Clinical trial results:
An International, Multicenter, Randomized, Double-Blind Study of Vorinostat (MK-0683) or Placebo in Combination with Bortezomib in Patients with Multiple Myeloma

Summary

EudraCT number	2008-003752-30
Trial protocol	ES DE BE FR AT CZ PT HU IT BG GB GR
Global end of trial date	30 June 2015

Results information

Result version number	v1 (current)
This version publication date	24 June 2016
First version publication date	24 June 2016

Trial information

Trial identification

Sponsor protocol code	0683-088

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00773747
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Registration Number: MK-0683-088

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 September 2011
Global end of trial reached?	Yes
Global end of trial date	30 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a multi-site, randomized, double-blind study to determine the safety and efficacy of vorinostat (MK-0683/Zolinza®) and bortezomib compared with placebo and bortezomib in participants with relapsed or refractory multiple myeloma. The primary measurement of efficacy was the duration of progression-free survival.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. Study-specific patient protections include implementation of a stopping rule for futility, stopping rule for overwhelming efficacy, and dose modification based on worst severity toxicities experienced by participants.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 29
Country: Number of subjects enrolled	Australia: 38
Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Brazil: 29
Country: Number of subjects enrolled	Bulgaria: 35
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	China: 81
Country: Number of subjects enrolled	Croatia: 13
Country: Number of subjects enrolled	Czech Republic: 33
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Greece: 23
Country: Number of subjects enrolled	Hong Kong: 6
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	India: 48

Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Korea, Republic of: 38
Country: Number of subjects enrolled	Malaysia: 8
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	New Zealand: 35
Country: Number of subjects enrolled	Philippines: 28
Country: Number of subjects enrolled	Poland: 12
Country: Number of subjects enrolled	Portugal: 7
Country: Number of subjects enrolled	Romania: 10
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	South Africa: 19
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	Taiwan: 11
Country: Number of subjects enrolled	Thailand: 14
Country: Number of subjects enrolled	United Kingdom: 11
Worldwide total number of subjects	637
EEA total number of subjects	224

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)	381
From 65 to 84 years	253
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

This study enrolled participants with an established diagnosis of multiple myeloma based on standard criteria that have received at least 1 but not more than 3 prior anti-myeloma regimens and have demonstrated progressive disease after the most recent treatment regimen. Additional inclusion and exclusion criteria applied.

Pre-assignment

Screening details:

637 participants were randomized to treatment and 635 participants received at least 1 dose of MK-0683 or placebo: 315 participants were treated with vorinostat + bortezomib and 320 participants were treated with placebo + bortezomib.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Vorinostat + Bortezomib

Arm description:

Participants will receive vorinostat four 100 mg capsules (400 mg total) orally 0-30 minutes after a meal on Days 1 through 14 of a 21-day treatment cycle and bortezomib 1.3 mg/m^2 by intravenous injection on Days 1, 4, 8, and 11 of a 21-day treatment cycle.

Arm type	Experimental
Investigational medicinal product name	Vorinostat 400 mg
Investigational medicinal product code	
Other name	ZOLINZA®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Vorinostat 400 mg orally 0-30 minutes after a meal on Days 1 through 14 of a 21-day treatment cycle

Investigational medicinal product name	Bortezomib 1.3 mg/m^2
Investigational medicinal product code	
Other name	VELCADE®
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Bortezomib 1.3 mg/m^2 by intravenous injection on Days 1, 4, 8, and 11 0f a 21-day treatment cycle

Arm title	Placebo + Bortezomib

Arm description:

Participants will receive four placebo capsules orally 0-30 minutes after a meal on Days 1 through 14 of a 21-day treatment cycle and bortezomib 1.3 mg/m^2 by intravenous injection on Days 1, 4, 8, and 11 0f a 21-day treatment cycle.

Arm type	Placebo

Investigational medicinal product name	Bortezomib 1.3 mg/m^2
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Bortezomib 1.3 mg/m^2 by intravenous injection on Days 1, 4, 8, and 11 0f a 21-day treatment cycle

Investigational medicinal product name	Matching Placebo for Vorinostat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo capsules orally 0-30 minutes after a meal on Days 1 through 14 of a 21-day treatment cycle

Number of subjects in period 1	Vorinostat + Bortezomib	Placebo + Bortezomib
Started	317	320
Completed	22	24
Not completed	295	296
Adverse event, serious fatal	5	8
Physician decision	26	18
Consent withdrawn by subject	89	61
Adverse event, non-fatal	61	62
Lost to follow-up	-	1
Lack of efficacy	112	144
Protocol deviation	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Vorinostat + Bortezomib
Reporting group description:	
Participants will receive vorinostat four 100 mg capsules (400 mg total) orally 0-30 minutes after a meal on Days 1 through 14 of a 21-day treatment cycle and bortezomib 1.3 mg/m^2 by intravenous injection on Days 1, 4, 8, and 11 of a 21-day treatment cycle.	
Reporting group title	Placebo + Bortezomib
Reporting group description:	
Participants will receive four placebo capsules orally 0-30 minutes after a meal on Days 1 through 14 of a 21-day treatment cycle and bortezomib 1.3 mg/m^2 by intravenous injection on Days 1, 4, 8, and 11 0f a 21-day treatment cycle.	

Reporting group values	Vorinostat + Bortezomib	Placebo + Bortezomib	Total
Number of subjects	317	320	637
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)	200	181	381
From 65-84 years	116	137	253
85 years and over	1	2	3
Age Continuous Units: years			
arithmetic mean	60.9	62.7	
standard deviation	± 10	± 10	-
Gender Categorical Units: Subjects			
Female	126	134	260
Male	191	186	377

End points

End points reporting groups

Reporting group title	Vorinostat + Bortezomib
Reporting group description:	
Participants will receive vorinostat four 100 mg capsules (400 mg total) orally 0-30 minutes after a meal on Days 1 through 14 of a 21-day treatment cycle and bortezomib 1.3 mg/m^2 by intravenous injection on Days 1, 4, 8, and 11 of a 21-day treatment cycle.	
Reporting group title	Placebo + Bortezomib
Reporting group description:	
Participants will receive four placebo capsules orally 0-30 minutes after a meal on Days 1 through 14 of a 21-day treatment cycle and bortezomib 1.3 mg/m^2 by intravenous injection on Days 1, 4, 8, and 11 0f a 21-day treatment cycle.	

Primary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)
End point description:	
Progression-free survival was measured from the start of the treatment to the time when the criteria for progression was met or death due to any cause (whichever is first recorded). Response to study therapy was assessed using European Blood and Marrow Transplantation Group (EBMT) Criteria. A stratified Cox proportional hazards model was used with Efron's likelihood approximation to account for ties in event times.	
End point type	Primary
End point timeframe:	
From randomization to event of disease progression or death assessed up to 32 months (final study analysis)	

End point values	Vorinostat + Bortezomib	Placebo + Bortezomib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	317[1]	320[2]		
Units: Months				
median (confidence interval 95%)	7.63 (6.87 to 8.4)	6.83 (5.67 to 7.73)		

Notes:

[1] - Intention to treat (ITT) population including all randomized participants.

[2] - ITT population including all randomized participants.

Statistical analyses

Statistical analysis title	Ratio of Hazard Rates Assessed up to 32 Months
Comparison groups	Vorinostat + Bortezomib v Placebo + Bortezomib
Number of subjects included in analysis	637
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.774

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.636
upper limit	0.941

Secondary: Number of Participants with Clinical and Laboratory Adverse Events (AEs)

End point title	Number of Participants with Clinical and Laboratory Adverse Events (AEs)

End point description:

An adverse event (AE) was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product/protocol-specified procedure, whether or not considered related to the medicinal product/protocol-specified procedure. Any worsening of a preexisting condition temporally associated with the use of the product was also an AE.

End point type	Secondary

End point timeframe:

From first dose up to 30 days after the last dose of study drug

End point values	Vorinostat + Bortezomib	Placebo + Bortezomib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	315[3]	320[4]		
Units: Participants	312	315		

Notes:

[3] - All Patients as Treated population: all randomized participants who received ≥1 dose of study drug

[4] - All Patients as Treated population: all randomized participants who received ≥1 dose of study drug

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival was measured from the start of the treatment to death due to any cause. Overall Survival is represented as the number of deaths per 100-person- months and was computed by dividing the number of participants with an event of death that occurred during the study follow-up period by the total duration of follow-up (in 100 months) for all the participants in each cohort since participants had different lengths of follow-up.

End point type	Secondary

End point timeframe:

From randomization up to 32 months (final study analysis)

End point values	Vorinostat + Bortezomib	Placebo + Bortezomib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	317[5]	320[6]		
Units: Events/100-person Months				
number (confidence interval 95%)	1.7 (1.56 to 1.84)	1.9 (1.75 to 2.05)		

Notes:

[5] - ITT population including all randomized participants.

[6] - ITT population including all randomized participants.

Statistical analyses

Statistical analysis title	Ratio of Hazard Rates Assessed up to 32 Months
Comparison groups	Vorinostat + Bortezomib v Placebo + Bortezomib
Number of subjects included in analysis	637
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Cox proportional hazard
Point estimate	0.858
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.622
upper limit	1.184

Secondary: Time to Progression

End point title	Time to Progression

End point description:

Time to progression was measured from the start of the treatment to the time when the criteria for progression was met or death due to myeloma (whichever is first recorded). Response to study therapy was assessed using European Blood and Marrow Transplantation Group (EBMT) Criteria. A stratified Cox proportional hazards model was used with Efron’s likelihood approximation to account for ties in event times.

End point type	Secondary

End point timeframe:

Baseline and at the end of each 21-day Cycle assessed up to 32 months (final study analysis)

End point values	Vorinostat + Bortezomib	Placebo + Bortezomib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	317[7]	320[8]		
Units: Months				
median (confidence interval 95%)	7.73 (7 to 8.53)	7.03 (6.33 to 7.73)		

Notes:

[7] - ITT population including all randomized participants.

[8] - ITT population including all randomized participants.

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate

End point title	Objective Response Rate

End point description:

Objective response rate was measured as the proportion of patients who achieved a confirmed partial response or better during the course of the study. Response to study therapy was assessed using EBMT Criteria and confirmed by Independent Adjudication Review.

End point type	Secondary

End point timeframe:

Baseline and at the end of each 21-day Cycle assessed up to 32 months (final study analysis)

End point values	Vorinostat + Bortezomib	Placebo + Bortezomib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	315[9]	320[10]		
Units: Percentage of Participants				
number (confidence interval 95%)	56.2 (50.5 to 61.7)	40.6 (35.2 to 46.2)		

Notes:

[9] - Full Analysis Set: all randomized patient who received ≥1 dose of study treatment

[10] - Full Analysis Set: all randomized patient who received ≥1 dose of study treatment

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose up to 30 days after the last dose of study drug	
Adverse event reporting additional description:	
AEs were reported for the All Patients as Treated Population that included all randomized participants who received at least one dose of study treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups	
Reporting group title	Placebo + Bortezomib
Reporting group description:	
Participants will receive four placebo capsules orally 0-30 minutes after a meal on Days 1 through 14 of a 21-day treatment cycle and bortezomib 1.3 mg/m^2 by intravenous injection on Days 1, 4, 8, and 11 0f a 21-day treatment cycle.	
Reporting group title	Vorinostat + Bortezomib
Reporting group description:	
Participants will receive vorinostat four 100 mg capsules (400 mg total) orally 0-30 minutes after a meal on Days 1 through 14 of a 21-day treatment cycle and bortezomib 1.3 mg/m^2 by intravenous injection on Days 1, 4, 8, and 11 of a 21-day treatment cycle.	

Serious adverse events	Placebo + Bortezomib	Vorinostat + Bortezomib	
Total subjects affected by serious adverse events			
subjects affected / exposed	138 / 320 (43.13%)	130 / 315 (41.27%)	
number of deaths (all causes)	17	11	
number of deaths resulting from adverse events	2	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	2 / 320 (0.63%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			

subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neoplasm malignant			
subjects affected / exposed	13 / 320 (4.06%)	10 / 315 (3.17%)	
occurrences causally related to treatment / all	0 / 13	0 / 10	
deaths causally related to treatment / all	0 / 5	0 / 4	
Squamous cell carcinoma			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	3 / 320 (0.94%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 320 (0.63%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			

subjects affected / exposed	0 / 320 (0.00%)	4 / 315 (1.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 320 (0.31%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	2 / 320 (0.63%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	1 / 2	1 / 1	
Fatigue			
subjects affected / exposed	5 / 320 (1.56%)	3 / 315 (0.95%)	
occurrences causally related to treatment / all	6 / 6	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			

subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pelvic mass			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (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	9 / 320 (2.81%)	6 / 315 (1.90%)	
occurrences causally related to treatment / all	4 / 12	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Apnoea			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dyspnoea exertional			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	2 / 320 (0.63%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 320 (0.00%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	2 / 320 (0.63%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Anxiety disorder			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (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	27 / 320 (8.44%)	32 / 315 (10.16%)	
occurrences causally related to treatment / all	0 / 43	0 / 52	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (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	1 / 320 (0.31%)	0 / 315 (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 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (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 myocardial infarction			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 320 (0.63%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			

subjects affected / exposed	0 / 320 (0.00%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	2 / 320 (0.63%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			

subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic coma			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (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	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (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	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			

subjects affected / exposed	2 / 320 (0.63%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	4 / 320 (1.25%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 320 (0.31%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 320 (0.63%)	4 / 315 (1.27%)	
occurrences causally related to treatment / all	0 / 2	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Febrile neutropenia			
subjects affected / exposed	0 / 320 (0.00%)	4 / 315 (1.27%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolysis			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	1 / 320 (0.31%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	3 / 320 (0.94%)	9 / 315 (2.86%)	
occurrences causally related to treatment / all	1 / 3	11 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	1 / 320 (0.31%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 320 (0.63%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	10 / 320 (3.13%)	9 / 315 (2.86%)	
occurrences causally related to treatment / all	9 / 10	12 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastritis			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 320 (0.00%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	2 / 320 (0.63%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (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	3 / 320 (0.94%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Odynophagia			

subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	2 / 320 (0.63%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis intestinalis			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	7 / 320 (2.19%)	8 / 315 (2.54%)	
occurrences causally related to treatment / all	6 / 8	7 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic necrosis			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 320 (0.31%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decubitus ulcer			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			

subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	4 / 320 (1.25%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Renal failure acute			
subjects affected / exposed	2 / 320 (0.63%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 320 (0.31%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperparathyroidism primary			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (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			
Arthritis			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 320 (0.31%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bone pain			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (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 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylitis			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial cyst			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 320 (0.94%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis pneumococcal			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			

subjects affected / exposed	1 / 320 (0.31%)	4 / 315 (1.27%)	
occurrences causally related to treatment / all	0 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cellulitis			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridial infection			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 320 (0.00%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conjunctivitis bacterial			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal infection			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	0 / 320 (0.00%)	6 / 315 (1.90%)	
occurrences causally related to treatment / all	0 / 0	7 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 320 (0.00%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal viral infection			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilus infection			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			

subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	6 / 320 (1.88%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	3 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster ophthalmic			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	2 / 320 (0.63%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal sepsis			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	13 / 320 (4.06%)	14 / 315 (4.44%)	
occurrences causally related to treatment / all	4 / 13	5 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 320 (0.31%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	5 / 320 (1.56%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Septic shock			
subjects affected / exposed	3 / 320 (0.94%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	3 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	3 / 320 (0.94%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	1 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection bacterial			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	4 / 320 (1.25%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 320 (0.31%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 320 (0.31%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	5 / 320 (1.56%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	4 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	2 / 320 (0.63%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 320 (0.00%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			

subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 320 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 320 (0.31%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 320 (0.00%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic disorder			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	1 / 320 (0.31%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	1 / 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	Placebo + Bortezomib	Vorinostat + Bortezomib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	306 / 320 (95.63%)	312 / 315 (99.05%)	
Investigations			
Blood creatinine increased			
subjects affected / exposed	11 / 320 (3.44%)	17 / 315 (5.40%)	
occurrences (all)	14	26	
Weight decreased			

subjects affected / exposed	22 / 320 (6.88%)	22 / 315 (6.98%)	
occurrences (all)	30	36	
Vascular disorders			
Hypertension			
subjects affected / exposed	13 / 320 (4.06%)	29 / 315 (9.21%)	
occurrences (all)	16	37	
Hypotension			
subjects affected / exposed	12 / 320 (3.75%)	19 / 315 (6.03%)	
occurrences (all)	15	23	
Nervous system disorders			
Dizziness			
subjects affected / exposed	27 / 320 (8.44%)	36 / 315 (11.43%)	
occurrences (all)	37	56	
Dysgeusia			
subjects affected / exposed	6 / 320 (1.88%)	23 / 315 (7.30%)	
occurrences (all)	8	28	
Headache			
subjects affected / exposed	34 / 320 (10.63%)	35 / 315 (11.11%)	
occurrences (all)	45	45	
Hypoaesthesia			
subjects affected / exposed	18 / 320 (5.63%)	10 / 315 (3.17%)	
occurrences (all)	26	12	
Neuralgia			
subjects affected / exposed	86 / 320 (26.88%)	82 / 315 (26.03%)	
occurrences (all)	125	124	
Neuropathy peripheral			
subjects affected / exposed	64 / 320 (20.00%)	62 / 315 (19.68%)	
occurrences (all)	97	94	
Paraesthesia			
subjects affected / exposed	12 / 320 (3.75%)	20 / 315 (6.35%)	
occurrences (all)	14	27	
Peripheral sensory neuropathy			
subjects affected / exposed	27 / 320 (8.44%)	33 / 315 (10.48%)	
occurrences (all)	39	58	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	79 / 320 (24.69%)	91 / 315 (28.89%)	
occurrences (all)	164	198	
Leukopenia			
subjects affected / exposed	32 / 320 (10.00%)	42 / 315 (13.33%)	
occurrences (all)	122	121	
Neutropenia			
subjects affected / exposed	95 / 320 (29.69%)	112 / 315 (35.56%)	
occurrences (all)	300	406	
Thrombocytopenia			
subjects affected / exposed	106 / 320 (33.13%)	172 / 315 (54.60%)	
occurrences (all)	384	749	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	40 / 320 (12.50%)	46 / 315 (14.60%)	
occurrences (all)	80	89	
Fatigue			
subjects affected / exposed	96 / 320 (30.00%)	125 / 315 (39.68%)	
occurrences (all)	176	350	
Oedema peripheral			
subjects affected / exposed	24 / 320 (7.50%)	24 / 315 (7.62%)	
occurrences (all)	27	28	
Pyrexia			
subjects affected / exposed	70 / 320 (21.88%)	66 / 315 (20.95%)	
occurrences (all)	130	114	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	17 / 320 (5.31%)	8 / 315 (2.54%)	
occurrences (all)	21	11	
Abdominal pain			
subjects affected / exposed	27 / 320 (8.44%)	22 / 315 (6.98%)	
occurrences (all)	40	37	
Abdominal pain upper			
subjects affected / exposed	13 / 320 (4.06%)	26 / 315 (8.25%)	
occurrences (all)	20	42	
Constipation			

subjects affected / exposed	86 / 320 (26.88%)	64 / 315 (20.32%)	
occurrences (all)	132	91	
Diarrhoea			
subjects affected / exposed	133 / 320 (41.56%)	194 / 315 (61.59%)	
occurrences (all)	275	604	
Dyspepsia			
subjects affected / exposed	26 / 320 (8.13%)	24 / 315 (7.62%)	
occurrences (all)	40	38	
Nausea			
subjects affected / exposed	126 / 320 (39.38%)	193 / 315 (61.27%)	
occurrences (all)	247	457	
Vomiting			
subjects affected / exposed	80 / 320 (25.00%)	140 / 315 (44.44%)	
occurrences (all)	127	280	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	48 / 320 (15.00%)	52 / 315 (16.51%)	
occurrences (all)	61	71	
Dyspnoea			
subjects affected / exposed	28 / 320 (8.75%)	26 / 315 (8.25%)	
occurrences (all)	35	36	
Oropharyngeal pain			
subjects affected / exposed	13 / 320 (4.06%)	16 / 315 (5.08%)	
occurrences (all)	16	17	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 320 (0.94%)	24 / 315 (7.62%)	
occurrences (all)	3	26	
Rash			
subjects affected / exposed	40 / 320 (12.50%)	31 / 315 (9.84%)	
occurrences (all)	61	43	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	29 / 320 (9.06%)	28 / 315 (8.89%)	
occurrences (all)	36	32	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	27 / 320 (8.44%)	26 / 315 (8.25%)	
occurrences (all)	40	34	
Back pain			
subjects affected / exposed	47 / 320 (14.69%)	49 / 315 (15.56%)	
occurrences (all)	69	67	
Bone pain			
subjects affected / exposed	24 / 320 (7.50%)	15 / 315 (4.76%)	
occurrences (all)	39	27	
Muscle spasms			
subjects affected / exposed	15 / 320 (4.69%)	21 / 315 (6.67%)	
occurrences (all)	17	25	
Pain in extremity			
subjects affected / exposed	38 / 320 (11.88%)	16 / 315 (5.08%)	
occurrences (all)	52	21	
Infections and infestations			
Herpes zoster			
subjects affected / exposed	19 / 320 (5.94%)	22 / 315 (6.98%)	
occurrences (all)	21	26	
Nasopharyngitis			
subjects affected / exposed	18 / 320 (5.63%)	16 / 315 (5.08%)	
occurrences (all)	20	22	
Upper respiratory tract infection			
subjects affected / exposed	38 / 320 (11.88%)	55 / 315 (17.46%)	
occurrences (all)	58	76	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	85 / 320 (26.56%)	75 / 315 (23.81%)	
occurrences (all)	139	123	
Hypokalaemia			
subjects affected / exposed	25 / 320 (7.81%)	35 / 315 (11.11%)	
occurrences (all)	40	57	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 June 2009	Global substantial Amendment 1 revised the study flow chart and reduced the eligibility criteria for minimal acceptable renal function at study entry.
06 January 2010	Global substantial Amendment 2 added a dose modification summary table and updated dose modification guidelines to clarify the sequence of drug modifications and whether modification was required or optional for each agent. Supportive care recommendations were also added.
05 November 2010	Global substantial Amendment 3 revised the study design to delete the second interim analysis, increase the efficacy target at final analysis, and to move the final analysis to an earlier date.
17 March 2011	Global substantial Amendment 4 incorporated end of study procedures and added an extension phase for the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported