Clinical trial results:
A Phase 2, Randomize d, Double-blind, Placebo-controlled Study Comparing the Combination of CNTO 328 (Anti-IL-6 Monoclonal Antibody) and VELCADE versus VELCADE Alone in Subjects with Relapsed or Refractory Multiple Myeloma

Summary

EudraCT number	2006-001904-36
Trial protocol	NL BE FR GB CZ PT DE GR BG SK ES
Global end of trial date	24 September 2019

Results information

Result version number	v1 (current)
This version publication date	04 October 2020
First version publication date	04 October 2020

Trial information

Trial identification

Sponsor protocol code	CR012784

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00401843
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	920 Route, 202 South Raritan, United States,
Public contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.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	17 June 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 September 2019
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 assess the safety (Part 1) and to compare the efficacy, in terms of progression-free survival (PFS) (Part 2), of CNTO 328 when administered as an intravenous (IV) infusion in combination with bortezomib in subjects with relapsed or refractory multiple myeloma.

Protection of trial subjects:

The investigator acknowledges that, within legal and regulatory restrictions and institutional and ethical considerations, Centocor, their designee, or responsible government agencies (as required by law) may, at any time, review or copy source documents (example, laboratory reports, electrocardiograms, X-rays, workbooks and subjects' medical records) in order to verify eCRF data. Safety evaluations for all subjects will include; physical exam and neurological exam, weight, vitals signs before and after CNTO 328 and bortezomib administrations, and monitoring of routine clinical laboratory assessments (hematology, coagulation, blood chemistry, lipid panel, amylase and lipase, urinalysis).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 November 2006
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Brazil: 10
Country: Number of subjects enrolled	Bulgaria: 26
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	Czech Republic: 24
Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Greece: 10
Country: Number of subjects enrolled	Hungary: 20
Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	Poland: 30
Country: Number of subjects enrolled	Portugal: 9
Country: Number of subjects enrolled	Romania: 13
Country: Number of subjects enrolled	Russian Federation: 48
Country: Number of subjects enrolled	Spain: 17

Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	United States: 26
Worldwide total number of subjects	307
EEA total number of subjects	211

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)	169
From 65 to 84 years	137
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

144 subjects were randomized to bortezomib plus placebo group; of which, 3 subjects received incorrect treatment (bortezomib plus siltuximab).

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, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1 - Bortezomib + Siltuximab

Arm description:

Subjects received siltuximab 6 milligram per kilogram (mg/kg) as intravenous infusion once every 2 weeks along with bortezomib 1.3 milligram per square meter (mg/m^2) during cycle 1 (22-day cycle).

Arm type	Experimental
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Bortezomib 1.3 mg/m^2 was administered as intravenous bolus once every 2 weeks during cycle 1 (22-day cycle) in Part 1.

Investigational medicinal product name	Siltuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Siltuximab 6 mg/kg was administered as intravenous infusion once every 2 weeks during cycle 1 (22-day cycle) in Part 1.

Arm title	Part 2 - Bortezomib + Placebo

Arm description:

Subjects received bortezomib 1.3 mg/m^2 will be administered as intravenous bolus along with matching placebo administered as intravenous infusion once every 2 weeks during 42-day treatment cycle during treatment phase. Bortezomib 1.3 mg/m^2 was administered as intravenous bolus along with matching placebo once every 2 weeks during 35-day treatment cycle during Maintenance Phase. Dexamethasone tablet was administered at first occurrence of documented disease progression or if bortezomib was discontinued due to intolerable toxicity.

Arm type	Placebo
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Bortezomib 1.3 mg/m^2 was administered as intravenous bolus during 42-day treatment phase and during 35-day Maintenance Phase in Part 2.

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

Dosage and administration details:

Matching placebo was administered as intravenous infusion once every 2 weeks during 42-day treatment phase and 35-day maintenance phase in Part 2.

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

Dosage and administration details:

Dexamethasone 40 or 20 milligram per day (mg/day) tablet was administered to the treatment regimen if bortezomib was discontinued.

Arm title	Part 2 - Bortezomib + Siltuximab

Arm description:

Subjects received bortezomib 1.3 mg/m^2 as intravenous bolus along with Siltuximab 6 mg/kg administered as intravenous infusion once every 2 weeks during 42-day treatment cycle during treatment phase. Bortezomib 1.3 mg/m^2 was administered as intravenous bolus along with Siltuximab 6 mg/kg administered as intravenous infusion once every 2 weeks for 35-day treatment cycle during Maintenance Phase. Dexamethasone tablet was administered at first occurrence of documented disease progression or if bortezomib was discontinued due to intolerable toxicity.

Arm type	Experimental
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Bortezomib 1.3 mg/m^2 was administered as intravenous bolus during 42-day treatment phase and during 35-day Maintenance Phase in Part 2.

Investigational medicinal product name	Siltuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Siltuximab 6 mg/kg was administered as intravenous infusion once every 2 weeks during 42-day Treatment Phase and 35-day Maintenance Phase in Part 2.

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection, Tablet
Routes of administration	Intravenous bolus use , Oral use

Dosage and administration details:

Dexamethasone 40 or 20 mg/day tablet was administered to the treatment regimen if bortezomib was discontinued.

Number of subjects in period 1	Part 1 - Bortezomib + Siltuximab	Part 2 - Bortezomib + Placebo	Part 2 - Bortezomib + Siltuximab
Started	21	144	142
Completed	0	0	0
Not completed	21	144	142
Adverse event, serious fatal	2	9	12
Physician decision	-	16	10
Disease progression	10	60	49
End of study	1	1	2
Consent withdrawn by subject	1	5	5
Adverse event, non-fatal	5	25	25
Randomized but not treated	-	2	3
Other	-	5	5
Withdrawal of consent to study agent tx	1	15	17
Achieved complete response	1	5	11
Unspecified	-	1	-
Lost to follow-up	-	-	2
Protocol deviation	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Part 1 - Bortezomib + Siltuximab
Reporting group description:	
Subjects received siltuximab 6 milligram per kilogram (mg/kg) as intravenous infusion once every 2 weeks along with bortezomib 1.3 milligram per square meter (mg/m^2) during cycle 1 (22-day cycle).	
Reporting group title	Part 2 - Bortezomib + Placebo
Reporting group description:	
Subjects received bortezomib 1.3 mg/m^2 will be administered as intravenous bolus along with matching placebo administered as intravenous infusion once every 2 weeks during 42-day treatment cycle during treatment phase. Bortezomib 1.3 mg/m^2 was administered as intravenous bolus along with matching placebo once every 2 weeks during 35-day treatment cycle during Maintenance Phase. Dexamethasone tablet was administered at first occurrence of documented disease progression or if bortezomib was discontinued due to intolerable toxicity.	
Reporting group title	Part 2 - Bortezomib + Siltuximab
Reporting group description:	
Subjects received bortezomib 1.3 mg/m^2 as intravenous bolus along with Siltuximab 6 mg/kg administered as intravenous infusion once every 2 weeks during 42-day treatment cycle during treatment phase. Bortezomib 1.3 mg/m^2 was administered as intravenous bolus along with Siltuximab 6 mg/kg administered as intravenous infusion once every 2 weeks for 35-day treatment cycle during Maintenance Phase. Dexamethasone tablet was administered at first occurrence of documented disease progression or if bortezomib was discontinued due to intolerable toxicity.	

Reporting group values	Part 1 - Bortezomib + Siltuximab	Part 2 - Bortezomib + Placebo	Part 2 - Bortezomib + Siltuximab
Number of subjects	21	144	142
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	9	86	74
From 65 to 84 years	11	58	68
85 years and over	1	0	0
Title for AgeContinuous Units: years			
arithmetic mean	66	62.3	63.5
standard deviation	± 10.76	± 9.65	± 9.32
Title for Gender Units: subjects			
Female	13	59	70
Male	8	85	72

Reporting group values	Total		
Number of subjects	307		
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	169		
From 65 to 84 years	137		
85 years and over	1		

Title for AgeContinuous Units: years arithmetic mean standard deviation	- 		
Title for Gender Units: subjects			
Female	142		
Male	165		

End points

End points reporting groups

Reporting group title	Part 1 - Bortezomib + Siltuximab

Reporting group description:

Subjects received siltuximab 6 milligram per kilogram (mg/kg) as intravenous infusion once every 2 weeks along with bortezomib 1.3 milligram per square meter (mg/m^2) during cycle 1 (22-day cycle).

Reporting group title	Part 2 - Bortezomib + Placebo

Reporting group description:

Subjects received bortezomib 1.3 mg/m^2 will be administered as intravenous bolus along with matching placebo administered as intravenous infusion once every 2 weeks during 42-day treatment cycle during treatment phase. Bortezomib 1.3 mg/m^2 was administered as intravenous bolus along with matching placebo once every 2 weeks during 35-day treatment cycle during Maintenance Phase. Dexamethasone tablet was administered at first occurrence of documented disease progression or if bortezomib was discontinued due to intolerable toxicity.

Reporting group title	Part 2 - Bortezomib + Siltuximab

Reporting group description:

Subjects received bortezomib 1.3 mg/m^2 as intravenous bolus along with Siltuximab 6 mg/kg administered as intravenous infusion once every 2 weeks during 42-day treatment cycle during treatment phase. Bortezomib 1.3 mg/m^2 was administered as intravenous bolus along with Siltuximab 6 mg/kg administered as intravenous infusion once every 2 weeks for 35-day treatment cycle during Maintenance Phase. Dexamethasone tablet was administered at first occurrence of documented disease progression or if bortezomib was discontinued due to intolerable toxicity.

Primary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)[1]

End point description:

PFS was defined as time interval between randomization and first documented sign of disease progression (including relapse from CR) by the European Bone Marrow Transplant (EBMT) criteria or death, whichever occurred first. Relapse from CR requires at least 1 of the following: Reappearance of serum or urinary M-protein on immunofixation or routine electrophoresis, confirmed by at least 1 further investigation and excluding oligoclonal immune reconstitution; >=5 percent (%) plasma cells either in a bone marrow aspirate or on trephine bone biopsy; Development of new lytic bone lesions or soft tissue plasmacytomas or definite increase in the size of residual bone lesions (development of a compression fracture does not exclude continued response and may not indicate progression); Development of hypercalcemia not attributable to any other cause. Intent-to-treat (ITT) population included all subjects randomized in Part 2. Subjects were analyzed as per initial randomization.

End point type	Primary

End point timeframe:

Randomization until disease progression or death, which ever occurred first (maximum up to 4.5 years)

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The analysis was planned only for the reported arms of Part 2 of baseline period.

End point values	Part 2 - Bortezomib + Placebo	Part 2 - Bortezomib + Siltuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	142		
Units: days				
median (confidence interval 95%)	232 (191 to 302)	245 (217 to 300)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part 2 - Bortezomib + Placebo v Part 2 - Bortezomib + Siltuximab
Number of subjects included in analysis	286
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.345
Method	Logrank
Parameter estimate	Log hazard ratio
Point estimate	0.869
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.162

Secondary: Percentage of Subjects With Confirmed Complete Response (CR Rate)

End point title	Percentage of Subjects With Confirmed Complete Response (CR Rate)[2]

End point description:

CR rate was defined as the percentage of subjects who achieved a confirmed CR before dexamethasone was added. CR: Absence of original M-protein in serum/urine by immunofixation,maintained for minimum of 6 weeks. The presence of oligoclonal bands consistent with oligoclonal immune reconstitution does not exclude CR; Less than 5 percent (%) plasma cells in bone marrow aspirate and also on trephine bone biopsy if biopsy is performed; No increase in size/number of lytic bone lesions; Disappearance of soft tissue plasmacytomas. Response-evaluable population:all participants in Part 2 with confirmed diagnosis of multiple myeloma and measurable,secretory disease:either serum M-protein 1 greater than or equal to (>=) gram per deciliter(g/dL)/urine M-protein >200 mg per 24 hours,at study entry;had at least 1 study agent administration;at least 1 post-baseline disease assessment before dexamethasone.

End point type	Secondary

End point timeframe:

Randomization until disease progression (maximum up to 4.5 years)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The analysis was planned only for the reported arms of Part 2 of baseline period.

End point values	Part 2 - Bortezomib + Placebo	Part 2 - Bortezomib + Siltuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	131		
Units: percentage of subjects				
number (not applicable)	7.3	10.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Best Confirmed Response of Complete Response (CR) or Partial Response (PR) (Overall Response Rate [ORR])

End point title	Percentage of Subjects With Best Confirmed Response of Complete Response (CR) or Partial Response (PR) (Overall Response Rate [ORR])[3]

End point description:

ORR was defined as best response for subject recorded from first administration of study agent/randomization (Part 2) until disease progression/recurrence and before dexamethasone. CR: Absence of Mprotein in serum/urine by immunofixation, maintained for minimum of 6 weeks. Presence of oligoclonal bands consistent with oligoclonal immune reconstitution does not exclude CR; >5% plasma cells in bone marrow aspirate and on trephine bone biopsy if performed; No increase in size/number of lytic bone lesions; Disappearance of soft tissue plasmacytomas. PR:>=50% reduction in level of serum M-protein, maintained for minimum of 6 weeks. Reduction in 24hour urinary light chain excretion either by >=90% or to <200mg, maintained for minimum of 6 weeks; >=50% reduction in size of soft tissue plasmacytomas; No increase in size/number of lytic bone lesions. Response-evaluable population was the subject population.

End point type	Secondary

End point timeframe:

Randomization until disease progression (maximum up to 4.5 years)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The analysis was planned only for the reported arms of Part 2 of baseline period.

End point values	Part 2 - Bortezomib + Placebo	Part 2 - Bortezomib + Siltuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	131		
Units: percentage of subjects				
number (not applicable)	46.7	55.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival[4]

End point description:

Overall survival was defined as the interval between the first administration of study agent or randomization (Part 2) and the participant's death from any cause. For participants with unknown survival status as of the data cut-off date, overall survival was censored at the last date known to be alive. Here '99999' signifies that upper limit of 95% CI which was not estimable due to high censorship rate and lesser number of events. ITT population included all subjects randomized in Part 2. Subjects were analyzed as per initial randomization.

End point type	Secondary

End point timeframe:

Up to 4.5 years

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The analysis was planned only for the reported arms of Part 2 of baseline period.

End point values	Part 2 - Bortezomib + Placebo	Part 2 - Bortezomib + Siltuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	142		
Units: days				
median (confidence interval 95%)	1121 (1038.0 to 99999)	937 (713 to 1127)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events (AEs) or Serious Adverse Events (SAEs)

End point title	Number of Subjects With Adverse Events (AEs) or Serious Adverse Events (SAEs)

End point description:

An AE is any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. An SAE is an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. The safety population included all subjects who received at least 1 dose of study treatment in Part 1 or Part 2. Subjects were analyzed as per actual treatment received.

End point type	Secondary

End point timeframe:

Up to 4.5 years

End point values	Part 1 - Bortezomib + Siltuximab	Part 2 - Bortezomib + Placebo	Part 2 - Bortezomib + Siltuximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	139	142	
Units: subjects				
Adverse Events (AEs)	21	138	140	
Serious Adverse Events (SAEs)	10	44	47	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 4.5 years

Adverse event reporting additional description:

The safety population included all subjects who received at least 1 dose of study treatment in Part 1 or Part 2. Subjects were analyzed as per actual treatment received.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Part 1 - Bortezomib + Siltuximab

Reporting group description:

Siltuximab 6 milligram per kilogram (mg/kg) will be administered as intravenous infusion once every 2 weeks along with bortezomib 1.3 milligram per square meter (mg/m^2) during cycle 1.

Reporting group title	Part 2 - Bortezomib + CNTO328

Reporting group description:

Bortezomib 1.3 mg/m^2 will be administered as intravenous bolus on Days 1, 4, 8, 11, followed by a 10- day rest period; and on Days 22, 25, 29, and 32 followed by a 10-day rest period along with Siltuximab administered as intravenous infusion once every 2 weeks during 42-day treatment phase. Bortezomib 1.3 mg/m^2 will be administered as intravenous bolus on Days 1, 8, 15, 22 followed by a 13-day rest period (cycle Days 23 to 35) along with Siltuximab administered as intravenous infusion once every 2 weeks for 35-day Maintenance Phase. Dexamethasone tablet will be administered at first occurrence of documented disease progression or if bortezomib was discontinued due to intolerable toxicity. Dexamethasone 40 mg/day was administered on days 1-4, 9-12, and 17-20 for four 28-day cycles then 40 mg/day for Days 1-4 for all subsequent cycles.

Reporting group title	Part 2 - Bortezomib + Placebo

Reporting group description:

Bortezomib 1.3 mg/m^2 will be administered as intravenous bolus on Days 1, 4, 8, 11, followed by a 10- day rest period; and on Days 22, 25, 29, and 32 followed by a 10-day rest period along with matching placebo administered as intravenous infusion once every 2 weeks during 42-day treatment phase. Bortezomib 1.3 mg/m^2 will be administered as intravenous bolus on Days 1, 8, 15, 22 followed by a 13- day rest period (cycle Days 23 to 35) along with matching placebo once every 2 weeks during 35-day Maintenance Phase. Dexamethasone tablet will be administered at first occurrence of documented disease progression or if bortezomib was discontinued due to intolerable toxicity. Dexamethasone 40 milligram per day (mg/day) was administered on days 1-4, 9-12, and 17-20 for four 28-day cycles then 40 mg/day for Days 1-4 for all subsequent cycles.

Serious adverse events	Part 1 - Bortezomib + Siltuximab	Part 2 - Bortezomib + CNTO328	Part 2 - Bortezomib + Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 21 (47.62%)	47 / 142 (33.10%)	44 / 139 (31.65%)
number of deaths (all causes)	1	13	10
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal Cell Carcinoma			

subjects affected / exposed	1 / 21 (4.76%)	2 / 142 (1.41%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder Transitional Cell Carcinoma			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon Adenoma			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningioma			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pancreatic Carcinoma Metastatic			
subjects affected / exposed	1 / 21 (4.76%)	0 / 142 (0.00%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Plasma Cell Leukaemia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Plasma Cell Myeloma			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Plasmacytoma			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep Vein Thrombosis			

subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 21 (0.00%)	2 / 142 (1.41%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemic Shock			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jugular Vein Thrombosis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic Hypotension			
subjects affected / exposed	1 / 21 (4.76%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 21 (4.76%)	1 / 142 (0.70%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			

subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic Fatigue Syndrome			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Face Oedema			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General Physical Health Deterioration			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mass			
subjects affected / exposed	1 / 21 (4.76%)	0 / 142 (0.00%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Performance Status Decreased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden Cardiac Death			

subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Sudden Death			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	2 / 139 (1.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Respiratory, thoracic and mediastinal disorders			
Acute Pulmonary Oedema			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Atelectasis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	1 / 21 (4.76%)	0 / 142 (0.00%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 21 (4.76%)	1 / 142 (0.70%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 21 (0.00%)	2 / 142 (1.41%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial Lung Disease			

subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mediastinal Shift			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural Effusion			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Embolism			
subjects affected / exposed	0 / 21 (0.00%)	2 / 142 (1.41%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary Oedema			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	3 / 139 (2.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Respiratory Arrest			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory Failure			
subjects affected / exposed	1 / 21 (4.76%)	0 / 142 (0.00%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle Fracture			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur Fracture			

subjects affected / exposed	1 / 21 (4.76%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip Fracture			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus Fracture			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Compression Fracture			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna Fracture			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Limb Fracture			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Disorder			
subjects affected / exposed	1 / 21 (4.76%)	0 / 142 (0.00%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Failure Congestive			

subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic Shock			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiopulmonary Failure			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Left Ventricular Dysfunction			
subjects affected / exposed	1 / 21 (4.76%)	0 / 142 (0.00%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular Fibrillation			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Nervous system disorders			
Cerebrovascular Accident			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cognitive Disorder			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic Stroke			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Mononeuritis			

subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral Sensory Neuropathy			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Cord Compression			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid Haemorrhage			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Syncope			
subjects affected / exposed	0 / 21 (0.00%)	2 / 142 (1.41%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viith Nerve Paralysis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vocal Cord Paresis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	3 / 139 (2.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile Neutropenia			

subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	2 / 139 (1.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	2 / 139 (1.44%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Eye Swelling			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal Detachment			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain Lower			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	2 / 139 (1.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Haemorrhoidal Haemorrhage			

subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mouth Ulceration			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retroperitoneal Haemorrhage			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small Intestinal Obstruction			
subjects affected / exposed	1 / 21 (4.76%)	0 / 142 (0.00%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic Function Abnormal			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Drug Eruption			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			

subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive Uropathy			
subjects affected / exposed	1 / 21 (4.76%)	0 / 142 (0.00%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Failure			
subjects affected / exposed	1 / 21 (4.76%)	2 / 142 (1.41%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Failure Acute			
subjects affected / exposed	1 / 21 (4.76%)	3 / 142 (2.11%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Impairment			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Retention			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bone Lesion			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank Pain			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle Haemorrhage			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal Chest Pain			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in Extremity			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Acute Hepatitis B			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	2 / 139 (1.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	0 / 21 (0.00%)	2 / 142 (1.41%)	3 / 139 (2.16%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 2
Endocarditis			

subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterobacter Bacteraemia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	2 / 139 (1.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Furuncle			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kidney Infection			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobar Pneumonia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	2 / 139 (1.44%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower Respiratory Tract Infection			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis Bacterial			

subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis Pneumococcal			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 21 (4.76%)	5 / 142 (3.52%)	6 / 139 (4.32%)
occurrences causally related to treatment / all	0 / 2	1 / 5	2 / 6
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia Pneumococcal			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia Streptococcal			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 21 (0.00%)	4 / 142 (2.82%)	2 / 139 (1.44%)
occurrences causally related to treatment / all	0 / 0	3 / 4	2 / 2
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Septic Shock			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Streptococcal Bacteraemia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Respiratory Tract Infection			

subjects affected / exposed	0 / 21 (0.00%)	2 / 142 (1.41%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperuricaemia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoalbuminaemia			

subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour Lysis Syndrome			
subjects affected / exposed	0 / 21 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Part 1 - Bortezomib + Siltuximab	Part 2 - Bortezomib + CNTO328	Part 2 - Bortezomib + Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 21 (100.00%)	140 / 142 (98.59%)	135 / 139 (97.12%)
Vascular disorders			
Haematoma			
subjects affected / exposed	2 / 21 (9.52%)	2 / 142 (1.41%)	1 / 139 (0.72%)
occurrences (all)	2	2	2
Hypertension			
subjects affected / exposed	4 / 21 (19.05%)	18 / 142 (12.68%)	9 / 139 (6.47%)
occurrences (all)	5	27	19
Hypotension			
subjects affected / exposed	4 / 21 (19.05%)	11 / 142 (7.75%)	12 / 139 (8.63%)
occurrences (all)	4	22	18
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 21 (23.81%)	24 / 142 (16.90%)	27 / 139 (19.42%)
occurrences (all)	10	35	51
Chills			
subjects affected / exposed	3 / 21 (14.29%)	6 / 142 (4.23%)	6 / 139 (4.32%)
occurrences (all)	3	7	13
Fatigue			
subjects affected / exposed	8 / 21 (38.10%)	39 / 142 (27.46%)	40 / 139 (28.78%)
occurrences (all)	13	68	73
Gait Disturbance			

subjects affected / exposed	2 / 21 (9.52%)	1 / 142 (0.70%)	1 / 139 (0.72%)
occurrences (all)	2	1	1
Influenza Like Illness			
subjects affected / exposed	3 / 21 (14.29%)	4 / 142 (2.82%)	5 / 139 (3.60%)
occurrences (all)	5	6	6
Oedema Peripheral			
subjects affected / exposed	4 / 21 (19.05%)	16 / 142 (11.27%)	16 / 139 (11.51%)
occurrences (all)	6	22	22
Pyrexia			
subjects affected / exposed	3 / 21 (14.29%)	8 / 142 (5.63%)	27 / 139 (19.42%)
occurrences (all)	5	8	56
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 21 (28.57%)	12 / 142 (8.45%)	18 / 139 (12.95%)
occurrences (all)	8	16	29
Dyspnoea			
subjects affected / exposed	6 / 21 (28.57%)	20 / 142 (14.08%)	14 / 139 (10.07%)
occurrences (all)	6	24	19
Epistaxis			
subjects affected / exposed	1 / 21 (4.76%)	8 / 142 (5.63%)	7 / 139 (5.04%)
occurrences (all)	1	9	9
Nasal Congestion			
subjects affected / exposed	2 / 21 (9.52%)	1 / 142 (0.70%)	1 / 139 (0.72%)
occurrences (all)	2	2	1
Oropharyngeal Pain			
subjects affected / exposed	2 / 21 (9.52%)	7 / 142 (4.93%)	9 / 139 (6.47%)
occurrences (all)	2	11	13
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 21 (19.05%)	8 / 142 (5.63%)	6 / 139 (4.32%)
occurrences (all)	4	8	16
Insomnia			
subjects affected / exposed	5 / 21 (23.81%)	15 / 142 (10.56%)	15 / 139 (10.79%)
occurrences (all)	6	18	18
Investigations			

Weight Decreased			
subjects affected / exposed	7 / 21 (33.33%)	20 / 142 (14.08%)	20 / 139 (14.39%)
occurrences (all)	10	35	30
Weight Increased			
subjects affected / exposed	3 / 21 (14.29%)	5 / 142 (3.52%)	3 / 139 (2.16%)
occurrences (all)	4	5	3
Nervous system disorders			
Balance Disorder			
subjects affected / exposed	2 / 21 (9.52%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences (all)	3	0	1
Dizziness			
subjects affected / exposed	4 / 21 (19.05%)	14 / 142 (9.86%)	10 / 139 (7.19%)
occurrences (all)	5	14	16
Dysgeusia			
subjects affected / exposed	2 / 21 (9.52%)	4 / 142 (2.82%)	2 / 139 (1.44%)
occurrences (all)	2	5	13
Headache			
subjects affected / exposed	8 / 21 (38.10%)	18 / 142 (12.68%)	14 / 139 (10.07%)
occurrences (all)	16	27	33
Hypoaesthesia			
subjects affected / exposed	0 / 21 (0.00%)	5 / 142 (3.52%)	7 / 139 (5.04%)
occurrences (all)	0	5	9
Lethargy			
subjects affected / exposed	0 / 21 (0.00%)	7 / 142 (4.93%)	7 / 139 (5.04%)
occurrences (all)	0	21	19
Neuralgia			
subjects affected / exposed	1 / 21 (4.76%)	31 / 142 (21.83%)	33 / 139 (23.74%)
occurrences (all)	1	72	59
Paraesthesia			
subjects affected / exposed	3 / 21 (14.29%)	14 / 142 (9.86%)	16 / 139 (11.51%)
occurrences (all)	3	30	34
Peripheral Motor Neuropathy			
subjects affected / exposed	1 / 21 (4.76%)	8 / 142 (5.63%)	8 / 139 (5.76%)
occurrences (all)	1	12	13
Peripheral Sensory Neuropathy			

subjects affected / exposed	9 / 21 (42.86%)	73 / 142 (51.41%)	73 / 139 (52.52%)
occurrences (all)	19	157	160
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 21 (42.86%)	45 / 142 (31.69%)	46 / 139 (33.09%)
occurrences (all)	13	138	129
Leukopenia			
subjects affected / exposed	8 / 21 (38.10%)	38 / 142 (26.76%)	16 / 139 (11.51%)
occurrences (all)	68	104	56
Lymphopenia			
subjects affected / exposed	8 / 21 (38.10%)	13 / 142 (9.15%)	5 / 139 (3.60%)
occurrences (all)	57	52	39
Neutropenia			
subjects affected / exposed	17 / 21 (80.95%)	86 / 142 (60.56%)	53 / 139 (38.13%)
occurrences (all)	122	481	191
Thrombocytopenia			
subjects affected / exposed	13 / 21 (61.90%)	83 / 142 (58.45%)	65 / 139 (46.76%)
occurrences (all)	69	454	334
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 21 (9.52%)	6 / 142 (4.23%)	6 / 139 (4.32%)
occurrences (all)	3	8	6
Eye disorders			
Chalazion			
subjects affected / exposed	2 / 21 (9.52%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences (all)	2	0	2
Conjunctivitis			
subjects affected / exposed	2 / 21 (9.52%)	7 / 142 (4.93%)	5 / 139 (3.60%)
occurrences (all)	2	8	5
Lacrimation Increased			
subjects affected / exposed	2 / 21 (9.52%)	3 / 142 (2.11%)	0 / 139 (0.00%)
occurrences (all)	2	4	0
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	3 / 21 (14.29%)	10 / 142 (7.04%)	10 / 139 (7.19%)
occurrences (all)	6	17	22
Abdominal Pain Upper			

subjects affected / exposed	4 / 21 (19.05%)	7 / 142 (4.93%)	8 / 139 (5.76%)
occurrences (all)	5	10	9
Aphthous Stomatitis			
subjects affected / exposed	2 / 21 (9.52%)	3 / 142 (2.11%)	0 / 139 (0.00%)
occurrences (all)	2	7	0
Constipation			
subjects affected / exposed	12 / 21 (57.14%)	31 / 142 (21.83%)	22 / 139 (15.83%)
occurrences (all)	18	47	38
Diarrhoea			
subjects affected / exposed	13 / 21 (61.90%)	53 / 142 (37.32%)	50 / 139 (35.97%)
occurrences (all)	44	131	136
Dyspepsia			
subjects affected / exposed	3 / 21 (14.29%)	13 / 142 (9.15%)	9 / 139 (6.47%)
occurrences (all)	3	16	9
Haemorrhoids			
subjects affected / exposed	2 / 21 (9.52%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences (all)	2	1	0
Nausea			
subjects affected / exposed	12 / 21 (57.14%)	40 / 142 (28.17%)	42 / 139 (30.22%)
occurrences (all)	28	70	80
Stomatitis			
subjects affected / exposed	3 / 21 (14.29%)	6 / 142 (4.23%)	4 / 139 (2.88%)
occurrences (all)	3	9	6
Vomiting			
subjects affected / exposed	4 / 21 (19.05%)	28 / 142 (19.72%)	28 / 139 (20.14%)
occurrences (all)	4	42	40
Hepatobiliary disorders			
Hepatic Function Abnormal			
subjects affected / exposed	1 / 21 (4.76%)	9 / 142 (6.34%)	14 / 139 (10.07%)
occurrences (all)	2	28	22
Hyperbilirubinaemia			
subjects affected / exposed	2 / 21 (9.52%)	5 / 142 (3.52%)	1 / 139 (0.72%)
occurrences (all)	27	10	1
Skin and subcutaneous tissue disorders			
Ecchymosis			

subjects affected / exposed	2 / 21 (9.52%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences (all)	4	0	2
Rash			
subjects affected / exposed	6 / 21 (28.57%)	15 / 142 (10.56%)	14 / 139 (10.07%)
occurrences (all)	9	21	27
Renal and urinary disorders			
Renal Failure			
subjects affected / exposed	2 / 21 (9.52%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences (all)	2	1	0
Renal Impairment			
subjects affected / exposed	2 / 21 (9.52%)	14 / 142 (9.86%)	4 / 139 (2.88%)
occurrences (all)	6	34	6
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 21 (19.05%)	23 / 142 (16.20%)	17 / 139 (12.23%)
occurrences (all)	7	31	29
Back Pain			
subjects affected / exposed	3 / 21 (14.29%)	21 / 142 (14.79%)	29 / 139 (20.86%)
occurrences (all)	4	35	40
Bone Pain			
subjects affected / exposed	4 / 21 (19.05%)	17 / 142 (11.97%)	15 / 139 (10.79%)
occurrences (all)	5	27	35
Muscle Spasms			
subjects affected / exposed	4 / 21 (19.05%)	11 / 142 (7.75%)	5 / 139 (3.60%)
occurrences (all)	4	13	10
Musculoskeletal Chest Pain			
subjects affected / exposed	5 / 21 (23.81%)	3 / 142 (2.11%)	6 / 139 (4.32%)
occurrences (all)	5	4	10
Musculoskeletal Pain			
subjects affected / exposed	2 / 21 (9.52%)	8 / 142 (5.63%)	10 / 139 (7.19%)
occurrences (all)	2	11	15
Myalgia			
subjects affected / exposed	3 / 21 (14.29%)	12 / 142 (8.45%)	7 / 139 (5.04%)
occurrences (all)	3	15	20
Pain in Extremity			

subjects affected / exposed	4 / 21 (19.05%)	25 / 142 (17.61%)	15 / 139 (10.79%)
occurrences (all)	6	63	35
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 21 (14.29%)	14 / 142 (9.86%)	11 / 139 (7.91%)
occurrences (all)	6	17	14
Ear Infection			
subjects affected / exposed	2 / 21 (9.52%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences (all)	2	1	0
Herpes Simplex			
subjects affected / exposed	2 / 21 (9.52%)	4 / 142 (2.82%)	2 / 139 (1.44%)
occurrences (all)	3	4	3
Herpes Zoster			
subjects affected / exposed	2 / 21 (9.52%)	4 / 142 (2.82%)	13 / 139 (9.35%)
occurrences (all)	3	5	21
Hordeolum			
subjects affected / exposed	3 / 21 (14.29%)	6 / 142 (4.23%)	2 / 139 (1.44%)
occurrences (all)	3	8	3
Nasopharyngitis			
subjects affected / exposed	3 / 21 (14.29%)	15 / 142 (10.56%)	13 / 139 (9.35%)
occurrences (all)	8	19	19
Pneumonia			
subjects affected / exposed	3 / 21 (14.29%)	7 / 142 (4.93%)	4 / 139 (2.88%)
occurrences (all)	3	8	4
Respiratory Tract Infection			
subjects affected / exposed	2 / 21 (9.52%)	14 / 142 (9.86%)	11 / 139 (7.91%)
occurrences (all)	2	16	20
Rhinitis			
subjects affected / exposed	1 / 21 (4.76%)	5 / 142 (3.52%)	7 / 139 (5.04%)
occurrences (all)	2	6	11
Upper Respiratory Tract Infection			
subjects affected / exposed	5 / 21 (23.81%)	14 / 142 (9.86%)	12 / 139 (8.63%)
occurrences (all)	11	28	17
Urinary Tract Infection			
subjects affected / exposed	3 / 21 (14.29%)	12 / 142 (8.45%)	7 / 139 (5.04%)
occurrences (all)	4	19	11

Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	6 / 21 (28.57%)	32 / 142 (22.54%)	28 / 139 (20.14%)
occurrences (all)	7	51	43
Dehydration			
subjects affected / exposed	4 / 21 (19.05%)	6 / 142 (4.23%)	2 / 139 (1.44%)
occurrences (all)	6	6	2
Enzyme Abnormality			
subjects affected / exposed	1 / 21 (4.76%)	5 / 142 (3.52%)	9 / 139 (6.47%)
occurrences (all)	1	5	16
Hyperamylasaemia			
subjects affected / exposed	3 / 21 (14.29%)	4 / 142 (2.82%)	2 / 139 (1.44%)
occurrences (all)	15	6	2
Hypercholesterolaemia			
subjects affected / exposed	5 / 21 (23.81%)	8 / 142 (5.63%)	8 / 139 (5.76%)
occurrences (all)	20	11	9
Hyperglycaemia			
subjects affected / exposed	0 / 21 (0.00%)	9 / 142 (6.34%)	1 / 139 (0.72%)
occurrences (all)	0	41	56
Hyperlipasaemia			
subjects affected / exposed	3 / 21 (14.29%)	4 / 142 (2.82%)	4 / 139 (2.88%)
occurrences (all)	11	5	4
Hypertriglyceridaemia			
subjects affected / exposed	3 / 21 (14.29%)	7 / 142 (4.93%)	6 / 139 (4.32%)
occurrences (all)	19	20	8
Hyperuricaemia			
subjects affected / exposed	2 / 21 (9.52%)	10 / 142 (7.04%)	7 / 139 (5.04%)
occurrences (all)	2	14	9
Hypocalcaemia			
subjects affected / exposed	0 / 21 (0.00%)	8 / 142 (5.63%)	13 / 139 (9.35%)
occurrences (all)	0	31	35
Hypokalaemia			
subjects affected / exposed	0 / 21 (0.00%)	17 / 142 (11.97%)	9 / 139 (6.47%)
occurrences (all)	0	21	11
Hypomagnesaemia			

subjects affected / exposed	1 / 21 (4.76%)	11 / 142 (7.75%)	3 / 139 (2.16%)
occurrences (all)	1	17	3
Hyponatraemia			
subjects affected / exposed	0 / 21 (0.00%)	9 / 142 (6.34%)	4 / 139 (2.88%)
occurrences (all)	0	14	8
Hypophosphataemia			
subjects affected / exposed	4 / 21 (19.05%)	16 / 142 (11.27%)	19 / 139 (13.67%)
occurrences (all)	11	26	43

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 October 2006	The first protocol amendment was adopted before any study related procedures were conducted or subjects were enrolled in the study.
01 May 2007	Approximately 6 subjects were enrolled in the study prior to the initiation of Amendment 2.
14 July 2008	Approximately 113 subjects were enrolled in the study prior to the initiation of Amendment 3.
01 November 2010	All subjects were enrolled in the study prior to the initiation of Amendment 4.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported