks.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Dose escalation PAN 10 mg + BTZ 1.0 mg/m2

Arm description:

Subjects received Panobinostat (PAN) three days per week and Bortezomib (BTZ) four times over the first eleven days, for at least one 21-day cycle. Subjects were permitted to remain on PAN until disease progression, unacceptable toxicity, subject refusal and/or at Investigator's own discretion. Dexamethasone (DEX; 20 mg oral) could be administered on the day of and the day after BTZ treatment from Cycle 2 onward at the Investigator's discretion. The maximum duration for BTZ and DEX treatment was eight cycles.

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

Dosage and administration details:

Subjects were administered a combination of 5 mg capsules for a total dose of 10 mg daily on Days 1, 3, 5, 8, 10, 12, 15, 17, 19, and 21 of each 21-day treatment cycle until disease progression, unacceptable toxicity, subject refusal and/or at Investigator's own discretion.

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

Dosage and administration details:

Subjects were administered a 3 to 5-second bolus intravenous (IV) injection for a total dose of 1.0 mg/m2 on Days 1, 4, 8, and 11 of each 21-day cycle, followed by a 10-day treatment holiday. The maximum duration for Bortezomib (BTZ) treatment was eight cycles.

Arm title	Dose escalation PAN 20 mg + BTZ 1.0 mg/m2
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Arm description:

Subjects received Panobinostat (PAN) three days per week and Bortezomib (BTZ) four times over the first eleven days, for at least one 21-day cycle. Subjects were permitted to remain on PAN until disease progression, unacceptable toxicity, subject refusal and/or at Investigator's own discretion. Dexamethasone (DEX; 20 mg oral) could be administered on the day of and the day after BTZ treatment from Cycle 2 onward at the Investigator's discretion. The maximum duration for Bortezomib (BTZ) and DEX treatment was eight cycles.

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

Dosage and administration details:

Subjects were administered a combination of 5 mg or 20 mg capsules for a total dose of 20 mg daily on Days 1, 3, 5, 8, 10, 12, 15, 17, 19, and 21 of each 21-day treatment cycle until disease progression, unacceptable toxicity, subject refusal and/or at Investigator's own discretion.

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

Dosage and administration details:

Subjects were administered a 3 to 5-second bolus intravenous (IV) injection for a total dose of 1.0 mg/m² on Days 1, 4, 8, and 11 of each 21-day cycle, followed by a 10-day treatment holiday. The maximum duration for Bortezomib (BTZ) treatment was eight cycles.

Arm title	Dose escalation PAN 20 mg + BTZ 1.3 mg/m ²
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Arm description:

Subjects received Panobinostat (PAN) three days per week and Bortezomib (BTZ) four times over the first eleven days, for at least one 21-day cycle. Subjects were permitted to remain on PAN until disease progression, unacceptable toxicity, subject refusal and/or at Investigator's own discretion. Dexamethasone (DEX; 20 mg oral) could be administered on the day of and the day after BTZ treatment from Cycle 2 onward at the Investigator's discretion. The maximum duration for BTZ and DEX treatment was eight cycles.

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

Dosage and administration details:

Subjects were administered a combination of 5 mg or 20 mg capsules for a total dose of 20 mg daily on Days 1, 3, 5, 8, 10, 12, 15, 17, 19, and 21 of each 21-day treatment cycle until disease progression, unacceptable toxicity, subject refusal and/or at Investigator's own discretion.

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

Dosage and administration details:

Subjects were administered a 3 to 5-second bolus intravenous (IV) injection for a total dose of 1.3 mg/m² on Days 1, 4, 8, and 11 of each 21-day cycle, followed by a 10-day treatment holiday. The maximum duration for Bortezomib (BTZ) treatment was eight cycles.

Arm title	Dose escalation PAN 30 mg + BTZ 1.3 mg/m ²
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Arm description:

Subjects received Panobinostat (PAN) three days per week and Bortezomib (BTZ) four times over the first eleven days, for at least one 21-day cycle. Subjects were permitted to remain on PAN until disease progression, unacceptable toxicity, subject refusal and/or at Investigator's own discretion. Dexamethasone (DEX; 20 mg oral) could be administered on the day of and the day after BTZ treatment from Cycle 2 onward at the Investigator's discretion. The maximum duration for BTZ and DEX treatment was eight cycles.

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

Dosage and administration details:

Subjects were administered a combination of 5 mg and 20 mg capsules for a total dose of 30 mg daily on Days 1, 3, 5, 8, 10, 12, 15, 17, 19, and 21 of each 21-day treatment cycle until disease progression, unacceptable toxicity, subject refusal and/or at Investigator's own discretion.

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

Dosage and administration details:

Subjects were administered a 3 to 5-second bolus intravenous (IV) injection for a total dose of 1.3 mg/m² on Days 1, 4, 8, and 11 of each 21-day cycle, followed by a 10-day treatment holiday. The maximum duration for Bortezomib (BTZ) treatment was eight cycles.

Arm title	Dose escalation PAN 25 mg + BTZ 1.3 mg/m ²
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Arm description:

Subjects received Panobinostat (PAN) three days per week and Bortezomib (BTZ) four times over the first eleven days, for at least one 21-day cycle. Subjects were permitted to remain on PAN until disease progression, unacceptable toxicity, subject refusal and/or at Investigator's own discretion. Dexamethasone (DEX; 20 mg oral) could be administered on the day of and the day after BTZ treatment from Cycle 2 onward at the Investigator's discretion. The maximum duration for BTZ and DEX treatment was eight cycles.

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

Dosage and administration details:

Subjects were administered a combination of 5 mg and 20 mg capsules for a total dose of 25 mg daily on Days 1, 3, 5, 8, 10, 12, 15, 17, 19, and 21 of each 21-day treatment cycle until disease progression, unacceptable toxicity, subject refusal and/or at Investigator's own discretion.

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

Dosage and administration details:

Subjects were administered a 3 to 5-second bolus intravenous (IV) injection for a total dose of 1.3 mg/m² on Days 1, 4, 8, and 11 of each 21-day cycle, followed by a 10-day treatment holiday. The maximum duration for Bortezomib (BTZ) treatment was eight cycles.

Arm title	Dose expansion PAN 20 mg + BTZ 1.3 mg/m ² + DEX 20 mg
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Arm description:

Subjects received Panobinostat (PAN) three days per week for two weeks, Bortezomib (BTZ) four times over the first eleven days, and Dexamethasone (DEX) four times per week for two weeks (Cycle 2 onwards), for at least one 21-day cycle. Subjects were permitted to remain on PAN until disease progression, unacceptable toxicity, subject refusal and/or at Investigator's own discretion. The maximum duration for BTZ and DEX treatment was eight cycles.

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

Dosage and administration details:

Subjects were administered a combination of 5 mg or 20 mg capsules for a total dose of 20 mg on Days 1, 3, 5, 8, 10, and 12 of each 21-day treatment cycle until disease progression, unacceptable toxicity, subject refusal and/or at Investigator's own discretion.

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

Dosage and administration details:

Subjects were administered a 3 to 5-second bolus intravenous (IV) injection for a total dose of 1.3 mg/m² twice weekly on Days 1, 4, 8, and 11 of each 21-day cycle, followed by a 10-day treatment holiday. The maximum duration for Bortezomib (BTZ) treatment was eight cycles.

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were administered 20 mg of DEX on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day treatment cycle starting with Cycle 2.

Number of subjects in period 1	Dose escalation PAN 10 mg + BTZ 1.0 mg/m ²	Dose escalation PAN 20 mg + BTZ 1.0 mg/m ²	Dose escalation PAN 20 mg + BTZ 1.3 mg/m ²
Started	7	7	17
Completed	0	0	0
Not completed	7	7	17
Adverse event, serious fatal	-	-	-
Subject withdrew consent	1	-	2
Disease progression	3	4	5
Adverse event, non-fatal	1	2	8
Administrative problems	1	1	2
Abnormal laboratory values	1	-	-

Number of subjects in period 1	Dose escalation PAN 30 mg + BTZ 1.3 mg/m ²	Dose escalation PAN 25 mg + BTZ 1.3 mg/m ²	Dose expansion PAN 20 mg + BTZ 1.3 mg/m ² + DEX 20 mg
Started	7	9	15
Completed	0	0	0
Not completed	7	9	15
Adverse event, serious fatal	-	-	1
Subject withdrew consent	1	1	2

Disease progression	2	4	6
Adverse event, non-fatal	4	3	5
Administrative problems	-	1	1
Abnormal laboratory values	-	-	-

Baseline characteristics

Reporting groups

Reporting group title	Dose escalation PAN 10 mg + BTZ 1.0 mg/m ²
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Reporting group description:

Subjects received Panobinostat (PAN) three days per week and Bortezomib (BTZ) four times over the first eleven days, for at least one 21-day cycle. Subjects were permitted to remain on PAN until disease progression, unacceptable toxicity, subject refusal and/or at Investigator's own discretion. Dexamethasone (DEX; 20 mg oral) could be administered on the day of and the day after BTZ treatment from Cycle 2 onward at the Investigator's discretion. The maximum duration for BTZ and DEX treatment was eight cycles.

Reporting group title	Dose escalation PAN 20 mg + BTZ 1.0 mg/m ²
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Reporting group description:

Subjects received Panobinostat (PAN) three days per week and Bortezomib (BTZ) four times over the first eleven days, for at least one 21-day cycle. Subjects were permitted to remain on PAN until disease progression, unacceptable toxicity, subject refusal and/or at Investigator's own discretion. Dexamethasone (DEX; 20 mg oral) could be administered on the day of and the day after BTZ treatment from Cycle 2 onward at the Investigator's discretion. The maximum duration for Bortezomib (BTZ) and DEX treatment was eight cycles.

Reporting group title	Dose escalation PAN 20 mg + BTZ 1.3 mg/m ²
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Reporting group description:

Subjects received Panobinostat (PAN) three days per week and Bortezomib (BTZ) four times over the first eleven days, for at least one 21-day cycle. Subjects were permitted to remain on PAN until disease progression, unacceptable toxicity, subject refusal and/or at Investigator's own discretion. Dexamethasone (DEX; 20 mg oral) could be administered on the day of and the day after BTZ treatment from Cycle 2 onward at the Investigator's discretion. The maximum duration for BTZ and DEX treatment was eight cycles.

Reporting group title	Dose escalation PAN 30 mg + BTZ 1.3 mg/m ²
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Reporting group description:

Subjects received Panobinostat (PAN) three days per week and Bortezomib (BTZ) four times over the first eleven days, for at least one 21-day cycle. Subjects were permitted to remain on PAN until disease progression, unacceptable toxicity, subject refusal and/or at Investigator's own discretion. Dexamethasone (DEX; 20 mg oral) could be administered on the day of and the day after BTZ treatment from Cycle 2 onward at the Investigator's discretion. The maximum duration for BTZ and DEX treatment was eight cycles.

Reporting group title	Dose escalation PAN 25 mg + BTZ 1.3 mg/m ²
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Reporting group description:

Subjects received Panobinostat (PAN) three days per week and Bortezomib (BTZ) four times over the first eleven days, for at least one 21-day cycle. Subjects were permitted to remain on PAN until disease progression, unacceptable toxicity, subject refusal and/or at Investigator's own discretion. Dexamethasone (DEX; 20 mg oral) could be administered on the day of and the day after BTZ treatment from Cycle 2 onward at the Investigator's discretion. The maximum duration for BTZ and DEX treatment was eight cycles.

Reporting group title	Dose expansion PAN 20 mg + BTZ 1.3 mg/m ² + DEX 20 mg
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Reporting group description:

Subjects received Panobinostat (PAN) three days per week for two weeks, Bortezomib (BTZ) four times over the first eleven days, and Dexamethasone (DEX) four times per week for two weeks (Cycle 2 onwards), for at least one 21-day cycle. Subjects were permitted to remain on PAN until disease progression, unacceptable toxicity, subject refusal and/or at Investigator's own discretion. The maximum duration for BTZ and DEX treatment was eight cycles.

Reporting group values	Dose escalation PAN 10 mg + BTZ 1.0 mg/m ²	Dose escalation PAN 20 mg + BTZ 1.0 mg/m ²	Dose escalation PAN 20 mg + BTZ 1.3 mg/m ²
Number of subjects	7	7	17
Age categorical			
Units: Subjects			
< 65 years	4	6	10

>/= 65 years	3	1	7
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Age continuous Units: years arithmetic mean standard deviation	61.1 ± 10.67	57.6 ± 10.49	64.4 ± 8.8
Gender categorical Units: Subjects			
Female	3	1	6
Male	4	6	11

Reporting group values	Dose escalation PAN 30 mg + BTZ 1.3 mg/m2	Dose escalation PAN 25 mg + BTZ 1.3 mg/m2	Dose expansion PAN 20 mg + BTZ 1.3 mg/m2 + DEX 20 mg
Number of subjects	7	9	15
Age categorical Units: Subjects			
< 65 years	6	6	12
>/= 65 years	1	3	3
Age continuous Units: years arithmetic mean standard deviation	60 ± 7.16	60.3 ± 8.62	60.8 ± 6.32
Gender categorical Units: Subjects			
Female	3	2	4
Male	4	7	11

Reporting group values	Total		
Number of subjects	62		
Age categorical Units: Subjects			
< 65 years	44		
>/= 65 years	18		
Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	19		
Male	43		

End points

End points reporting groups

Reporting group title	Dose escalation PAN 10 mg + BTZ 1.0 mg/m ²
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Reporting group description:

Subjects received Panobinostat (PAN) three days per week and Bortezomib (BTZ) four times over the first eleven days, for at least one 21-day cycle. Subjects were permitted to remain on PAN until disease progression, unacceptable toxicity, subject refusal and/or at Investigator's own discretion. Dexamethasone (DEX; 20 mg oral) could be administered on the day of and the day after BTZ treatment from Cycle 2 onward at the Investigator's discretion. The maximum duration for BTZ and DEX treatment was eight cycles.

Reporting group title	Dose escalation PAN 20 mg + BTZ 1.0 mg/m ²
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Reporting group description:

Subjects received Panobinostat (PAN) three days per week and Bortezomib (BTZ) four times over the first eleven days, for at least one 21-day cycle. Subjects were permitted to remain on PAN until disease progression, unacceptable toxicity, subject refusal and/or at Investigator's own discretion. Dexamethasone (DEX; 20 mg oral) could be administered on the day of and the day after BTZ treatment from Cycle 2 onward at the Investigator's discretion. The maximum duration for Bortezomib (BTZ) and DEX treatment was eight cycles.

Reporting group title	Dose escalation PAN 20 mg + BTZ 1.3 mg/m ²
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Reporting group description:

Subjects received Panobinostat (PAN) three days per week and Bortezomib (BTZ) four times over the first eleven days, for at least one 21-day cycle. Subjects were permitted to remain on PAN until disease progression, unacceptable toxicity, subject refusal and/or at Investigator's own discretion. Dexamethasone (DEX; 20 mg oral) could be administered on the day of and the day after BTZ treatment from Cycle 2 onward at the Investigator's discretion. The maximum duration for BTZ and DEX treatment was eight cycles.

Reporting group title	Dose escalation PAN 30 mg + BTZ 1.3 mg/m ²
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Reporting group description:

Subjects received Panobinostat (PAN) three days per week and Bortezomib (BTZ) four times over the first eleven days, for at least one 21-day cycle. Subjects were permitted to remain on PAN until disease progression, unacceptable toxicity, subject refusal and/or at Investigator's own discretion. Dexamethasone (DEX; 20 mg oral) could be administered on the day of and the day after BTZ treatment from Cycle 2 onward at the Investigator's discretion. The maximum duration for BTZ and DEX treatment was eight cycles.

Reporting group title	Dose escalation PAN 25 mg + BTZ 1.3 mg/m ²
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Reporting group description:

Subjects received Panobinostat (PAN) three days per week and Bortezomib (BTZ) four times over the first eleven days, for at least one 21-day cycle. Subjects were permitted to remain on PAN until disease progression, unacceptable toxicity, subject refusal and/or at Investigator's own discretion. Dexamethasone (DEX; 20 mg oral) could be administered on the day of and the day after BTZ treatment from Cycle 2 onward at the Investigator's discretion. The maximum duration for BTZ and DEX treatment was eight cycles.

Reporting group title	Dose expansion PAN 20 mg + BTZ 1.3 mg/m ² + DEX 20 mg
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Reporting group description:

Subjects received Panobinostat (PAN) three days per week for two weeks, Bortezomib (BTZ) four times over the first eleven days, and Dexamethasone (DEX) four times per week for two weeks (Cycle 2 onwards), for at least one 21-day cycle. Subjects were permitted to remain on PAN until disease progression, unacceptable toxicity, subject refusal and/or at Investigator's own discretion. The maximum duration for BTZ and DEX treatment was eight cycles.

Primary: Number of Subjects With Dose-Limiting Toxicities

End point title	Number of Subjects With Dose-Limiting Toxicities ^{[1][2]}
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End point description:

A dose limiting toxicity (DLT) was defined as an adverse event (AE) or abnormal laboratory value assessed as clinically relevant and occurring \leq 21 days following the first dose of study treatment in Cycle 1.

This endpoint analyzed the Maximum Tolerated Dose Determining Set (MTD Determining Set), defined as

End point type	Primary
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End point timeframe:

Up to 21 days after the start of treatment

Notes:

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

Justification: No statistical analysis was planned for this primary outcome measure.

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

Justification: Data for dose-limiting toxicities were not collected from subjects in the dose-expansion arm of the study.

End point values	Dose escalation PAN 10 mg + BTZ 1.0 mg/m2	Dose escalation PAN 20 mg + BTZ 1.0 mg/m2	Dose escalation PAN 20 mg + BTZ 1.3 mg/m2	Dose escalation PAN 30 mg + BTZ 1.3 mg/m2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	15	6
Units: subjects	0	0	3	4

End point values	Dose escalation PAN 25 mg + BTZ 1.3 mg/m2			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: subjects	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under The Concentration-Time Curve From Time Zero to 48 Hours (AUC0-48) of Panobinostat During Cycle 1 of Dose Escalation

End point title	Area Under The Concentration-Time Curve From Time Zero to 48 Hours (AUC0-48) of Panobinostat During Cycle 1 of Dose Escalation ^[3]
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End point description:

This endpoint analyzed the Pharmacokinetic Set for panobinostat (PK set-panobinostat), defined as subjects with at least one evaluable PK profile of panobinostat.

End point type	Secondary
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End point timeframe:

Up to 48 hours post-dose on Days 8 and 15 of Cycle 1

Notes:

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

Justification: The end point is not reporting statistics for all the arms; only arms defined.

End point values	Dose escalation PAN 10 mg + BTZ 1.0 mg/m ²	Dose escalation PAN 20 mg + BTZ 1.0 mg/m ²	Dose escalation PAN 20 mg + BTZ 1.3 mg/m ²	Dose escalation PAN 30 mg + BTZ 1.3 mg/m ²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	6 ^[4]	16 ^[5]	6 ^[6]
Units: ng.h/mL				
geometric mean (geometric coefficient of variation)				
Day 8	27.8 (± 38.6)	111.4 (± 95.6)	107.8 (± 64.6)	134.6 (± 38.4)
Day 15	25.5 (± 39)	82.6 (± 61.4)	91.9 (± 91.9)	171.3 (± 85.7)

Notes:

[4] - n = 6, 4

[5] - n = 15, 14

[6] - n = 5, 4

End point values	Dose escalation PAN 25 mg + BTZ 1.3 mg/m ²			
Subject group type	Reporting group			
Number of subjects analysed	8 ^[7]			
Units: ng.h/mL				
geometric mean (geometric coefficient of variation)				
Day 8	134.7 (± 36.9)			
Day 15	95.1 (± 142.4)			

Notes:

[7] - n = 7, 7

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Concentration (C_{max}) of Panobinostat During Cycle 1 of Dose Escalation

End point title	Maximum Observed Concentration (C _{max}) of Panobinostat During Cycle 1 of Dose Escalation ^[8]
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End point description:

This endpoint analyzed the Pharmacokinetic Set for panobinostat (PK set-panobinostat), defined as subjects with at least one evaluable PK profile of panobinostat.

End point type	Secondary
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End point timeframe:

Up to 48 hours post-dose on Days 8 and 15 of Cycle 1

Notes:

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

End point values	Dose escalation PAN 10 mg + BTZ 1.0 mg/m ²	Dose escalation PAN 20 mg + BTZ 1.0 mg/m ²	Dose escalation PAN 20 mg + BTZ 1.3 mg/m ²	Dose escalation PAN 30 mg + BTZ 1.3 mg/m ²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	6 ^[9]	16 ^[10]	6 ^[11]
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Day 8	3.5 (± 10.8)	10.8 (± 125.5)	15.8 (± 63.2)	14.5 (± 74.8)
Day 15	4.8 (± 68.8)	7.6 (± 50.6)	12.2 (± 103.3)	19.8 (± 109.6)

Notes:

[9] - n = 6, 4

[10] - n = 15, 14

[11] - n = 5, 4

End point values	Dose escalation PAN 25 mg + BTZ 1.3 mg/m ²			
Subject group type	Reporting group			
Number of subjects analysed	8 ^[12]			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Day 8	18 (± 47.6)			
Day 15	12 (± 105.4)			

Notes:

[12] - n = 7, 7

Statistical analyses

No statistical analyses for this end point

Secondary: Last Measurable Concentration (Clast) of Panobinostat During Cycle 1 of Dose Escalation

End point title	Last Measurable Concentration (Clast) of Panobinostat During Cycle 1 of Dose Escalation ^[13]
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End point description:

This endpoint analyzed the Pharmacokinetic Set for panobinostat (PK set-panobinostat), defined as subjects with at least one evaluable PK profile of panobinostat.

End point type	Secondary
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End point timeframe:

Up to 48 hours post-dose on Days 8 and 15 of Cycle 1

Notes:

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

Justification: The end point is not reporting statistics for all the arms; only arms defined.

End point values	Dose escalation PAN 10 mg + BTZ 1.0 mg/m ²	Dose escalation PAN 20 mg + BTZ 1.0 mg/m ²	Dose escalation PAN 20 mg + BTZ 1.3 mg/m ²	Dose escalation PAN 30 mg + BTZ 1.3 mg/m ²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	6 ^[14]	16 ^[15]	6 ^[16]
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Day 8	0.7 (± 24.8)	1.3 (± 63.1)	0.9 (± 31.8)	1.1 (± 61.1)
Day 15	0.8 (± 18.2)	1.1 (± 159.4)	0.8 (± 44.2)	0.9 (± 53.6)

Notes:

[14] - n = 6, 4

[15] - n = 15, 14

[16] - n = 5, 4

End point values	Dose escalation PAN 25 mg + BTZ 1.3 mg/m ²			
Subject group type	Reporting group			
Number of subjects analysed	8 ^[17]			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Day 8	1 (± 26)			
Day 15	1 (± 51.6)			

Notes:

[17] - n = 7, 7

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Concentration (Tmax) of Panobinostat During Cycle 1 of Dose Escalation

End point title	Time to Maximum Concentration (Tmax) of Panobinostat During Cycle 1 of Dose Escalation ^[18]
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End point description:

This endpoint analyzed the Pharmacokinetic Set for panobinostat (PK set-panobinostat), defined as subjects with at least one evaluable PK profile of panobinostat.

End point type	Secondary
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End point timeframe:

Up to 48 hours post-dose on Days 8 and 15 of Cycle 1

Notes:

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

Justification: The end point is not reporting statistics for all the arms; only arms defined.

End point values	Dose escalation PAN 10 mg + BTZ 1.0 mg/m2	Dose escalation PAN 20 mg + BTZ 1.0 mg/m2	Dose escalation PAN 20 mg + BTZ 1.3 mg/m2	Dose escalation PAN 30 mg + BTZ 1.3 mg/m2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	6 ^[19]	16 ^[20]	6 ^[21]
Units: hours				
median (full range (min-max))				
Day 8	2 (1 to 2)	2.4 (1 to 3)	1 (0.1 to 6)	1 (1 to 3)
Day 15	1 (0.5 to 2.8)	2 (1 to 3.9)	1.8 (0.5 to 3)	1.8 (0.5 to 3.5)

Notes:

[19] - n = 6, 4

[20] - n = 15, 14

[21] - n = 5, 4

End point values	Dose escalation PAN 25 mg + BTZ 1.3 mg/m2			
Subject group type	Reporting group			
Number of subjects analysed	8 ^[22]			
Units: hours				
median (full range (min-max))				
Day 8	2 (0.5 to 3)			
Day 15	2 (0.9 to 6)			

Notes:

[22] - n = 7, 7

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Elimination Half-life (T1/2) of Panobinostat During Cycle 1 of Dose Escalation

End point title	Time to Elimination Half-life (T1/2) of Panobinostat During Cycle 1 of Dose Escalation ^[23]
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End point description:

This endpoint analyzed the Pharmacokinetic Set for panobinostat (PK set-panobinostat), defined as subjects with at least one evaluable PK profile of panobinostat.

End point type	Secondary
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End point timeframe:

Up to 48 hours post-dose on Days 8 and 15 of Cycle 1

Notes:

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

Justification: The end point is not reporting statistics for all the arms; only arms defined.

End point values	Dose escalation PAN 10 mg + BTZ 1.0 mg/m2	Dose escalation PAN 20 mg + BTZ 1.0 mg/m2	Dose escalation PAN 20 mg + BTZ 1.3 mg/m2	Dose escalation PAN 30 mg + BTZ 1.3 mg/m2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	6 ^[24]	16 ^[25]	6 ^[26]
Units: hours				

geometric mean (geometric coefficient of variation)				
Day 8	7.4 (± 90)	13.8 (± 3.3)	13.2 (± 65.6)	18.7 (± 41.4)
Day 15	6.2 (± 68.1)	14.4 (± 56.7)	14.1 (± 62.3)	14.9 (± 23.4)

Notes:

[24] - n = 5, 4

[25] - n = 15, 14

[26] - n = 5, 4

End point values	Dose escalation PAN 25 mg + BTZ 1.3 mg/m2			
Subject group type	Reporting group			
Number of subjects analysed	8 ^[27]			
Units: hours				
geometric mean (geometric coefficient of variation)				
Day 8	15.1 (± 26.4)			
Day 15	10.8 (± 60.5)			

Notes:

[27] - n = 7, 7

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Last Measurable Concentration (Tlast) of Panobinostat During Cycle 1 of Dose Escalation

End point title	Time to Last Measurable Concentration (Tlast) of Panobinostat During Cycle 1 of Dose Escalation ^[28]
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End point description:

This endpoint analyzed the Pharmacokinetic Set for panobinostat (PK set-panobinostat), defined as subjects with at least one evaluable PK profile of panobinostat.

End point type	Secondary
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End point timeframe:

Up to 48 hours post-dose on Days 8 and 15 of Cycle 1

Notes:

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

Justification: The end point is not reporting statistics for all the arms; only arms defined.

End point values	Dose escalation PAN 10 mg + BTZ 1.0 mg/m2	Dose escalation PAN 20 mg + BTZ 1.0 mg/m2	Dose escalation PAN 20 mg + BTZ 1.3 mg/m2	Dose escalation PAN 30 mg + BTZ 1.3 mg/m2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	6 ^[29]	16 ^[30]	6 ^[31]
Units: hours				
median (full range (min-max))				
Day 8	16 (8 to 24.5)	24.5 (22.8 to 48)	46 (8 to 48.8)	47.1 (24 to 48)
Day 15	8 (7.8 to 24.1)	48 (23.5 to 49.8)	47 (8 to 51.1)	47.7 (46.8 to 48.2)

Notes:

[29] - n = 6, 4

[30] - n = 15, 14

[31] - n = 5, 4

End point values	Dose escalation PAN 25 mg + BTZ 1.3 mg/m ²			
Subject group type	Reporting group			
Number of subjects analysed	8 ^[32]			
Units: hours				
median (full range (min-max))				
Day 8	46.5 (23.9 to 49.2)			
Day 15	46.3 (5.3 to 48.8)			

Notes:

[32] - n = 7, 7

Statistical analyses

No statistical analyses for this end point

Secondary: Total Body Clearance of Drug From The Plasma (CL/F) of Panobinostat During Cycle 1 of Dose Escalation

End point title	Total Body Clearance of Drug From The Plasma (CL/F) of Panobinostat During Cycle 1 of Dose Escalation ^[33]
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End point description:

This endpoint analyzed the Pharmacokinetic Set for panobinostat (PK set-panobinostat), defined as subjects with at least one evaluable PK profile of panobinostat.

End point type	Secondary
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End point timeframe:

Up to 48 hours post-dose on Days 8 and 15 of Cycle 1

Notes:

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

Justification: The end point is not reporting statistics for all the arms; only arms defined.

End point values	Dose escalation PAN 10 mg + BTZ 1.0 mg/m ²	Dose escalation PAN 20 mg + BTZ 1.0 mg/m ²	Dose escalation PAN 20 mg + BTZ 1.3 mg/m ²	Dose escalation PAN 30 mg + BTZ 1.3 mg/m ²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	6 ^[34]	16 ^[35]	6 ^[36]
Units: L/h				
geometric mean (geometric coefficient of variation)				
Day 8	358.4 (± 55.3)	150.6 (± 108.5)	167.1 (± 71.8)	184 (± 34.2)
Day 15	418.5 (± 54.7)	191.9 (± 74.5)	193.3 (± 103.7)	156.2 (± 81.1)

Notes:

[34] - n = 5, 4

[35] - n = 15, 14

[36] - n = 5, 4

End point values	Dose escalation PAN 25 mg + BTZ 1.3 mg/m ²			
Subject group type	Reporting group			
Number of subjects analysed	8 ^[37]			
Units: L/h				
geometric mean (geometric coefficient of variation)				
Day 8	166.3 (± 40.6)			
Day 15	245.5 (± 166)			

Notes:

[37] - n = 7, 7

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution During The Terminal Phase (Associated With λ_z) (V_z/F) of Panobinostat During Cycle 1 of Dose Escalation

End point title	Apparent Volume of Distribution During The Terminal Phase (Associated With λ _z) (V _z /F) of Panobinostat During Cycle 1 of Dose Escalation ^[38]
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End point description:

This endpoint analyzed the Pharmacokinetic Set for panobinostat (PK set-panobinostat), defined as subjects with at least one evaluable PK profile of panobinostat.

End point type	Secondary
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End point timeframe:

Up to 48 hours post-dose on Days 8 and 15 of Cycle 1

Notes:

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

Justification: The end point is not reporting statistics for all the arms; only arms defined.

End point values	Dose escalation PAN 10 mg + BTZ 1.0 mg/m ²	Dose escalation PAN 20 mg + BTZ 1.0 mg/m ²	Dose escalation PAN 20 mg + BTZ 1.3 mg/m ²	Dose escalation PAN 30 mg + BTZ 1.3 mg/m ²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	6 ^[39]	16 ^[40]	6 ^[41]
Units: Litres				
geometric mean (geometric coefficient of variation)				
Day 8	3815.5 (± 28.3)	2990.8 (± 113.1)	3175.2 (± 54)	4962.7 (± 58.2)
Day 15	3722.4 (± 11.4)	3989.3 (± 105.9)	3930 (± 56.6)	3360.5 (± 106.2)

Notes:

[39] - n = 5, 4

[40] - n = 15, 14

End point values	Dose escalation PAN 25 mg + BTZ 1.3 mg/m ²			
Subject group type	Reporting group			
Number of subjects analysed	8 ^[42]			
Units: Litres				
geometric mean (geometric coefficient of variation)				
Day 8	3624.2 (± 31.2)			
Day 15	3833.6 (± 81.9)			

Notes:

[42] - n = 7, 7

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under The Concentration-Time Curve From Time Zero to 24 Hours (AUC0-24), 48 Hours (AUC0-48), Time of Last Measurable Concentration (AUC0-tlast), and Infinity (AUC0-inf) of Bortezomib on Day 8 of Cycle 1 of Dose Escalation

End point title	Area Under The Concentration-Time Curve From Time Zero to 24 Hours (AUC0-24), 48 Hours (AUC0-48), Time of Last Measurable Concentration (AUC0-tlast), and Infinity (AUC0-inf) of Bortezomib on Day 8 of Cycle 1 of Dose Escalation ^[43]
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End point description:

This endpoint analyzed the Pharmacokinetic Set for bortezomib (PK set-bortezomib), defined as subjects with at least one evaluable PK profile of bortezomib.

End point type	Secondary
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End point timeframe:

Up to 48 hours post-dose on Days 8 of Cycle 1

Notes:

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

Justification: The end point is not reporting statistics for all the arms; only arms defined.

End point values	Dose escalation PAN 10 mg + BTZ 1.0 mg/m ²	Dose escalation PAN 20 mg + BTZ 1.0 mg/m ²	Dose escalation PAN 20 mg + BTZ 1.3 mg/m ²	Dose escalation PAN 30 mg + BTZ 1.3 mg/m ²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	7	14	5
Units: ng.h/mL				
geometric mean (geometric coefficient of variation)				
AUC0-inf	160.4 (± 59.1)	256.2 (± 48.7)	247.3 (± 59.9)	192.9 (± 37.8)
AUC0-tlast	79 (± 27.2)	132.6 (± 58.6)	155.4 (± 49.7)	109 (± 16.8)
AUC0-24	55.9 (± 29.3)	95.9 (± 74.1)	117.2 (± 58.8)	77.1 (± 16.4)
AUC0-48	79.4 (± 26.8)	132.6 (± 59)	158.2 (± 51.6)	109.7 (± 16.8)

End point values	Dose escalation PAN 25 mg + BTZ 1.3 mg/m ²			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: ng.h/mL				
geometric mean (geometric coefficient of variation)				
AUC _{0-inf}	196.9 (± 74.8)			
AUC _{0-tlast}	123.3 (± 45.5)			
AUC ₀₋₂₄	88.6 (± 38.9)			
AUC ₀₋₄₈	123.9 (± 44.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Concentration (C_{max}) and Last Measurable Concentration (C_{last}) of Bortezomib on Day 8 of Cycle 1 of Dose Escalation

End point title	Maximum Observed Concentration (C _{max}) and Last Measurable Concentration (C _{last}) of Bortezomib on Day 8 of Cycle 1 of Dose Escalation ^[44]
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End point description:

This endpoint analyzed the Pharmacokinetic Set for bortezomib (PK set-bortezomib), defined as subjects with at least one evaluable PK profile of bortezomib.

End point type	Secondary
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End point timeframe:

Up to 48 hours post-dose on Days 8 of Cycle 1

Notes:

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

Justification: The end point is not reporting statistics for all the arms; only arms defined.

End point values	Dose escalation PAN 10 mg + BTZ 1.0 mg/m ²	Dose escalation PAN 20 mg + BTZ 1.0 mg/m ²	Dose escalation PAN 20 mg + BTZ 1.3 mg/m ²	Dose escalation PAN 30 mg + BTZ 1.3 mg/m ²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	7	14	5
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
C _{max}	72.7 (± 49.5)	179.5 (± 223.3)	157.9 (± 65.5)	76.8 (± 43.1)
C _{last}	0.9 (± 36.5)	1.1 (± 35.1)	1.3 (± 55.1)	1.2 (± 25.7)

End point values	Dose escalation PAN 25 mg + BTZ 1.3 mg/m ²			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
C _{max}	101.9 (± 26.5)			
C _{last}	1.2 (± 73.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Observed Concentration (T_{max}) and Last Measurable Concentration (T_{last}) of Bortezomib on Day 8 of Cycle 1 of Dose Escalation

End point title	Time to Maximum Observed Concentration (T _{max}) and Last Measurable Concentration (T _{last}) of Bortezomib on Day 8 of Cycle 1 of Dose Escalation ^[45]
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End point description:

This endpoint analyzed the Pharmacokinetic Set for bortezomib (PK set-bortezomib), defined as subjects with at least one evaluable PK profile of bortezomib.

End point type	Secondary
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End point timeframe:

Up to 48 hours post-dose on Days 8 of Cycle 1

Notes:

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

Justification: The end point is not reporting statistics for all the arms; only arms defined.

End point values	Dose escalation PAN 10 mg + BTZ 1.0 mg/m ²	Dose escalation PAN 20 mg + BTZ 1.0 mg/m ²	Dose escalation PAN 20 mg + BTZ 1.3 mg/m ²	Dose escalation PAN 30 mg + BTZ 1.3 mg/m ²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	7	14	5
Units: hours				
median (full range (min-max))				
T _{max}	0.1 (0.1 to 0.2)	0.1 (0 to 0.1)	0.1 (0 to 1.3)	0.1 (0.1 to 0.1)
T _{last}	47.5 (47 to 48.1)	48 (46.8 to 49)	47.9 (24 to 49)	47.3 (46.5 to 48)

End point values	Dose escalation PAN 25 mg + BTZ 1.3			
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	mg/m ²			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: hours				
median (full range (min-max))				
Tmax	0.1 (0.1 to 0.1)			
Tlast	47.4 (46.3 to 49.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under The Concentration-Time Curve From Time Zero to 24 Hours (AUC₀₋₂₄) of Panobinostat on Day 8 of Cycles 1 and 2 of Dose Expansion

End point title	Area Under The Concentration-Time Curve From Time Zero to 24 Hours (AUC ₀₋₂₄) of Panobinostat on Day 8 of Cycles 1 and 2 of Dose Expansion ^[46]
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End point description:

This endpoint analyzed the Pharmacokinetic Set for panobinostat (PK set-panobinostat), defined as subjects with at least one evaluable PK profile of panobinostat.

End point type	Secondary
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End point timeframe:

Up to 48 hours post-dose on Days 8 of Cycle 1 and 2

Notes:

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

Justification: The end point is not reporting statistics for all the arms; only arms defined.

End point values	Dose expansion PAN 20 mg + BTZ 1.3 mg/m ² + DEX 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	15 ^[47]			
Units: ng.h/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1	61.8 (± 60.9)			
Cycle 2	47.5 (± 76.8)			

Notes:

[47] - n = 15, 12

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Concentration (C_{max}) of Panobinostat on Day 8 of Cycles 1 and 2 of Dose Expansion

End point title	Maximum Observed Concentration (C _{max}) of Panobinostat on
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End point description:

This endpoint analyzed the Pharmacokinetic Set for panobinostat (PK set-panobinostat), defined as subjects with at least one evaluable PK profile of panobinostat.

End point type	Secondary
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End point timeframe:

Up to 48 hours post-dose on Days 8 of Cycle 1 and 2

Notes:

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

Justification: The end point is not reporting statistics for all the arms; only arms defined.

End point values	Dose expansion PAN 20 mg + BTZ 1.3 mg/m ² + DEX 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	15 ^[49]			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1	9.5 (± 60.4)			
Cycle 2	8.1 (± 90.3)			

Notes:

[49] - n = 15, 12

Statistical analyses

No statistical analyses for this end point

Secondary: Last Measurable Concentration (Clast) of Panobinostat on Day 8 of Cycles 1 and 2 of Dose Expansion

End point title	Last Measurable Concentration (Clast) of Panobinostat on Day 8 of Cycles 1 and 2 of Dose Expansion ^[50]
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End point description:

This endpoint analyzed the Pharmacokinetic Set for panobinostat (PK set-panobinostat), defined as subjects with at least one evaluable PK profile of panobinostat.

End point type	Secondary
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End point timeframe:

Up to 48 hours post-dose on Days 8 of Cycle 1 and 2

Notes:

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

Justification: The end point is not reporting statistics for all the arms; only arms defined.

End point values	Dose expansion PAN 20 mg + BTZ 1.3 mg/m ² + DEX 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	15 ^[51]			
Units: ng/mL				

geometric mean (geometric coefficient of variation)				
Cycle 1	0.8 (± 52.5)			
Cycle 2	0.7 (± 81.2)			

Notes:

[51] - n = 15, 12

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Observed Concentration (Tmax) of Panobinostat on Day 8 of Cycles 1 and 2 of Dose Expansion

End point title	Time to Maximum Observed Concentration (Tmax) of Panobinostat on Day 8 of Cycles 1 and 2 of Dose Expansion ^[52]
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End point description:

This endpoint analyzed the Pharmacokinetic Set for panobinostat (PK set-panobinostat), defined as subjects with at least one evaluable PK profile of panobinostat.

End point type	Secondary
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End point timeframe:

Up to 48 hours post-dose on Days 8 of Cycle 1 and 2

Notes:

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

Justification: The end point is not reporting statistics for all the arms; only arms defined.

End point values	Dose expansion PAN 20 mg + BTZ 1.3 mg/m ² + DEX 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	15 ^[53]			
Units: hours				
median (full range (min-max))				
Cycle 1	2 (0.5 to 3)			
Cycle 2	1 (0.5 to 6.3)			

Notes:

[53] - n = 15, 12

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Elimination Half-life (T1/2) of Panobinostat on Day 8 of Cycles 1 and 2 of Dose Expansion

End point title	Time to Elimination Half-life (T1/2) of Panobinostat on Day 8 of Cycles 1 and 2 of Dose Expansion ^[54]
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End point description:

This endpoint analyzed the Pharmacokinetic Set for panobinostat (PK set-panobinostat), defined as subjects with at least one evaluable PK profile of panobinostat.

End point type	Secondary
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End point timeframe:

Up to 48 hours post-dose on Days 8 of Cycle 1 and 2

Notes:

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

Justification: The end point is not reporting statistics for all the arms; only arms defined.

End point values	Dose expansion PAN 20 mg + BTZ 1.3 mg/m ² + DEX 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	15 ^[55]			
Units: hours				
geometric mean (geometric coefficient of variation)				
Cycle 1	13.3 (± 34.7)			
Cycle 2	15.9 (± 29.2)			

Notes:

[55] - n = 15, 12

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Last Measurable Concentration (Tlast) of Panobinostat on Day 8 of Cycles 1 and 2 of Dose Expansion

End point title	Time to Last Measurable Concentration (Tlast) of Panobinostat on Day 8 of Cycles 1 and 2 of Dose Expansion ^[56]
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End point description:

This endpoint analyzed the Pharmacokinetic Set for panobinostat (PK set-panobinostat), defined as subjects with at least one evaluable PK profile of panobinostat.

End point type	Secondary
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End point timeframe:

Up to 48 hours post-dose on Days 8 of Cycle 1 and 2

Notes:

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

Justification: The end point is not reporting statistics for all the arms; only arms defined.

End point values	Dose expansion PAN 20 mg + BTZ 1.3 mg/m ² + DEX 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	15 ^[57]			
Units: hours				
median (full range (min-max))				
Cycle 1	28 (23.9 to 47.7)			
Cycle 2	28 (25.6 to 28.5)			

Notes:

[57] - n = 15, 12

Statistical analyses

No statistical analyses for this end point

Secondary: Total Body Clearance of Drug From The Plasma (CL/F) of Panobinostat on Day 8 of Cycles 1 and 2 of Dose Expansion

End point title	Total Body Clearance of Drug From The Plasma (CL/F) of Panobinostat on Day 8 of Cycles 1 and 2 of Dose Expansion ^[58]
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End point description:

This endpoint analyzed the Pharmacokinetic Set for panobinostat (PK set-panobinostat), defined as subjects with at least one evaluable PK profile of panobinostat.

End point type	Secondary
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End point timeframe:

Up to 48 hours post-dose on Days 8 of Cycle 1 and 2

Notes:

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

Justification: The end point is not reporting statistics for all the arms; only arms defined.

End point values	Dose expansion PAN 20 mg + BTZ 1.3 mg/m ² + DEX 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	15 ^[59]			
Units: L/h				
geometric mean (geometric coefficient of variation)				
Cycle 1	241.5 (± 60.8)			
Cycle 2	285.2 (± 79.4)			

Notes:

[59] - n = 15, 12

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution During The Terminal Phase (Associated With λ_z) (V_z/F) of Panobinostat on Day 8 of Cycles 1 and 2 of Dose Expansion

End point title	Apparent Volume of Distribution During The Terminal Phase (Associated With λ_z) (V _z /F) of Panobinostat on Day 8 of Cycles 1 and 2 of Dose Expansion ^[60]
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End point description:

This endpoint analyzed the Pharmacokinetic Set for panobinostat (PK set-panobinostat), defined as subjects with at least one evaluable PK profile of panobinostat.

End point type	Secondary
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End point timeframe:

Up to 48 hours post-dose on Days 8 of Cycle 1 and 2

Notes:

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

Justification: The end point is not reporting statistics for all the arms; only arms defined.

End point values	Dose expansion PAN 20 mg + BTZ 1.3 mg/m ² + DEX 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	15 ^[61]			
Units: Litres				
geometric mean (geometric coefficient of variation)				
Cycle 1	4632.6 (± 71.5)			
Cycle 2	6539 (± 81)			

Notes:

[61] - n = 15, 12

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under The Concentration-Time Curve From Time Zero to 24 Hours (AUC0-24) of Bortezomib on Day 8 of Cycles 1 and 2 of Dose Expansion

End point title	Area Under The Concentration-Time Curve From Time Zero to 24 Hours (AUC0-24) of Bortezomib on Day 8 of Cycles 1 and 2 of Dose Expansion ^[62]
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End point description:

This endpoint analyzed the Pharmacokinetic Set for bortezomib (PK set-bortezomib), defined as subjects with at least one evaluable PK profile of bortezomib.

End point type	Secondary
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End point timeframe:

Up to 48 hours post-dose on Days 8 of Cycle 1 and 2

Notes:

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

Justification: The end point is not reporting statistics for all the arms; only arms defined.

End point values	Dose expansion PAN 20 mg + BTZ 1.3 mg/m ² + DEX 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	15 ^[63]			
Units: ng.h/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1	91.7 (± 87.5)			
Cycle 2	94.3 (± 40)			

Notes:

[63] - n = 15, 12

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Concentration (Cmax) of Bortezomib on Day 8 of Cycles 1 and 2 of Dose Expansion

End point title	Maximum Observed Concentration (Cmax) of Bortezomib on Day 8 of Cycles 1 and 2 of Dose Expansion ^[64]
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End point description:

This endpoint analyzed the Pharmacokinetic Set for bortezomib (PK set-bortezomib), defined as subjects with at least one evaluable PK profile of bortezomib.

End point type	Secondary
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End point timeframe:

Up to 48 hours post-dose on Days 8 of Cycle 1 and 2

Notes:

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

Justification: The end point is not reporting statistics for all the arms; only arms defined.

End point values	Dose expansion PAN 20 mg + BTZ 1.3 mg/m ² + DEX 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	15 ^[65]			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1	107.9 (± 114.6)			
Cycle 2	81.4 (± 87.7)			

Notes:

[65] - n = 15, 12

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Observed Concentration (Tmax) of Bortezomib on Day 8 of Cycles 1 and 2 of Dose Expansion

End point title	Time to Maximum Observed Concentration (Tmax) of Bortezomib on Day 8 of Cycles 1 and 2 of Dose Expansion ^[66]
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End point description:

This endpoint analyzed the Pharmacokinetic Set for bortezomib (PK set-bortezomib), defined as subjects with at least one evaluable PK profile of bortezomib

End point type	Secondary
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End point timeframe:

Up to 48 hours post-dose on Days 8 of Cycle 1 and 2

Notes:

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

Justification: The end point is not reporting statistics for all the arms; only arms defined.

End point values	Dose expansion PAN 20 mg + BTZ 1.3 mg/m ² + DEX 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	15 ^[67]			
Units: hours				
median (full range (min-max))				
Cycle 1	0.1 (0.1 to 0.5)			
Cycle 2	0.1 (0.1 to 1)			

Notes:

[67] - n = 15, 12

Statistical analyses

No statistical analyses for this end point

Secondary: Last Measurable Concentration (Clast) of Bortezomib on Day 8 of Cycles 1 and 2 of Dose Expansion

End point title	Last Measurable Concentration (Clast) of Bortezomib on Day 8 of Cycles 1 and 2 of Dose Expansion ^[68]
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End point description:

This endpoint analyzed the Pharmacokinetic Set for bortezomib (PK set-bortezomib), defined as subjects with at least one evaluable PK profile of bortezomib

End point type	Secondary
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End point timeframe:

Up to 48 hours post-dose on Days 8 of Cycle 1 and 2

Notes:

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

Justification: The end point is not reporting statistics for all the arms; only arms defined.

End point values	Dose expansion PAN 20 mg + BTZ 1.3 mg/m ² + DEX 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	15 ^[69]			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1	1.4 (± 52.1)			
Cycle 2	2.1 (± 92.2)			

Notes:

[69] - n = 15, 12

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Last Measurable Concentration (Tlast) of Bortezomib on Day 8 of Cycles 1 and 2 of Dose Expansion

End point title	Time to Last Measurable Concentration (Tlast) of Bortezomib on Day 8 of Cycles 1 and 2 of Dose Expansion ^[70]
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End point description:

This endpoint analyzed the Pharmacokinetic Set for bortezomib (PK set-bortezomib), defined as subjects with at least one evaluable PK profile of bortezomib

End point type	Secondary
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End point timeframe:

Up to 48 hours post-dose on Days 8 of Cycle 1 and 2

Notes:

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

Justification: The end point is not reporting statistics for all the arms; only arms defined.

End point values	Dose expansion PAN 20 mg + BTZ 1.3 mg/m ² + DEX 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	15 ^[71]			
Units: hours				
median (full range (min-max))				
Cycle 1	28.1 (23.9 to 47.7)			
Cycle 2	28 (25.9 to 28.5)			

Notes:

[71] - n = 15, 12

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects Who Responded to Treatment During The Dose Escalation Phase

End point title	Percent of Subjects Who Responded to Treatment During The Dose Escalation Phase ^[72]
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End point description:

Response was defined as the overall response rate (rate of stringent complete response [sCR] + complete response [CR] + very good partial response [VGPR] + partial response [PR]). This endpoint analyzed the Full Analysis Set, defined as all subjects who received one dose of study treatment.

End point type	Secondary
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End point timeframe:

From the start of treatment through the end of the dose escalation phase

Notes:

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

Justification: The end point is not reporting statistics for all the arms; only arms defined.

End point values	Dose escalation PAN 10 mg + BTZ 1.0 mg/m2	Dose escalation PAN 20 mg + BTZ 1.0 mg/m2	Dose escalation PAN 20 mg + BTZ 1.3 mg/m2	Dose escalation PAN 30 mg + BTZ 1.3 mg/m2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	7	17	7
Units: percent of subjects				
number (confidence interval 95%)	14.3 (0.4 to 57.9)	28.6 (3.7 to 71)	52.9 (27.8 to 77)	57.1 (18.4 to 90.1)

End point values	Dose escalation PAN 25 mg + BTZ 1.3 mg/m2			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: percent of subjects				
number (confidence interval 95%)	55.6 (21.2 to 86.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects Who Responded to Treatment During The Dose Expansion Phase

End point title	Percent of Subjects Who Responded to Treatment During The Dose Expansion Phase ^[73]
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End point description:

Response was defined as the overall response rate (rate of stringent complete response [sCR] + complete response [CR] + very good partial response [VGPR] + partial response [PR]). This endpoint analyzed the Full Analysis Set, defined as all subjects who received one dose of study treatment.

End point type	Secondary
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End point timeframe:

From the start of treatment through the end of the dose escalation phase

Notes:

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

Justification: The end point is not reporting statistics for all the arms; only arms defined.

End point values	Dose expansion PAN 20 mg + BTZ 1.3 mg/m ² + DEX 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: percent of subjects				
number (confidence interval 95%)	73.3 (44.9 to 92.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects Who Responded to Treatment During The Dose Escalation Phase - Investigator's Assessment of Bortezomib-Refractory Subjects

End point title	Percent of Subjects Who Responded to Treatment During The Dose Escalation Phase - Investigator's Assessment of Bortezomib-Refractory Subjects ^[74]
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End point description:

Response was defined as the overall response rate (rate of stringent complete response [sCR] + complete response [CR] + very good partial response [VGPR] + partial response [PR]). This endpoint analyzed the Full Analysis Set, defined as all subjects who received one dose of study treatment.

End point type	Secondary
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End point timeframe:

From the start of treatment through the end of the dose escalation phase

Notes:

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

Justification: The end point is not reporting statistics for all the arms; only arms defined.

End point values	Dose escalation PAN 10 mg + BTZ 1.0 mg/m ²	Dose escalation PAN 20 mg + BTZ 1.0 mg/m ²	Dose escalation PAN 20 mg + BTZ 1.3 mg/m ²	Dose escalation PAN 25 mg + BTZ 1.3 mg/m ²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	4	2
Units: percent of subjects				
number (not applicable)	0	20	0	100

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects Who Responded to Treatment During The Dose Expansion Phase - Investigator's Assessment of Bortezomib-Refractory Subjects

End point title	Percent of Subjects Who Responded to Treatment During The Dose Expansion Phase - Investigator's Assessment of Bortezomib-Refractory Subjects ^[75]
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End point description:

Response was defined as the overall response rate (rate of stringent complete response [sCR] + complete response [CR] + very good partial response [VGPR] + partial response [PR]).
This endpoint analyzed the Full Analysis Set, defined as all subjects who received one dose of study treatment.

End point type	Secondary
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End point timeframe:

From the start of treatment through the end of the dose escalation phase

Notes:

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

Justification: The end point is not reporting statistics for all the arms; only arms defined.

End point values	Dose expansion PAN 20 mg + BTZ 1.3 mg/m ² + DEX 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: percent of subjects				
number (not applicable)	50			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events are monitored from date of First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All other adverse events are monitored from First Patient First Treatment until Last Patient Last Visit.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	PAN 20 mg + BTZ 1.0 mg/m2
Reporting group description:	PAN 20 mg + BTZ 1.0 mg/m2
Reporting group title	PAN 10 mg + BTZ 1.0 mg/m2
Reporting group description:	PAN 10 mg + BTZ 1.0 mg/m2
Reporting group title	PAN 20 mg + BTZ 1.3 mg/m2 (MTD)
Reporting group description:	PAN 20 mg + BTZ 1.3 mg/m2 (MTD)
Reporting group title	PAN 30 mg + BTZ 1.3 mg/m2
Reporting group description:	PAN 30 mg + BTZ 1.3 mg/m2
Reporting group title	PAN 25 mg + BTZ 1.3 mg/m2
Reporting group description:	PAN 25 mg + BTZ 1.3 mg/m2
Reporting group title	PAN 20 mg (2 weeks on/ 1 week off) + BTZ 1.3 mg/m2 + DEX 20 mg
Reporting group description:	PAN 20 mg (2 weeks on/ 1 week off) + BTZ 1.3 mg/m2 + DEX 20 mg

Serious adverse events	PAN 20 mg + BTZ 1.0 mg/m2	PAN 10 mg + BTZ 1.0 mg/m2	PAN 20 mg + BTZ 1.3 mg/m2 (MTD)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 7 (28.57%)	4 / 7 (57.14%)	13 / 17 (76.47%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 17 (11.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
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			
Asthenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (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
Chills			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (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	1 / 7 (14.29%)	2 / 7 (28.57%)	2 / 17 (11.76%)
occurrences causally related to treatment / all	0 / 2	0 / 4	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (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
Lung consolidation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (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
Lung infiltration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (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
Oropharyngeal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (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

Productive cough			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 17 (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
Respiratory failure			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	2 / 17 (11.76%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (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 urea increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (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			
Fall			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (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
Rib fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 17 (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			
Atrial fibrillation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (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
Tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (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
Autonomic neuropathy			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (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
Cerebral haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (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
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (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
Ischaemic stroke			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (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
Neuropathy peripheral			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (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
Stupor			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (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
Syncope			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	1 / 2	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (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
Gastric haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (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 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 17 (11.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (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
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Alpha haemolytic streptococcal infection			

subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 17 (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
Bacteraemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (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
Device related infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 17 (11.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (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
Lobar pneumonia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (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
Pyelonephritis			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (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 tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 17 (11.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 17 (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
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (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 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (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
Failure to thrive			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (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
Hyperphosphataemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (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
Hyperuricaemia			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (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
Tumour lysis syndrome			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (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	PAN 30 mg + BTZ 1.3 mg/m ²	PAN 25 mg + BTZ 1.3 mg/m ²	PAN 20 mg (2 weeks on/ 1 week off) + BTZ 1.3 mg/m ² + DEX 20 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 7 (42.86%)	7 / 9 (77.78%)	6 / 15 (40.00%)
number of deaths (all causes)	0	0	2
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (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 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (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			
Asthenia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			

subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (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	1 / 7 (14.29%)	2 / 9 (22.22%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	1 / 1	1 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung consolidation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (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
Lung infiltration			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (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
Oropharyngeal pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (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
Productive cough			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (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
Pulmonary embolism			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			

subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 15 (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
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 15 (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
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (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
Blood urea increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (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			
Fall			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Head injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (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			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Rib fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Spinal fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (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			
Atrial fibrillation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Myocardial infarction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (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			
Aphasia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autonomic neuropathy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ischaemic stroke			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Neuropathy peripheral			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 15 (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
Stupor			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (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 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Neutropenia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 9 (22.22%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	1 / 1	1 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			

subjects affected / exposed	1 / 7 (14.29%)	2 / 9 (22.22%)	4 / 15 (26.67%)
occurrences causally related to treatment / all	1 / 1	2 / 2	7 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 7 (14.29%)	2 / 9 (22.22%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (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 haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Haematochezia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Ileus			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (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
Nausea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (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
Renal and urinary disorders			

Renal failure			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (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
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (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			
Rheumatoid arthritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (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			
Alpha haemolytic streptococcal infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Bacteraemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Bronchitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			

subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (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
Gastrointestinal infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 15 (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
Lobar pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Pneumocystis jirovecii infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 15 (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
Pneumonia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (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
Sepsis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Urinary tract infection			

subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Hypercalcaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (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
Hyperphosphataemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (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
Hyperuricaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (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
Hypokalaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour lysis syndrome			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (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

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

Non-serious adverse events	PAN 20 mg + BTZ 1.0 mg/m ²	PAN 10 mg + BTZ 1.0 mg/m ²	PAN 20 mg + BTZ 1.3 mg/m ² (MTD)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	7 / 7 (100.00%)	17 / 17 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Hot flush			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Haematoma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	2 / 17 (11.76%)
occurrences (all)	1	0	2
Hypotension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	3 / 17 (17.65%)
occurrences (all)	0	0	4
Orthostatic hypotension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	0	2
Phlebitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	0	2
Shock			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Thrombophlebitis			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Venous thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	8 / 17 (47.06%)
occurrences (all)	1	1	12
Chills			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	3 / 17 (17.65%)
occurrences (all)	0	1	3
Chest pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Exercise tolerance decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	4 / 7 (57.14%)	4 / 7 (57.14%)	7 / 17 (41.18%)
occurrences (all)	4	4	13
Face oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Feeling cold			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Gait disturbance			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
General physical health deterioration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Generalised oedema			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Irritability			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Local swelling			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	4
Malaise			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	4 / 17 (23.53%)
occurrences (all)	2	0	7
Pyrexia			
subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	7 / 17 (41.18%)
occurrences (all)	2	1	15
Pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Sensation of foreign body			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Suprapubic pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Temperature intolerance			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Thirst			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 17 (0.00%) 0
Immune system disorders Cytokine release syndrome subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 17 (0.00%) 0
Reproductive system and breast disorders Benign prostatic hyperplasia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1
Pruritus genital subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 17 (0.00%) 0
Scrotal oedema subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 17 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1
Dysphonia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 7 (14.29%) 1	1 / 17 (5.88%) 2
Cough subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 7 (14.29%) 1	5 / 17 (29.41%) 7
Dyspnoea subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	2 / 7 (28.57%) 3	3 / 17 (17.65%) 4
Dyspnoea exertional subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 17 (0.00%) 0
Epistaxis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1	3 / 17 (17.65%) 6

Hiccups			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Lung infiltration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Nasal cyst			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Pharyngeal inflammation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Productive cough			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	2
Rhinalgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Respiratory tract irritation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Rhinitis allergic			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Sneezing			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1

Throat irritation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Apathy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Confusional state			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Depressed mood			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Disorientation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	2 / 17 (11.76%)
occurrences (all)	2	1	2
Mental status changes			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Mood altered			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Nightmare			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Sleep disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	0	3
Tearfulness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Amylase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	0	2
Beta 2 microglobulin increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Band neutrophil percentage increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Blood albumin decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	2
Blood chloride increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	5
Blood fibrinogen increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Blood creatinine increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	3 / 17 (17.65%)
occurrences (all)	2	0	3
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Blood phosphorus decreased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Blood potassium decreased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	0	2
Blood urea increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	0	3
Blood uric acid increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	1	0	1
Body temperature increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
C-reactive protein increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	3 / 17 (17.65%)
occurrences (all)	0	0	4
Calcium ionised increased			

subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Ejection fraction decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Foetal haemoglobin increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Glutamate dehydrogenase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Monocyte count increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Neutrophil count decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Neutrophil count increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Serum ferritin increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0

Rubulavirus test positive subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 17 (0.00%) 0
Weight decreased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 2	3 / 17 (17.65%) 3
White blood cell count decreased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 17 (5.88%) 2
Weight increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1
Injury, poisoning and procedural complications			
Allergic transfusion reaction subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 17 (0.00%) 0
Arthropod bite subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 17 (0.00%) 0
Eye injury subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1
Contusion subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 17 (0.00%) 0
Fall subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1
Post-traumatic pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 17 (0.00%) 0
Limb injury subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 17 (0.00%) 0
Procedural pain			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Rib fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Spinal compression fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Thermal burn			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	2 / 17 (11.76%)
occurrences (all)	0	1	2
Atrial fibrillation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Bradycardia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Cardiac failure congestive			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Myocardial infarction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Sinus tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Palpitations			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	0	1	0

Supraventricular extrasystoles subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1
Nervous system disorders			
Ageusia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1
Areflexia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 17 (0.00%) 0
Depressed level of consciousness subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 17 (0.00%) 0
Coma subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 17 (0.00%) 0
Dizziness subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1	7 / 17 (41.18%) 8
Dizziness postural subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1
Dysaesthesia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1
Dysgeusia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 7 (14.29%) 1	3 / 17 (17.65%) 4
Head discomfort subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 17 (5.88%) 2
Headache subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	2 / 7 (28.57%) 2	3 / 17 (17.65%) 4
Hypoaesthesia			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Intercostal neuralgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Mental impairment			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Motor dysfunction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Neuralgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Myoclonus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	4 / 17 (23.53%)
occurrences (all)	0	0	6
Orthostatic intolerance			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	0	3
Parosmia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Peripheral motor neuropathy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	2 / 17 (11.76%)
occurrences (all)	1	0	2
Polyneuropathy			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	3 / 17 (17.65%)
occurrences (all)	0	0	4
Post herpetic neuralgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Restless legs syndrome			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	2
Syncope			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 7 (85.71%)	3 / 7 (42.86%)	10 / 17 (58.82%)
occurrences (all)	13	8	29
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Febrile neutropenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Leukocytosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Leukopenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	6 / 17 (35.29%)
occurrences (all)	0	0	17
Lymphopenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	3 / 17 (17.65%)
occurrences (all)	0	0	7
Monocytosis			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	0	3
Neutropenia			
subjects affected / exposed	4 / 7 (57.14%)	4 / 7 (57.14%)	14 / 17 (82.35%)
occurrences (all)	8	12	51
Neutrophilia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	6 / 7 (85.71%)	6 / 7 (85.71%)	16 / 17 (94.12%)
occurrences (all)	17	16	55
Thrombocytosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Tinnitus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Blindness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Cataract			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Conjunctivitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	3 / 17 (17.65%)
occurrences (all)	0	0	4
Dry eye			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Eye pruritus			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	0	2
Eye swelling			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Eyelid oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Ocular hyperaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Lacrimation increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Ocular surface disease			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	0	2
Abdominal distension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	0	3
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	4 / 17 (23.53%)
occurrences (all)	0	0	5
Aerophagia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	1 / 17 (5.88%)
occurrences (all)	1	1	1

Anal fissure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	0 / 7 (0.00%)	4 / 7 (57.14%)	3 / 17 (17.65%)
occurrences (all)	0	4	7
Diarrhoea			
subjects affected / exposed	2 / 7 (28.57%)	3 / 7 (42.86%)	14 / 17 (82.35%)
occurrences (all)	6	3	47
Dry mouth			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 7 (28.57%)	1 / 17 (5.88%)
occurrences (all)	1	2	1
Dysphagia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	0	2	0
Faecal incontinence			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Faeces discoloured			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Flatulence			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	5 / 17 (29.41%)
occurrences (all)	0	0	6
Gastric disorder			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	1	0	1
Gastritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	2

Gingival bleeding			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	2
Haematemesis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Haematochezia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Haemorrhoids			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Mouth haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	1 / 7 (14.29%)	3 / 7 (42.86%)	13 / 17 (76.47%)
occurrences (all)	2	5	27
Mouth ulceration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Odynophagia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	0	3
Oesophagitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Oral discomfort			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Oral mucosal erythema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Oral pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	0	2

Pancreatitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Stomatitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	7 / 17 (41.18%)
occurrences (all)	1	2	17
Toothache			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Blister			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Cutaneous lupus erythematosus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Dermatitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Dermatitis allergic			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Dermatitis contact			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Dyshidrotic eczema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Erythema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Ecchymosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Leukocytoclastic vasculitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Nail disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Night sweats			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	3
Pain of skin			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Papule			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	1	0	1
Petechiae			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Photosensitivity reaction			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Rash			

subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 2	0 / 7 (0.00%) 0	4 / 17 (23.53%) 4
Rash papular subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1
Urticaria subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1
Skin hyperpigmentation subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1
Renal and urinary disorders			
Acute prerenal failure subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 17 (0.00%) 0
Dysuria subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1
Bladder spasm subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 17 (5.88%) 2
Enuresis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 17 (0.00%) 0
Incontinence subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1
Haematuria subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 17 (0.00%) 0
Micturition disorder subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 17 (0.00%) 0
Nephropathy toxic subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1

Micturition urgency			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Pyelocaliectasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Renal failure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	3 / 17 (17.65%)
occurrences (all)	0	0	13
Renal impairment			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Ureteric stenosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Urinary hesitation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	0	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	2 / 17 (11.76%)
occurrences (all)	1	1	2
Back pain			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	2 / 17 (11.76%)
occurrences (all)	0	2	5
Bone pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	2 / 17 (11.76%)
occurrences (all)	0	1	2
Flank pain			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	0	2
Limb discomfort			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Muscle tightness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	2 / 17 (11.76%)
occurrences (all)	0	1	2
Muscular weakness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	3 / 17 (17.65%)
occurrences (all)	0	0	3
Neck pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	0	2
Myalgia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	2 / 17 (11.76%)
occurrences (all)	1	0	2
Pain in extremity			
subjects affected / exposed	1 / 7 (14.29%)	2 / 7 (28.57%)	3 / 17 (17.65%)
occurrences (all)	1	2	5
Pain in jaw			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Rhabdomyolysis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Rheumatoid arthritis			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 17 (5.88%) 4
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 17 (0.00%) 0
Bacterial disease carrier			
subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1
Arthritis infective			
subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 17 (0.00%) 0
Bronchitis			
subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1
Clostridium difficile colitis			
subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 17 (0.00%) 0
Candida infection			
subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 17 (0.00%) 0
Device related infection			
subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 17 (5.88%) 2
Eye infection			
subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 17 (0.00%) 0
Ear infection			
subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1	0 / 17 (0.00%) 0
Folliculitis			
subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 17 (0.00%) 0
Gastroenteritis viral			
subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 17 (0.00%) 0

Gastrointestinal candidiasis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 17 (5.88%)
occurrences (all)	0	1	1
Gastrointestinal infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	2
Gingivitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Herpes zoster			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Laryngitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Lobar pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	3 / 17 (17.65%)
occurrences (all)	2	0	13
Neutropenic infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	0	2
Oral herpes			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1

Pharyngitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Rash pustular			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	4 / 17 (23.53%)
occurrences (all)	0	0	8
Rhinitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Skin candida			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Tinea pedis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Tooth infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	2 / 17 (11.76%)
occurrences (all)	0	1	3
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	2 / 17 (11.76%)
occurrences (all)	0	2	3
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	10 / 17 (58.82%)
occurrences (all)	2	0	14
Hypercalcaemia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	0 / 17 (0.00%)
occurrences (all)	0	3	0
Dehydration			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	4 / 17 (23.53%)
occurrences (all)	0	1	7
Hyperkalaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Hyperphosphataemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	2
Hyperuricaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	1	0	1
Hypocalcaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	4
Hypochloraemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			

subjects affected / exposed	0 / 7 (0.00%)	3 / 7 (42.86%)	5 / 17 (29.41%)
occurrences (all)	0	3	8
Hypomagnesaemia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	1 / 17 (5.88%)
occurrences (all)	1	2	6
Hypophagia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Hyponatraemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	3 / 17 (17.65%)
occurrences (all)	0	0	7
Hypophosphataemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Hypoproteinaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Metabolic acidosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	PAN 30 mg + BTZ 1.3 mg/m ²	PAN 25 mg + BTZ 1.3 mg/m ²	PAN 20 mg (2 weeks on/ 1 week off) + BTZ 1.3 mg/m ² + DEX 20 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	9 / 9 (100.00%)	15 / 15 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Hot flush			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0

Haematoma			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	1	2
Hypertension			
subjects affected / exposed	3 / 7 (42.86%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	8	1	2
Hypotension			
subjects affected / exposed	2 / 7 (28.57%)	2 / 9 (22.22%)	3 / 15 (20.00%)
occurrences (all)	4	5	3
Orthostatic hypotension			
subjects affected / exposed	1 / 7 (14.29%)	2 / 9 (22.22%)	2 / 15 (13.33%)
occurrences (all)	1	2	2
Phlebitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Shock			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Thrombophlebitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Venous thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 7 (71.43%)	5 / 9 (55.56%)	7 / 15 (46.67%)
occurrences (all)	8	12	9
Chills			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences (all)	1	0	4
Chest pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Exercise tolerance decreased			

subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	4 / 7 (57.14%)	3 / 9 (33.33%)	11 / 15 (73.33%)
occurrences (all)	6	4	14
Face oedema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Feeling cold			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	2	4
Gait disturbance			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
General physical health deterioration			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Generalised oedema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Influenza like illness			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Irritability			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Local swelling			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Non-cardiac chest pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			

subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	2 / 9 (22.22%) 5	5 / 15 (33.33%) 6
Pyrexia subjects affected / exposed occurrences (all)	4 / 7 (57.14%) 5	5 / 9 (55.56%) 7	6 / 15 (40.00%) 6
Pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	1 / 15 (6.67%) 2
Sensation of foreign body subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Suprapubic pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	1 / 15 (6.67%) 1
Temperature intolerance subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	1 / 15 (6.67%) 1
Thirst subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Immune system disorders Cytokine release syndrome subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	1 / 15 (6.67%) 1
Reproductive system and breast disorders Benign prostatic hyperplasia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Pruritus genital subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Scrotal oedema subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	1 / 15 (6.67%) 1
Respiratory, thoracic and mediastinal disorders			

Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Dysphonia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	3 / 15 (20.00%)
occurrences (all)	0	1	3
Cough			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	6 / 15 (40.00%)
occurrences (all)	1	1	7
Dyspnoea			
subjects affected / exposed	3 / 7 (42.86%)	1 / 9 (11.11%)	4 / 15 (26.67%)
occurrences (all)	5	2	8
Dyspnoea exertional			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	2 / 7 (28.57%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	2	1	0
Hiccups			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Lung infiltration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Nasal congestion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Nasal cyst			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Pharyngeal inflammation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Oropharyngeal pain			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 9 (11.11%) 1	3 / 15 (20.00%) 4
Productive cough subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 9 (11.11%) 1	0 / 15 (0.00%) 0
Rhinalgia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	1 / 15 (6.67%) 1
Respiratory tract irritation subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Rhinitis allergic subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 9 (0.00%) 0	1 / 15 (6.67%) 1
Sneezing subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	3 / 15 (20.00%) 3
Throat irritation subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 9 (11.11%) 1	0 / 15 (0.00%) 0
Wheezing subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	1 / 15 (6.67%) 1
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	1 / 15 (6.67%) 1
Apathy subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 9 (11.11%) 1	0 / 15 (0.00%) 0
Confusional state subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0

Depressed mood subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	1 / 15 (6.67%) 1
Disorientation subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	1 / 15 (6.67%) 1
Depression subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 9 (11.11%) 1	0 / 15 (0.00%) 0
Insomnia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	2 / 9 (22.22%) 2	4 / 15 (26.67%) 6
Mental status changes subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Mood altered subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	1 / 15 (6.67%) 1
Nightmare subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Sleep disorder subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 2	1 / 9 (11.11%) 2	1 / 15 (6.67%) 2
Tearfulness subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	1 / 15 (6.67%) 1
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 9 (11.11%) 1	2 / 15 (13.33%) 4
Amylase increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	1 / 15 (6.67%) 2
Aspartate aminotransferase increased			

subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	2 / 15 (13.33%)
occurrences (all)	2	1	2
Beta 2 microglobulin increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Band neutrophil percentage increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Blood albumin decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Blood chloride increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	2	1
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 7 (28.57%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences (all)	4	0	3
Blood fibrinogen increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Blood creatinine increased			
subjects affected / exposed	1 / 7 (14.29%)	3 / 9 (33.33%)	4 / 15 (26.67%)
occurrences (all)	2	4	6
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	2 / 15 (13.33%)
occurrences (all)	1	4	7
Blood phosphorus decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Blood potassium decreased			

subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Blood urea increased			
subjects affected / exposed	2 / 7 (28.57%)	1 / 9 (11.11%)	2 / 15 (13.33%)
occurrences (all)	4	1	5
Blood uric acid increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Body temperature increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
C-reactive protein increased			
subjects affected / exposed	0 / 7 (0.00%)	2 / 9 (22.22%)	2 / 15 (13.33%)
occurrences (all)	0	4	10
Calcium ionised increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Ejection fraction decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Foetal haemoglobin increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 7 (28.57%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences (all)	2	0	5
Glomerular filtration rate decreased			

subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Glutamate dehydrogenase increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	2 / 15 (13.33%)
occurrences (all)	0	1	7
Monocyte count increased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	1	2	0
Neutrophil count decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Neutrophil count increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Platelet count decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Serum ferritin increased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Rubulavirus test positive			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	1 / 7 (14.29%)	3 / 9 (33.33%)	5 / 15 (33.33%)
occurrences (all)	1	4	10
White blood cell count decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Weight increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Allergic transfusion reaction			

subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Arthropod bite			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Eye injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Fall			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Post-traumatic pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Limb injury			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Procedural pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Rib fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Spinal compression fracture			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Thermal burn			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0

Atrial fibrillation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Bradycardia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Cardiac failure congestive			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Myocardial infarction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Sinus tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Palpitations			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Supraventricular extrasystoles			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Ageusia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Areflexia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Depressed level of consciousness			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Coma			

subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	3 / 7 (42.86%)	1 / 9 (11.11%)	7 / 15 (46.67%)
occurrences (all)	6	3	15
Dizziness postural			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Dysaesthesia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Dysgeusia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 9 (22.22%)	6 / 15 (40.00%)
occurrences (all)	0	2	7
Head discomfort			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	3 / 7 (42.86%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	4	0	3
Hypoaesthesia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Intercostal neuralgia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Mental impairment			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Motor dysfunction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Neuralgia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Myoclonus			

subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Neuropathy peripheral			
subjects affected / exposed	1 / 7 (14.29%)	3 / 9 (33.33%)	7 / 15 (46.67%)
occurrences (all)	2	4	9
Orthostatic intolerance			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Paraesthesia			
subjects affected / exposed	2 / 7 (28.57%)	2 / 9 (22.22%)	1 / 15 (6.67%)
occurrences (all)	3	3	1
Parosmia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Peripheral motor neuropathy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	3 / 15 (20.00%)
occurrences (all)	0	1	3
Polyneuropathy			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Post herpetic neuralgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Restless legs syndrome			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Syncope			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Tremor			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	5 / 7 (71.43%)	5 / 9 (55.56%)	5 / 15 (33.33%)
occurrences (all)	12	9	14
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Febrile neutropenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Leukocytosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	3
Leukopenia			
subjects affected / exposed	3 / 7 (42.86%)	1 / 9 (11.11%)	6 / 15 (40.00%)
occurrences (all)	8	4	22
Lymphopenia			
subjects affected / exposed	2 / 7 (28.57%)	1 / 9 (11.11%)	5 / 15 (33.33%)
occurrences (all)	4	4	29
Monocytosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	13
Neutropenia			
subjects affected / exposed	6 / 7 (85.71%)	5 / 9 (55.56%)	8 / 15 (53.33%)
occurrences (all)	37	68	30
Neutrophilia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 9 (22.22%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Thrombocytopenia			
subjects affected / exposed	7 / 7 (100.00%)	8 / 9 (88.89%)	9 / 15 (60.00%)
occurrences (all)	22	29	41
Thrombocytosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	3
Ear and labyrinth disorders			

Ear pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Tinnitus			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Blindness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	3
Cataract			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Dry eye			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Eye pruritus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Eye swelling			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Eyelid oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Ocular hyperaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Lacrimation increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Ocular surface disease			

subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Vision blurred			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	6 / 15 (40.00%)
occurrences (all)	0	1	7
Abdominal distension			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	1	2
Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)	2 / 9 (22.22%)	7 / 15 (46.67%)
occurrences (all)	0	3	10
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	4 / 15 (26.67%)
occurrences (all)	0	2	8
Aerophagia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Anal fissure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	1 / 7 (14.29%)	2 / 9 (22.22%)	8 / 15 (53.33%)
occurrences (all)	3	2	8
Diarrhoea			
subjects affected / exposed	7 / 7 (100.00%)	6 / 9 (66.67%)	13 / 15 (86.67%)
occurrences (all)	17	27	34
Dry mouth			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	2 / 7 (28.57%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences (all)	2	0	4

Dysphagia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Faecal incontinence			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Faeces discoloured			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	2 / 15 (13.33%)
occurrences (all)	0	1	2
Gastric disorder			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Gingival bleeding			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Haematemesis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Haematochezia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Mouth haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0

Nausea			
subjects affected / exposed	5 / 7 (71.43%)	6 / 9 (66.67%)	10 / 15 (66.67%)
occurrences (all)	11	17	17
Mouth ulceration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Odynophagia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	2 / 15 (13.33%)
occurrences (all)	0	1	2
Oesophagitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Oral discomfort			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Oral mucosal erythema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Oral pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Pancreatitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences (all)	1	0	3
Vomiting			
subjects affected / exposed	4 / 7 (57.14%)	4 / 9 (44.44%)	7 / 15 (46.67%)
occurrences (all)	8	6	11
Toothache			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Hepatotoxicity			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 9 (11.11%) 1	0 / 15 (0.00%) 0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	1 / 15 (6.67%) 1
Blister			
subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	1 / 15 (6.67%) 1
Cutaneous lupus erythematosus			
subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Dermatitis			
subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 9 (11.11%) 1	0 / 15 (0.00%) 0
Dermatitis allergic			
subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Dry skin			
subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	2 / 15 (13.33%) 2
Dermatitis contact			
subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Dyshidrotic eczema			
subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Erythema			
subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 9 (0.00%) 0	1 / 15 (6.67%) 3
Ecchymosis			
subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	1 / 15 (6.67%) 2
Leukocytoclastic vasculitis			
subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0

Nail disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Pain of skin			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Papule			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Petechiae			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Photosensitivity reaction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	3 / 15 (20.00%)
occurrences (all)	1	1	6
Rash papular			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Skin hyperpigmentation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Acute prerenal failure			

subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Dysuria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Bladder spasm			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Enuresis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Incontinence			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	0 / 7 (0.00%)	2 / 9 (22.22%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Micturition disorder			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Nephropathy toxic			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Micturition urgency			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Pollakiuria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Pyelocaliectasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Renal failure			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	2	1	0
Renal impairment			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 9 (11.11%) 1	0 / 15 (0.00%) 0
Ureteric stenosis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Urinary hesitation subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	1 / 15 (6.67%) 1
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 2	1 / 9 (11.11%) 1	1 / 15 (6.67%) 1
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	2 / 9 (22.22%) 2	4 / 15 (26.67%) 4
Back pain subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 9 (11.11%) 1	3 / 15 (20.00%) 4
Bone pain subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	2 / 9 (22.22%) 2	2 / 15 (13.33%) 5
Flank pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	1 / 15 (6.67%) 1
Muscle spasms subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	1 / 15 (6.67%) 2
Limb discomfort subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	1 / 15 (6.67%) 1
Muscle tightness subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0	1 / 15 (6.67%) 1
Musculoskeletal chest pain			

subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	3
Muscular weakness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Neck pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Myalgia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	4 / 15 (26.67%)
occurrences (all)	0	1	5
Pain in extremity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	4 / 15 (26.67%)
occurrences (all)	0	0	4
Pain in jaw			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	3
Rhabdomyolysis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Rheumatoid arthritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Bacterial disease carrier			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Arthritis infective			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1

Bronchitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Clostridium difficile colitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Candida infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Device related infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Eye infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Ear infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Folliculitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Gastroenteritis viral			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Gastrointestinal candidiasis			
subjects affected / exposed	0 / 7 (0.00%)	2 / 9 (22.22%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Gingivitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Herpes zoster			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1

Infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Laryngitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Lobar pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 7 (0.00%)	2 / 9 (22.22%)	3 / 15 (20.00%)
occurrences (all)	0	4	4
Neutropenic infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Oral candidiasis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Oral herpes			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	1 / 7 (14.29%)	2 / 9 (22.22%)	0 / 15 (0.00%)
occurrences (all)	1	4	0
Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Rash pustular			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection			
subjects affected / exposed	3 / 7 (42.86%)	2 / 9 (22.22%)	3 / 15 (20.00%)
occurrences (all)	6	2	8

Rhinitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	2 / 15 (13.33%)
occurrences (all)	0	1	2
Sinusitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Skin candida			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Tinea pedis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Tooth infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	6 / 15 (40.00%)
occurrences (all)	0	1	7
Urinary tract infection			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	3	1	1
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 7 (42.86%)	5 / 9 (55.56%)	9 / 15 (60.00%)
occurrences (all)	4	8	14
Hypercalcaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Dehydration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	3 / 15 (20.00%)
occurrences (all)	0	0	4
Hyperglycaemia			

subjects affected / exposed	3 / 7 (42.86%)	3 / 9 (33.33%)	1 / 15 (6.67%)
occurrences (all)	5	4	6
Hyperkalaemia			
subjects affected / exposed	2 / 7 (28.57%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	4	1	0
Hyperphosphataemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	5	0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Hyperuricaemia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 9 (22.22%)	0 / 15 (0.00%)
occurrences (all)	0	5	0
Hypoalbuminaemia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 9 (22.22%)	3 / 15 (20.00%)
occurrences (all)	1	4	3
Hypocalcaemia			
subjects affected / exposed	1 / 7 (14.29%)	3 / 9 (33.33%)	4 / 15 (26.67%)
occurrences (all)	4	4	10
Hypochloraemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Hypokalaemia			
subjects affected / exposed	2 / 7 (28.57%)	3 / 9 (33.33%)	5 / 15 (33.33%)
occurrences (all)	4	5	7
Hypomagnesaemia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 9 (22.22%)	1 / 15 (6.67%)
occurrences (all)	0	6	1
Hypophagia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Hyponatraemia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	3 / 15 (20.00%)
occurrences (all)	2	1	5
Hypophosphataemia			

subjects affected / exposed	1 / 7 (14.29%)	2 / 9 (22.22%)	5 / 15 (33.33%)
occurrences (all)	2	6	20
Hypoproteinaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Metabolic acidosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 April 2008	The primary reason for this protocol amendment was to adjust the prior distribution assumptions that underlie the Bayesian logistical model. In amendment 1 to the protocol, the probability of experiencing DLT when treated with 0.7 mg/m ² , 1.0 mg/m ² and 1.3 mg/m ² of BTZ alone was revised to be 0.05, 0.1 and 0.15, respectively. In addition, a baseline chest X-ray assessment was introduced due to Health Authority recommendation. Amendment 1 to the protocol also improved the clarity and feasibility of certain protocol sections.
19 March 2010	Amendment 2 to the protocol was performed for following reasons: <ul style="list-style-type: none">- To amend the dosing schedule by introducing a week of treatment holiday for PAN in the dose expansion phase. The purpose was to allow for accelerated platelet recovery and thus minimize dose interruptions and dose reductions due to thrombocytopenia.- To introduce Dex in all dose expansion phase patients, in contrast to dose escalation phase, where Dex was introduced only in patients with a suboptimal response to the combination.- To investigate the effect of Dex on the pharmacokinetics of both PAN and BTZ. PK evaluations of PAN and BTZ without and with Dex were planned in 12-15 patients to evaluate any potential enzyme induction effect.- In order to do this, and allow rationally a Dex-free period, Dex was introduced in all patients at Cycle 2 in this cohort. The PK profiles of PAN and BTZ without (in Cycle 1) and with (in Cycle 2) was to be compared.- To document with appropriate blood count sampling the kinetic profile of thrombocytopenia during the treatment cycle including recovery profile during the week of treatment holiday.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported