Clinical trial results:
A multicenter, randomized, double-blind, placebocontrolled phase III study of panobinostat in combination with bortezomib and dexamethasone in patients with relapsed multiple myeloma

Summary

EudraCT number	2009-015507-52
Trial protocol	SE FI DE NL BE DK IT FR ES CZ PL GB AT GR
Global end of trial date	30 July 2015

Results information

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

Trial information

Trial identification

Sponsor protocol code	CLBH589D2308

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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 612341111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 612341111,

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	30 July 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to compare progression-free survival (PFS) in patients treated with panobinostat (PAN) in combination with bortezomib (BTZ)/dexamethasone (Dex) vs. patients treated with placebo (PBO) in combination with bortezomib/dexamethasone. The key secondary objective was to compare overall survival (OS) between treatment arms.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 December 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	28 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 9
Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	Brazil: 37
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	China: 45
Country: Number of subjects enrolled	Czech Republic: 13
Country: Number of subjects enrolled	Denmark: 16
Country: Number of subjects enrolled	Egypt: 16
Country: Number of subjects enrolled	Finland: 6
Country: Number of subjects enrolled	France: 24
Country: Number of subjects enrolled	Germany: 63
Country: Number of subjects enrolled	Greece: 17
Country: Number of subjects enrolled	Hong Kong: 6
Country: Number of subjects enrolled	Israel: 5

Country: Number of subjects enrolled	Italy: 45
Country: Number of subjects enrolled	Japan: 34
Country: Number of subjects enrolled	Korea, Republic of: 68
Country: Number of subjects enrolled	Lebanon: 5
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Netherlands: 12
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Poland: 21
Country: Number of subjects enrolled	Russian Federation: 17
Country: Number of subjects enrolled	Singapore: 10
Country: Number of subjects enrolled	South Africa: 7
Country: Number of subjects enrolled	Spain: 38
Country: Number of subjects enrolled	Sweden: 25
Country: Number of subjects enrolled	Taiwan: 18
Country: Number of subjects enrolled	Thailand: 45
Country: Number of subjects enrolled	Turkey: 21
Country: Number of subjects enrolled	United Kingdom: 30
Country: Number of subjects enrolled	United States: 54
Worldwide total number of subjects	768
EEA total number of subjects	335

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)	445
From 65 to 84 years	323
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 768 eligible patients were randomized 1:1 to the panobinostat and control arms. Central randomization was stratified 1) by number of prior lines of anti-myeloma therapy: 1 vs. 2 or 3 and 2) by prior use of bortezomib: Yes vs. No.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Panobinostat + Bortezomib + Dexamethasone

Arm description:

Panobinostat was given 20 mg hard gelatin capsules . Bortezomib was given at 1.3 mg/m2 as a 3 to 5 second bolus intravenous (IV)injection. Dexamethasone was given as an oral dose of 20 mg/day.

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

Dosage and administration details:

Panobinostat was given 20 mg capsules

Arm title	Placebo + Bortezomib + Dexamethasone

Arm description:

Placebo was given as a hard gelatin capsule in the image of Panobinostat . Bortezomib was given at 1.3 mg/m2 as a 3 to 5 second bolus intravenous (IV) injection. Dexamethasone was given as an oral dose of 20 mg/day.

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

Dosage and administration details:

placebo hard capsule match of panobinostat

Number of subjects in period 1	Panobinostat + Bortezomib + Dexamethasone	Placebo + Bortezomib + Dexamethasone
Started	387	381
Completed	102	102
Not completed	285	279
Adverse event, serious fatal	21	17
Consent withdrawn by subject	34	18
Disease progression	82	153
Adverse event, non-fatal	130	66
New Cancer therapy	4	7
Administrative problems	2	1
Untreated	5	5
Abnormal test proceedure results	3	8
Lost to follow-up	1	-
Protocol deviation	3	4

Baseline characteristics

Reporting groups	
Reporting group title	Panobinostat + Bortezomib + Dexamethasone
Reporting group description:	
Panobinostat was given 20 mg hard gelatin capsules . Bortezomib was given at 1.3 mg/m2 as a 3 to 5 second bolus intravenous (IV)injection. Dexamethasone was given as an oral dose of 20 mg/day.	
Reporting group title	Placebo + Bortezomib + Dexamethasone
Reporting group description:	
Placebo was given as a hard gelatin capsule in the image of Panobinostat . Bortezomib was given at 1.3 mg/m2 as a 3 to 5 second bolus intravenous (IV) injection. Dexamethasone was given as an oral dose of 20 mg/day.	

Reporting group values	Panobinostat + Bortezomib + Dexamethasone	Placebo + Bortezomib + Dexamethasone	Total
Number of subjects	387	381	768
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	225	220	445
From 65-84 years	162	161	323
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	62.4	61.8	
standard deviation	± 9.34	± 9.43	-
Gender, Male/Female Units: participants			
Female	185	176	361
Male	202	205	407
Race/Ethnicity, Customized Units: Subjects			
Caucasian	249	250	499
Asian	128	104	232
Black	5	17	22
Other	5	10	15

End points

End points reporting groups

Reporting group title	Panobinostat + Bortezomib + Dexamethasone
Reporting group description:	
Panobinostat was given 20 mg hard gelatin capsules . Bortezomib was given at 1.3 mg/m2 as a 3 to 5 second bolus intravenous (IV)injection. Dexamethasone was given as an oral dose of 20 mg/day.	
Reporting group title	Placebo + Bortezomib + Dexamethasone
Reporting group description:	
Placebo was given as a hard gelatin capsule in the image of Panobinostat . Bortezomib was given at 1.3 mg/m2 as a 3 to 5 second bolus intravenous (IV) injection. Dexamethasone was given as an oral dose of 20 mg/day.	

Primary: Progression-free survival events in patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone.

End point title	Progression-free survival events in patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone.
End point description:	
End point type	Primary
End point timeframe:	
45 months	

End point values	Panobinostat + Bortezomib + Dexamethasone	Placebo + Bortezomib + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	387	381		
Units: number of events	207	260		

Statistical analyses

Statistical analysis title	investigator assessment using mEBMT
Comparison groups	Panobinostat + Bortezomib + Dexamethasone v Placebo + Bortezomib + Dexamethasone
Number of subjects included in analysis	768
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	0.76

Primary: Progression Free Survival in patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone.

End point title	Progression Free Survival in patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone.
End point description:	
End point type	Primary
End point timeframe:	
45 months	

End point values	Panobinostat + Bortezomib + Dexamethasone	Placebo + Bortezomib + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	387	381		
Units: months				
median (confidence interval 95%)	11.99 (10.32 to 12.94)	8.8 (7.56 to 9.23)		

Statistical analyses

Statistical analysis title	PFS (investigator’s assessment) overall
Comparison groups	Panobinostat + Bortezomib + Dexamethasone v Placebo + Bortezomib + Dexamethasone
Number of subjects included in analysis	768
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	0.76

Secondary: Final analysis of overall survival events in patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone

End point title	Final analysis of overall survival events in patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone

End point description:

Number of OS events

End point type	Secondary

End point timeframe:

Survival follow-up continued until 415 survival events had occurred. Data cut off was 29-Jun-2015 and the last patient last visit was on 30-Jul-2015.

End point values	Panobinostat + Bortezomib + Dexamethasone	Placebo + Bortezomib + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	387	381		
Units: Number of OS events	204	211		

Statistical analyses

No statistical analyses for this end point

Secondary: Final analysis of overall survival in patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone

End point title	Final analysis of overall survival in patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone

End point description:

survival time in months

End point type	Secondary

End point timeframe:

Survival follow-up continued until 415 survival events had occurred. Data cut off was 29-Jun-2015 and the last patient last visit was on 30-Jul-2015.

End point values	Panobinostat + Bortezomib + Dexamethasone	Placebo + Bortezomib + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	387	381		
Units: months				
median (confidence interval 95%)	40.28 (35.02 to 44.81)	35.78 (28.98 to 40.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate in patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone.

End point title	Overall response rate in patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone.

End point description:

Best overall response based on mEBMT criteria per investigator assessment

End point type	Secondary

End point timeframe:

45 months

End point values	Panobinostat + Bortezomib + Dexamethasone	Placebo + Bortezomib + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	387	381		
Units: % participants with response				
number (not applicable)	60.7	54.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response per investigator assessment (mEBMT criteria) of response patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone.

End point title	Time to response per investigator assessment (mEBMT criteria) of response patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone.

End point description:

End point type	Secondary

End point timeframe:

45 months

End point values	Panobinostat + Bortezomib + Dexamethasone	Placebo + Bortezomib + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	387	381		
Units: time to response in months				
median (confidence interval 95%)	1.51 (1.41 to 1.64)	2 (1.61 to 2.79)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response per investigator assessment (mEBMT criteria) patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone.

End point title	Duration of response per investigator assessment (mEBMT criteria) patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone.

End point description:

End point type	Secondary

End point timeframe:

45 months

End point values	Panobinostat + Bortezomib + Dexamethasone	Placebo + Bortezomib + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	387	381		
Units: duration of response in months				
median (confidence interval 95%)	13.14 (11.76 to 14.92)	10.87 (9.23 to 11.76)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression/relapse per investigator assessment (mEBMT criteria) patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone.

End point title	Time to progression/relapse per investigator assessment (mEBMT criteria) patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone.

End point description:

End point type	Secondary

End point timeframe:

45 months

End point values	Panobinostat + Bortezomib + Dexamethasone	Placebo + Bortezomib + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	387	381		
Units: response in months				
median (confidence interval 95%)	12.71 (11.3 to 14.06)	8.54 (7.66 to 9.72)		

Statistical analyses

No statistical analyses for this end point

Secondary: EORTC QLQ-MY20-Change from Baseline by treatment group

End point title	EORTC QLQ-MY20-Change from Baseline by treatment group

End point description:

Higher values in the disease symptoms and side effects of treatment scores indicate worsening. Higher scores in the future perspective and body image scores indicate improvement. LS Means and SEM are estimated from the repeated measures model. Following factors and covariates are included in the repeated measurement model: time, treatment, treatment by time interaction, number of prior lines of anti-MM therapy (1/ 2 and 3), prior use of BTZ (Yes/ No), baseline score.

End point type	Secondary

End point timeframe:

12, 24 and 48 weeks

End point values	Panobinostat + Bortezomib + Dexamethasone	Placebo + Bortezomib + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	387	381		
Units: score on a scale				
least squares mean (confidence interval 95%)				
Disease Symptom wk 12 change baseline (n=215,243)	-4.795 (-6.76 to -2.83)	-4.865 (-6.75 to -2.98)		
Disease Symptom wk 24 change baseline (n=148,177)	-4.401 (-6.53 to -2.27)	-6.797 (-8.79 to -4.81)		
Disease Symptom wk 48 change baseline (n=37,26)	-2.836 (-6.76 to -1.084)	-6.626 (-11.1 to -2.12)		
Side effects of treatment wk 12 chge (n=213,242)	8.162 (6.51 to 9.814)	5.524 (3.933 to 7.115)		
Side effects of treatment wk 24 chge (n=148,175)	9.016 (6.955 to 11.08)	7.731 (5.795 to 9.668)		
Side effects of treatment wk 48 chge (n=37,26)	3.357 (0.442 to 6.273)	3.654 (0.352 to 6.956)		
Future perspective wk 12 chge (n=214,242)	5.319 (2.893 to 7.744)	6.194 (3.854 to 8.533)		
Future perspective wk 24 chge (n=148,176)	3.877 (0.977 to 6.778)	5.839 (3.103 to 8.575)		
Future perspective wk 48 chge (n=37,26)	4.331 (-0.142 to 8.804)	6.951 (1.807 to 12.1)		
Body image wk 12 chge (n=213,240)	-7.178 (-10.5 to -3.87)	-6.22 (-9.41 to -3.03)		
Body image wk 24 chge (n=147,175)	-11.463 (-15.3 to -7.66)	-7.358 (-10.9 to -3.81)		
Body image wk 48 chge (n=37,26)	-2.161 (-7.73 to 3.41)	-4.666 (-11.1 to 1.729)		

Statistical analyses

No statistical analyses for this end point

Secondary: EORTC QLQ-C30 - Summary Statistics by treatment group

End point title	EORTC QLQ-C30 - Summary Statistics by treatment group

End point description:

The EORTC QLQ-C30 measures functional dimensions (physical, role, emotional, cognitive, and social), three multi-item symptom scales (fatigue, nausea/vomiting, and pain), six single-item symptom scales (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea and financial impact) and a global health status/QoL scale

End point type	Secondary

End point timeframe:

12, 24 and 48 weeks

End point values	Panobinostat + Bortezomib + Dexamethasone	Placebo + Bortezomib + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	387	381		
Units: score on a scale				
least squares mean (confidence interval 95%)				
Global health wk 12 change baseline (n=216,239)	-9.853 (-12.5 to -7.2)	-4.044 (-6.6 to -1.49)		
Global health wk 24 change baseline (n=150,176)	-7.867 (-10.7 to -5.08)	-1.518 (-4.11 to -1.075)		
Global health wk 48 change baseline (n=38,26)	-2.986 (-7.21 to 1.237)	4.345 (-0.416 to 9.106)		
Physical functioning wk 12 chge (n=217,242)	-9.67 (-12 to -7.38)	-5.393 (-76.3 to -3.16)		
Physical functioning wk 24 chge (n=151,177)	-9.516 (-12.2 to -7.38)	-6.456 (-8.98 to -3.93)		
Physical functioning wk 48 chge (n=38,26)	-2.88 (-6.41 to 0.651)	2.037 (-2.07 to 6.147)		
Role functioning wk 12 chge (n=215,237)	-11.159 (-14.6 to -7.74)	-6.762 (-10.1 to -3.45)		
Role functioning wk 24 chge (n=150,176)	-11.875 (-15.7 to -8.01)	-11.263 (-14.9 to -7.61)		
Role functioning wk 48 chge (n=38,26)	-5.927 (-11.4 to -0.424)	-0.401 (-6.73 to 5.924)		
Cognitive functioning wk 12 chge (n=216,240)	-4.464 (-6.89 to -2.04)	-1.023 (-3.36 to 1.318)		
Cognitive functioning wk 24 chge (n=149,176)	-6.053 (-8.87 to -3.24)	-3.542 (-6.22 to -0.865)		
Cognitive functioning wk 48 chge (n=38,26)	-5.568 (-9.79 to -1.34)	-4.042 (-8.99 to 0.902)		
Social functioning wk 12 chge (n=216,240)	-8.502 (-11.6 to -5.44)	-3.991 (-6.97 to 1.02)		
Social functioning wk 24 chge (n=148,171)	-8.925 (-12.4 to -5.42)	-6.338 (-9.66 to -3.02)		
Social functioning wk 48 chge (n=37,26)	-6.104 (-11 to -1.22)	4.617 (-0.93 to 10.16)		
Fatigue wk 12 chge (n=217,241)	15.122 (12.27 to 17.98)	7.939 (5.174 to 10.7)		
Fatigue wk 24 chge (n=151,176)	12.677 (9.419 to 15.94)	9.203 (6.136 to 12.27)		
Fatigue wk 48 chge(n=38,26)	4.646 (0.086 to 9.206)	-2.625 (-7.88 to 2.628)		
Dyspnea wk 12 chge (n=217,240)	13.964 (10.6 to 17.33)	6.266 (3.012 to 9.521)		
Dyspnea wk 24 chge (n=151,177)	7.939 (4.639 to 11.24)	5.308 (2.221 to 8.394)		
Dyspnea wk 48 chge (n=38,26)	4.118 (-1.58 to 9.813)	2.82 (-3.88 to 9.523)		
Insomnia wk 12 chge (n=216,239)	6.283 (2.851 to 9.715)	7.625 (4.331 to 10.92)		
Insomnia wk 24 chge (n=149,176)	10.023 (6.038 to 14.01)	6.104 (2.381 to 9.827)		
Insomnia wk 48 chge (n=38,26)	-2.464 (-8.74 to 3.811)	-3.442 (-10.9 to 4.017)		
Appetite loss wk 12 chge (n=217,239)	15.167 (11.6 to 18.74)	5.383 (1.925 to 8.841)		
Appetite loss wk 24 chge (n=151,176)	16.574 (12.39 to 20.76)	5.861 (1.918 to 9.804)		

Appetite loss wk 48 chge (n=38,26)	3.999 (-2.08 to 10.07)	-2.963 (-9.99 to 4.061)		
Constipation wk 12 chge (n=215,240)	4.135 (0.667 to 7.603)	6.42 (3.104 to 9.735)		
Constipation wk 24 chge (n=151,177)	-0.153 (-3.64 to 3.337)	0.524 (-2.73 to 5.782)		
Constipation wk 48 chge (n=38,25)	-0.358 (-5.57 to 4.851)	-0.946 (-7.26 to 5.373)		
Diarrhea wk 12 chge (n=217,241)	18.888 (15.04 to 22.74)	10.206 (6.452 to 13.96)		
Diarrhea wk 24 chge (n=150,177)	23.163 (18.46 to 27.87)	16.406 (11.98 to 20.83)		
Diarrhea wk 48 chge (n=38,26)	20.48 (14.02 to 26.94)	10.996 (3.422 to 18.57)		

Statistical analyses

No statistical analyses for this end point

Secondary: Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-NTX) Change from Baseline by treatment group

End point title	Functional Assessment of Cancer Therapy/Gynecologic Oncology Group- Neurotoxicity (FACT/GOG-NTX) Change from Baseline by treatment group

End point description:

The FACT/GOG-NTX was developed from the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System and focuses on four general quality of life domains for physical well being, functional wellbeing,
social/family well-being, and emotional well-being, and includes additional items to characterize treatment-related neurotoxicity. Higher subscales/total scores represent higher QOL. In the case of the neurotoxicity subscale, lower scores correspond to higher neurotoxicity. The recall period referenced in the
questionnaire is the past 7 days.Ranges for FACT-G subscales are as follows:.PWB, SWB and FWB scale 0
-28, EWB scale 0-24, NtxS scale 0-44, FACT/GOG-Ntx trial outcome index scale is 0-100 and FACT-G scale is
also scaled 0-100. An increase from baseline in these scores indicate improvement.

End point type	Secondary

End point timeframe:

12, 24 and 48 weeks

End point values	Panobinostat + Bortezomib + Dexamethasone	Placebo + Bortezomib + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	387	381		
Units: score on a scale				
least squares mean (confidence interval 95%)				
Neurotoxicity wk 12 change baseline (n=212,240)	-4.481 (-5.33 to -3.63)	-3.337 (-4.17 to -2.5)		

Neurotoxicity wk 24 change baseline (n=148,174)	-4.564 (-5.49 to -3.64)	-4.739 (-5.61 to -3.86)		
Neurotoxicity wk 48 change baseline (n=35,26)	-3.158 (-4.52 to -1.79)	-2.133 (-3.64 to -0.627)		
Physical wellbeing wk 12 chge (n=215,240)	-3.29 (-3.94 to -2.64)	-1.952 (-2.58 to -1.32)		
Physical wellbeingwk 24 chge (n=150,176)	-3.044 (-3.74 to -2.35)	-2.259 (-2.92 to -1.6)		
Physical wellbeing wk 48 chge (n=38,26)	-2.037 (-3.08 to -0.992)	0.203 (-1.03 to 1.439)		
Trial Outcomes wk 12 chge (n=209,236)	-10.573 (-12.2 to -8.86)	-6.874 (-8.55 to -5.19)		
Trial Outcomes wk 24 chge (n=148,173)	-9.84 (-11.7 to -7.98)	-8.894 (-10.7 to -7.13)		
Trial Outcomes wk 48 chge (n=35,26)	-6.633 (-9.28 to -3.98)	-2.821 (-5.76 to 0.122)		
FACT-G Total wk 12 chge (n=213,240)	-6.658 (-8.23 to -5.09)	-4.106 (-5.64 to -2.57)		
FACT-G Totalwk 24 chge (n=147,175)	-6.076 (-7.84 to -4.31)	-4.609 (-6.3 to -2.92)		
FACT-G Total wk 48 chge (n=37,26)	-2.704 (-5.29 to -0.118)	-1.435 (-4.42 to 1.547)		
FACT/GOGNTX Total wk 12 chge (n=206,230)	-11.176 (-13.3 to -9.03)	-7.524 (-9.64 to -5.41)		
FACT/GOGNTX Total wk 24 chge (n=146,172)	-10.581 (-12.9 to -8.23)	-9.179 (-9.64 to -5.41)		
FACT/GOGNTX Total wk 48 chge (n=35,26)	-5.871 (-9.24 to -2.5)	-3.151 (-6.92 to 0.614)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	PAN+BTZ+Dex

Reporting group description:

PAN+BTZ+Dex

Reporting group title	PBO+BTZ+Dex

Reporting group description:

PBO+BTZ+Dex

Serious adverse events	PAN+BTZ+Dex	PBO+BTZ+Dex	
Total subjects affected by serious adverse events			
subjects affected / exposed	228 / 381 (59.84%)	157 / 377 (41.64%)	
number of deaths (all causes)	30	18	
number of deaths resulting from adverse events	7	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			

subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			
subjects affected / exposed	0 / 381 (0.00%)	2 / 377 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	2 / 381 (0.52%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	2 / 381 (0.52%)	3 / 377 (0.80%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	5 / 381 (1.31%)	2 / 377 (0.53%)	
occurrences causally related to treatment / all	3 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			

subjects affected / exposed	3 / 381 (0.79%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	9 / 381 (2.36%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	7 / 9	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	1 / 381 (0.26%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	15 / 381 (3.94%)	6 / 377 (1.59%)	
occurrences causally related to treatment / all	6 / 18	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	1 / 381 (0.26%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			

subjects affected / exposed	11 / 381 (2.89%)	2 / 377 (0.53%)	
occurrences causally related to treatment / all	10 / 12	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 381 (0.52%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothermia			
subjects affected / exposed	0 / 381 (0.00%)	2 / 377 (0.53%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 381 (0.26%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 381 (0.26%)	3 / 377 (0.80%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	16 / 381 (4.20%)	11 / 377 (2.92%)	
occurrences causally related to treatment / all	5 / 17	4 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			

subjects affected / exposed	1 / 381 (0.26%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 381 (0.00%)	2 / 377 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	3 / 381 (0.79%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Aspiration			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			

subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	4 / 381 (1.05%)	7 / 377 (1.86%)	
occurrences causally related to treatment / all	1 / 4	4 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	2 / 381 (0.52%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoventilation			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthopnoea			
subjects affected / exposed	1 / 381 (0.26%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			

subjects affected / exposed	4 / 381 (1.05%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 381 (0.26%)	3 / 377 (0.80%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	5 / 381 (1.31%)	4 / 377 (1.06%)	
occurrences causally related to treatment / all	2 / 5	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 381 (0.26%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

subjects affected / exposed	5 / 381 (1.31%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 5	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Tachypnoea			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 381 (0.26%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomania			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 381 (0.26%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase			

increased			
subjects affected / exposed	1 / 381 (0.26%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 381 (0.26%)	2 / 377 (0.53%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood potassium decreased			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure decreased			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	2 / 381 (0.52%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 381 (0.00%)	2 / 377 (0.53%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			

subjects affected / exposed	4 / 381 (1.05%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	3 / 381 (0.79%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	2 / 381 (0.52%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 381 (0.26%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			

subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional overdose			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Laceration			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion reaction			

subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	2 / 381 (0.52%)	2 / 377 (0.53%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	4 / 381 (1.05%)	2 / 377 (0.53%)	
occurrences causally related to treatment / all	2 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	2 / 381 (0.52%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 381 (0.52%)	2 / 377 (0.53%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	1 / 2	0 / 1	
Cardiac failure			

subjects affected / exposed	1 / 381 (0.26%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiopulmonary failure			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Left ventricular dysfunction			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 381 (0.52%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	2 / 381 (0.52%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pericardial effusion			

subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	2 / 381 (0.52%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autonomic neuropathy			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain compression			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain injury			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Brain oedema			

subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system haemorrhage			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system necrosis			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 381 (0.26%)	2 / 377 (0.53%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 1	1 / 1	
Cerebrovascular accident			
subjects affected / exposed	3 / 381 (0.79%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coma			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cranial nerve paralysis			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			

subjects affected / exposed	5 / 381 (1.31%)	2 / 377 (0.53%)	
occurrences causally related to treatment / all	2 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 381 (0.26%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperreflexia			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar infarction			
subjects affected / exposed	1 / 381 (0.26%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	5 / 381 (1.31%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	3 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	1 / 381 (0.26%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			

subjects affected / exposed	3 / 381 (0.79%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post herpetic neuralgia			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sensory loss			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			

subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Speech disorder			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	5 / 381 (1.31%)	2 / 377 (0.53%)	
occurrences causally related to treatment / all	3 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIIth nerve paralysis			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	14 / 381 (3.67%)	3 / 377 (0.80%)	
occurrences causally related to treatment / all	10 / 15	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 381 (0.79%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	3 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperviscosity syndrome			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			

subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	2 / 381 (0.52%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monocytosis			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 381 (0.52%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 381 (0.26%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	28 / 381 (7.35%)	8 / 377 (2.12%)	
occurrences causally related to treatment / all	28 / 35	6 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exophthalmos			

subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic ischaemic neuropathy			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	3 / 381 (0.79%)	3 / 377 (0.80%)	
occurrences causally related to treatment / all	4 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	3 / 381 (0.79%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	3 / 381 (0.79%)	3 / 377 (0.80%)	
occurrences causally related to treatment / all	2 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	43 / 381 (11.29%)	9 / 377 (2.39%)	
occurrences causally related to treatment / all	35 / 54	7 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	2 / 381 (0.52%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	2 / 381 (0.52%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 381 (0.52%)	3 / 377 (0.80%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			

subjects affected / exposed	2 / 381 (0.52%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	5 / 381 (1.31%)	3 / 377 (0.80%)	
occurrences causally related to treatment / all	4 / 5	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	2 / 381 (0.52%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	7 / 381 (1.84%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	6 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising oesophagitis			

subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	2 / 381 (0.52%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal necrosis			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 381 (0.26%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 381 (0.52%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	12 / 381 (3.15%)	3 / 377 (0.80%)	
occurrences causally related to treatment / all	11 / 12	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary dyskinesia			

subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 381 (0.26%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatomegaly			
subjects affected / exposed	1 / 381 (0.26%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Acute febrile neutrophilic dermatosis			
subjects affected / exposed	1 / 381 (0.26%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis allergic			

subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	2 / 381 (0.52%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling face			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	7 / 381 (1.84%)	9 / 377 (2.39%)	
occurrences causally related to treatment / all	0 / 7	0 / 9	
deaths causally related to treatment / all	0 / 2	0 / 0	
Anuria			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Azotaemia			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oliguria			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	4 / 381 (1.05%)	5 / 377 (1.33%)	
occurrences causally related to treatment / all	3 / 4	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			

subjects affected / exposed	1 / 381 (0.26%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 381 (0.52%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	3 / 381 (0.79%)	2 / 377 (0.53%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 381 (0.26%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint swelling			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			

subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 381 (0.26%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	2 / 381 (0.52%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myopathy			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 381 (0.26%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			

subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergillus infection			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteriuria			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	3 / 381 (0.79%)	2 / 377 (0.53%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 381 (0.26%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			

subjects affected / exposed	2 / 381 (0.52%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	2 / 381 (0.52%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus colitis			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated tuberculosis			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis infectious			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			

subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	6 / 381 (1.57%)	2 / 377 (0.53%)	
occurrences causally related to treatment / all	2 / 6	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed	2 / 381 (0.52%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilus sepsis			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	3 / 381 (0.79%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	4 / 381 (1.05%)	5 / 377 (1.33%)	
occurrences causally related to treatment / all	1 / 4	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			

subjects affected / exposed	5 / 381 (1.31%)	2 / 377 (0.53%)	
occurrences causally related to treatment / all	4 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 381 (0.26%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	3 / 381 (0.79%)	3 / 377 (0.80%)	
occurrences causally related to treatment / all	2 / 5	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	3 / 381 (0.79%)	2 / 377 (0.53%)	
occurrences causally related to treatment / all	1 / 3	2 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nasopharyngitis			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	0 / 381 (0.00%)	2 / 377 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neutropenic sepsis			
subjects affected / exposed	2 / 381 (0.52%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oral candidiasis			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			

subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periodontitis			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	2 / 381 (0.52%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal sepsis			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	56 / 381 (14.70%)	40 / 377 (10.61%)	
occurrences causally related to treatment / all	35 / 66	16 / 47	
deaths causally related to treatment / all	2 / 2	1 / 3	
Pneumonia bacterial			
subjects affected / exposed	0 / 381 (0.00%)	2 / 377 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	2 / 381 (0.52%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia haemophilus			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			

subjects affected / exposed	2 / 381 (0.52%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal bacteraemia			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 381 (0.26%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Respiratory tract infection			
subjects affected / exposed	4 / 381 (1.05%)	2 / 377 (0.53%)	
occurrences causally related to treatment / all	2 / 4	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	9 / 381 (2.36%)	7 / 377 (1.86%)	
occurrences causally related to treatment / all	3 / 9	1 / 7	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			

subjects affected / exposed	9 / 381 (2.36%)	2 / 377 (0.53%)	
occurrences causally related to treatment / all	1 / 9	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 381 (0.26%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	3 / 381 (0.79%)	3 / 377 (0.80%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	8 / 381 (2.10%)	4 / 377 (1.06%)	
occurrences causally related to treatment / all	2 / 11	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Varicella			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral haemorrhagic cystitis			

subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	4 / 381 (1.05%)	2 / 377 (0.53%)	
occurrences causally related to treatment / all	3 / 5	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	11 / 381 (2.89%)	5 / 377 (1.33%)	
occurrences causally related to treatment / all	4 / 12	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			

subjects affected / exposed	1 / 381 (0.26%)	3 / 377 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	2 / 381 (0.52%)	3 / 377 (0.80%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypochloraemia			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 381 (0.26%)	2 / 377 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	8 / 381 (2.10%)	4 / 377 (1.06%)	
occurrences causally related to treatment / all	7 / 11	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	4 / 381 (1.05%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	3 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	2 / 381 (0.52%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			

subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	0 / 381 (0.00%)	1 / 377 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	1 / 381 (0.26%)	0 / 377 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	PAN+BTZ+Dex	PBO+BTZ+Dex	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	379 / 381 (99.48%)	366 / 377 (97.08%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	28 / 381 (7.35%)	23 / 377 (6.10%)	
occurrences (all)	33	36	
Hypotension			
subjects affected / exposed	49 / 381 (12.86%)	34 / 377 (9.02%)	
occurrences (all)	62	38	
Orthostatic hypotension			
subjects affected / exposed	22 / 381 (5.77%)	11 / 377 (2.92%)	
occurrences (all)	28	15	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	77 / 381 (20.21%)	51 / 377 (13.53%)	
occurrences (all)	132	70	
Fatigue			
subjects affected / exposed	155 / 381 (40.68%)	109 / 377 (28.91%)	
occurrences (all)	217	161	
Oedema peripheral			

subjects affected / exposed	104 / 381 (27.30%)	69 / 377 (18.30%)	
occurrences (all)	147	88	
Pyrexia			
subjects affected / exposed	90 / 381 (23.62%)	48 / 377 (12.73%)	
occurrences (all)	137	60	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	81 / 381 (21.26%)	70 / 377 (18.57%)	
occurrences (all)	110	96	
Dyspnoea			
subjects affected / exposed	53 / 381 (13.91%)	40 / 377 (10.61%)	
occurrences (all)	59	51	
Productive cough			
subjects affected / exposed	18 / 381 (4.72%)	19 / 377 (5.04%)	
occurrences (all)	25	27	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	73 / 381 (19.16%)	61 / 377 (16.18%)	
occurrences (all)	89	64	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	22 / 381 (5.77%)	19 / 377 (5.04%)	
occurrences (all)	30	36	
Blood creatinine increased			
subjects affected / exposed	37 / 381 (9.71%)	21 / 377 (5.57%)	
occurrences (all)	71	29	
Blood urea increased			
subjects affected / exposed	20 / 381 (5.25%)	10 / 377 (2.65%)	
occurrences (all)	46	21	
Platelet count decreased			
subjects affected / exposed	44 / 381 (11.55%)	17 / 377 (4.51%)	
occurrences (all)	82	31	
Weight decreased			
subjects affected / exposed	44 / 381 (11.55%)	17 / 377 (4.51%)	
occurrences (all)	49	17	
Nervous system disorders			

Dizziness			
subjects affected / exposed	66 / 381 (17.32%)	61 / 377 (16.18%)	
occurrences (all)	84	95	
Dysgeusia			
subjects affected / exposed	36 / 381 (9.45%)	26 / 377 (6.90%)	
occurrences (all)	39	27	
Headache			
subjects affected / exposed	51 / 381 (13.39%)	40 / 377 (10.61%)	
occurrences (all)	67	65	
Hypoaesthesia			
subjects affected / exposed	29 / 381 (7.61%)	34 / 377 (9.02%)	
occurrences (all)	33	39	
Neuralgia			
subjects affected / exposed	38 / 381 (9.97%)	44 / 377 (11.67%)	
occurrences (all)	51	57	
Neuropathy peripheral			
subjects affected / exposed	117 / 381 (30.71%)	133 / 377 (35.28%)	
occurrences (all)	145	178	
Paraesthesia			
subjects affected / exposed	24 / 381 (6.30%)	27 / 377 (7.16%)	
occurrences (all)	29	37	
Peripheral sensory neuropathy			
subjects affected / exposed	42 / 381 (11.02%)	46 / 377 (12.20%)	
occurrences (all)	49	64	
Polyneuropathy			
subjects affected / exposed	28 / 381 (7.35%)	28 / 377 (7.43%)	
occurrences (all)	35	36	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	155 / 381 (40.68%)	125 / 377 (33.16%)	
occurrences (all)	305	231	
Leukopenia			
subjects affected / exposed	61 / 381 (16.01%)	31 / 377 (8.22%)	
occurrences (all)	173	77	
Lymphopenia			

subjects affected / exposed	52 / 381 (13.65%)	35 / 377 (9.28%)	
occurrences (all)	149	113	
Neutropenia			
subjects affected / exposed	112 / 381 (29.40%)	40 / 377 (10.61%)	
occurrences (all)	296	102	
Thrombocytopenia			
subjects affected / exposed	238 / 381 (62.47%)	150 / 377 (39.79%)	
occurrences (all)	697	342	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	28 / 381 (7.35%)	31 / 377 (8.22%)	
occurrences (all)	32	36	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	30 / 381 (7.87%)	26 / 377 (6.90%)	
occurrences (all)	32	31	
Abdominal pain			
subjects affected / exposed	50 / 381 (13.12%)	38 / 377 (10.08%)	
occurrences (all)	76	44	
Abdominal pain upper			
subjects affected / exposed	43 / 381 (11.29%)	36 / 377 (9.55%)	
occurrences (all)	54	51	
Constipation			
subjects affected / exposed	102 / 381 (26.77%)	122 / 377 (32.36%)	
occurrences (all)	135	159	
Diarrhoea			
subjects affected / exposed	254 / 381 (66.67%)	157 / 377 (41.64%)	
occurrences (all)	655	342	
Dyspepsia			
subjects affected / exposed	47 / 381 (12.34%)	43 / 377 (11.41%)	
occurrences (all)	52	54	
Nausea			
subjects affected / exposed	138 / 381 (36.22%)	78 / 377 (20.69%)	
occurrences (all)	212	118	
Vomiting			

subjects affected / exposed	91 / 381 (23.88%)	47 / 377 (12.47%)	
occurrences (all)	141	54	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	33 / 381 (8.66%)	23 / 377 (6.10%)	
occurrences (all)	40	32	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	25 / 381 (6.56%)	26 / 377 (6.90%)	
occurrences (all)	28	35	
Back pain			
subjects affected / exposed	45 / 381 (11.81%)	46 / 377 (12.20%)	
occurrences (all)	51	51	
Bone pain			
subjects affected / exposed	21 / 381 (5.51%)	31 / 377 (8.22%)	
occurrences (all)	24	37	
Muscle spasms			
subjects affected / exposed	23 / 381 (6.04%)	21 / 377 (5.57%)	
occurrences (all)	29	25	
Muscular weakness			
subjects affected / exposed	24 / 381 (6.30%)	20 / 377 (5.31%)	
occurrences (all)	26	21	
Myalgia			
subjects affected / exposed	24 / 381 (6.30%)	24 / 377 (6.37%)	
occurrences (all)	32	30	
Pain in extremity			
subjects affected / exposed	40 / 381 (10.50%)	54 / 377 (14.32%)	
occurrences (all)	47	61	
Infections and infestations			
Bronchitis			
subjects affected / exposed	20 / 381 (5.25%)	25 / 377 (6.63%)	
occurrences (all)	23	28	
Herpes zoster			
subjects affected / exposed	15 / 381 (3.94%)	36 / 377 (9.55%)	
occurrences (all)	16	42	
Nasopharyngitis			

subjects affected / exposed	49 / 381 (12.86%)	43 / 377 (11.41%)	
occurrences (all)	59	60	
Respiratory tract infection			
subjects affected / exposed	17 / 381 (4.46%)	20 / 377 (5.31%)	
occurrences (all)	27	39	
Upper respiratory tract infection			
subjects affected / exposed	66 / 381 (17.32%)	54 / 377 (14.32%)	
occurrences (all)	104	84	
Urinary tract infection			
subjects affected / exposed	23 / 381 (6.04%)	15 / 377 (3.98%)	
occurrences (all)	30	19	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	106 / 381 (27.82%)	46 / 377 (12.20%)	
occurrences (all)	152	58	
Hyperglycaemia			
subjects affected / exposed	30 / 381 (7.87%)	25 / 377 (6.63%)	
occurrences (all)	53	46	
Hypoalbuminaemia			
subjects affected / exposed	21 / 381 (5.51%)	8 / 377 (2.12%)	
occurrences (all)	32	8	
Hypocalcaemia			
subjects affected / exposed	35 / 381 (9.19%)	32 / 377 (8.49%)	
occurrences (all)	60	46	
Hypokalaemia			
subjects affected / exposed	100 / 381 (26.25%)	53 / 377 (14.06%)	
occurrences (all)	197	91	
Hyponatraemia			
subjects affected / exposed	48 / 381 (12.60%)	18 / 377 (4.77%)	
occurrences (all)	77	29	
Hypophosphataemia			
subjects affected / exposed	42 / 381 (11.02%)	32 / 377 (8.49%)	
occurrences (all)	91	98	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 June 2010	This amendment was a local, country-specific amendment for Japan whose main purpose was to include hospitalization of Japanese patients during the first cycle of treatment in order to comply with the local bortezomib label. Secondly, this amendment included PK sampling on Cycle 1 Day 1 and Cycle 1 Day 8 in Japanese patients. Thirdly, this amendment added the commercially available dosage form of bortezomib available in Japan as part of the global protocol. As of the release date of this amendment, 34 patients had been randomized worldwide
22 December 2011	As of 17-Nov-2011, 668 patients had been randomized worldwide. This amendment was a global amendment to adjust the sample size to compensate for a higher than expected drop-out rate in the absence of any safety concerns. The study design was based on the best available information from the literature, other ongoing panobinostat trials, historical data and expert opinion. A review of blinded data concluded that the drop-out rate was higher than originally assumed. The main reason for the drop-out rate was that patients who discontinued treatment withdrew their consent to be followed for response assessment as per protocol. As a consequence, the expected drop-out rate as written in the statistical section of the original protocol needed to be updated. The sample size was therefore recalculated in order to attain the targeted number of PFS events while maintaining the original statistical assumptions. In addition to the increased sample size, an operational action plan for new and ongoing patients was put into place to follow patients for disease assessment after treatment discontinuation
07 March 2012	This amendment is a global amendment to enhance robustness of analysis at the second interim analysis (IA2), in order to provide a more precise estimate of the treatment effect and to increase probability of detecting a treatment effect at IA2. Consequently, this amendment increases the event (PFS) fraction for IA2 from 67% to 80% (306 to 368 events). In case the study is stopped at IA2 with higher fraction of the planned PFS events, the risk of an overestimation of the treatment effect would be reduced. As outlined in the statistical design, the group-sequential plan of the original CLBH589D2308 protocol stipulated two interim analyses corresponding to the time point when 33% (IA1:153 PFS events) and 67% (IA2:306 PFS events) of the total planned 460 PFS events have occurred. These time points were expected 13 months after start of randomization for IA1, 20 months for IA2, and 29 months for the final PFS analysis, respectively under the assumption of 30 patients / month accrual and 10% dropout rate. In this amendment the assumptions on the treatment effect (HR 0.74) are unchanged. The power to detect the treatment effect and to stop the study at IA2 for efficacy is increased from 53% to 71%. The cumulative type I error is unchanged (less than 5 %, two-sided).
02 October 2012	The main aim of this global amendment is to clarify that the collection of serum calcium variables (ionized serum calcium and/or total serum calcium and serum albumin for the derivation of albumin-adjusted serum calcium) should continue after the end of treatment until the end of follow-up for disease evaluations. The collection of these variables is already described in the Novartis Guidelines for response assessment in Multiple Myeloma (Post-text supplement 2), and is mandatory to identify hypercalcemia as part of progressive disease and relapse criteria, during treatment phase and for all patients who have entered or will enter post-treatment disease evaluations.

06 May 2013	For efficacy assessments, the study protocol requires measurement of the monoclonal protein (M-protein) spike by protein electrophoresis (PEP) in serum and urine as per modified EBMT criteria. Sites participating in the study used their local laboratories to perform the M-protein assessments. However, it was recently identified, that some study patients were monitored using either PEP without specific measurement of the M-protein spike (e.g. globulin gamma fraction was used as indicator for M-component IgG) or by alternative methods, other than PEP (e.g. nephelometric quantification of immunoglobulin levels). Although these methods are used in routine clinical practice, they are not a part of mEBMT criteria. The objective of this protocol amendment is: a. to document use of PEP results without specific measurement of the M-protein spike. b. to document use of measurement methods other than PEP (e.g. nephelometry) Regardless of the method used before this amendment, patients should continue to be followed with the same method throughout the study to ensure intra-patient consistency. The primary PFS analysis remains based on the Investigator's response assessment following the ITT principle. The newly collected data will be used in sensitivity analyses of PFS and other efficacy related endpoints, including an analysis using independent response assessment in patients for whom M-protein was not measured by electrophoresis or electrophoresis was used without measurement of M-protein spike. This specific assessment will be done by an Independent Review Committee (IRC). Detailed instructions on the independent review process will be included in the IRC Charter. Additional sensitivity analyses will be presented in detail in the Report Analysis Plan.
21 August 2014	Based on the trial's positive outcome for the final analysis of the primary endpoint PFS, Novartis has submitted the study results to several health authorities seeking regulatory approval of panobinostat in multiple myeloma. Overall survival (OS) is a key secondary endpoint in this study. The final analysis of OS is planned to be performed when approximately 415 survival events have been documented. The main purpose of this amendment is to introduce an additional (fourth) OS interim analysis when approximately 90% of the targeted number of OS events have been reached, in order to support the benefit/risk assessment of the studied investigational treatment prior to the final OS analysis, as agreed with the FDA. The OS alpha spending function for the additional IA and the final analysis will be adjusted to ensure control of the overall type I error.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported