

**Clinical trial results:****A Randomized Controlled Study of DOXIL®/CAELYX® (doxorubicin HCL liposome injection) and VELCADE™ (bortezomib) or VELCADE Monotherapy for the Treatment of Relapsed Multiple Myeloma**

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2004-001842-34
Trial protocol	AT CZ GB ES IT
Global end of trial date	05 June 2014

Results information

Result version number	v2 (current)
This version publication date	01 July 2016
First version publication date	06 August 2015
Version creation reason	• Correction of full data set Review of data

Trial information**Trial identification**

Sponsor protocol code	DOXIL-MMY-3001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00103506
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Johnson & Johnson Pharmaceutical Research and Development
Sponsor organisation address	Berkeley, California, United States,
Public contact	Clinical Registry Group, Johnson & Johnson Pharmaceutical Research and Development, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Johnson & Johnson Pharmaceutical Research and Development, 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	05 June 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	05 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to test the hypothesis that treatment with DOXIL/CAELYX and VELCADE in combination, will result in a longer time to progression (TTP) than VELCADE monotherapy in subjects with relapsed multiple myeloma.

Protection of trial subjects:

The safety assessments included, clinical laboratory results, tests for cardiac function (multiple-gated acquisition scan/echocardiogram and electrocardiogram) and adverse events were monitored throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 December 2004
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	8 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 15
Country: Number of subjects enrolled	Australia: 62
Country: Number of subjects enrolled	Austria: 18
Country: Number of subjects enrolled	Belgium: 20
Country: Number of subjects enrolled	Canada: 43
Country: Number of subjects enrolled	Czech Republic: 36
Country: Number of subjects enrolled	France: 49
Country: Number of subjects enrolled	Israel: 46
Country: Number of subjects enrolled	Italy: 28
Country: Number of subjects enrolled	Netherlands: 61
Country: Number of subjects enrolled	Poland: 52
Country: Number of subjects enrolled	Portugal: 20
Country: Number of subjects enrolled	Russian Federation: 72
Country: Number of subjects enrolled	Singapore: 5
Country: Number of subjects enrolled	South Africa: 28
Country: Number of subjects enrolled	Spain: 35
Country: Number of subjects enrolled	United Kingdom: 15

Country: Number of subjects enrolled	United States: 41
Worldwide total number of subjects	646
EEA total number of subjects	334

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)	396
From 65 to 84 years	247
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 646 participants were enrolled into the study, with 324 subjects randomized to receive DOXIL/CAELYX and VELCADE combination therapy and 322 participants randomized to receive VELCADE monotherapy.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Velcade (Bortezomib) Monotherapy

Arm description:

Velcade (bortezomib) 1.3 milligram/meter per square (mg/m²) by rapid (bolus) intravenous (IV) administration given on Day 1, 4, 8, and 11 of each 21-day cycle for up to 8 cycles.

Arm type	Experimental
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	PS-341
Other name	VELCADE
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Participants were administered 1.3 milligram (mg) of Bortezomib by rapid bolus intravenous (i.v.) administration given on Days 1, 4, 8, and 11 of each 21-day cycle for up to 8 cycles

Arm title	Doxil/Caelyx Plus Velcade (Bortezomib)
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Arm description:

Velcade (bortezomib) 1.3 milligram per meter square (mg/m²) by rapid (bolus) IV administration given on Day 1, 4, 8, and 11 of each 21-day cycle for up to 8 cycles. Doxorubicin hydrochloride (DOXIL/CAELYX) 30 mg/m² by IV infusion will be given on Day 4 of every 21-day cycle after the administration of VELCADE (bortezomib) up to 8 cycles.

Arm type	Active comparator
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	PS-341
Other name	VELCADE
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Participants were administered 1.3 milligram (mg) of Bortezomib by rapid bolus intravenous (i.v.) administration given on Days 1, 4, 8, and 11 of each 21-day cycle for up to 8 cycles

Investigational medicinal product name	Doxorubicin hydrochloride
Investigational medicinal product code	Doxorubicin HCL Liposome Injection
Other name	DOXIL/CAELYX
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants were administered Doxorubicin hydrochloride (DOXIL/CAELYX) 30 milligram per metere

sqaure (mg/m2) by intravenous (i.v) infusion on Day 4 of every 21-day cycle after the administration of bortezomib (VELCADE) for up to 8 cycles.

Number of subjects in period 1	Velcade (Bortezomib) Monotherapy	Doxil/Caelyx Plus Velcade (Bortezomib)
Started	322	324
Completed	0	0
Not completed	322	324
Consent withdrawn by subject	13	24
Physician decision	6	9
Adverse event, non-fatal	81	105
Other	218	181
Adverse event, serious non-fatal	2	5
Lost to follow-up	2	-

Baseline characteristics

Reporting groups

Reporting group title	Velcade (Bortezomib) Monotherapy
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Reporting group description:

Velcade (bortezomib) 1.3 milligram/meter per square (mg/m²) by rapid (bolus) intravenous (IV) administration given on Day 1, 4, 8, and 11 of each 21-day cycle for up to 8 cycles.

Reporting group title	Doxil/Caelyx Plus Velcade (Bortezomib)
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Reporting group description:

Velcade (bortezomib) 1.3 milligram per meter square (mg/m²) by rapid (bolus) IV administration given on Day 1, 4, 8, and 11 of each 21-day cycle for up to 8 cycles. Doxorubicin hydrochloride (DOXIL/CAELYX) 30 mg/m² by IV infusion will be given on Day 4 of every 21-day cycle after the administration of VELCADE (bortezomib) up to 8 cycles.

Reporting group values	Velcade (Bortezomib) Monotherapy	Doxil/Caelyx Plus Velcade (Bortezomib)	Total
Number of subjects	322	324	646
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	193	203	396
From 65 to 84 years	127	120	247
85 years and over	2	1	3
Title for AgeContinuous Units: years			
arithmetic mean	61.5	61.4	
standard deviation	± 9.56	± 9.61	-
Title for Gender Units: subjects			
Female	148	135	283
Male	174	189	363

End points

End points reporting groups

Reporting group title	Velcade (Bortezomib) Monotherapy
Reporting group description: Velcade (bortezomib) 1.3 milligram/meter per square (mg/m ²) by rapid (bolus) intravenous (IV) administration given on Day 1, 4, 8, and 11 of each 21-day cycle for up to 8 cycles.	
Reporting group title	Doxil/Caelyx Plus Velcade (Bortezomib)
Reporting group description: Velcade (bortezomib) 1.3 milligram per meter square (mg/m ²) by rapid (bolus) IV administration given on Day 1, 4, 8, and 11 of each 21-day cycle for up to 8 cycles. Doxorubicin hydrochloride (DOXIL/CAELYX) 30 mg/m ² by IV infusion will be given on Day 4 of every 21-day cycle after the administration of VELCADE (bortezomib) up to 8 cycles.	

Primary: Time to Progression (TTP)

End point title	Time to Progression (TTP) ^[1]
End point description: Median time to progression of disease is assessed according to International Myeloma Working Group (IMWG) criteria or death from any cause. IMWG criteria: increase of less than or equal (\geq) 25% from lowest level in Serum M-component or (the absolute increase must be \geq 0.5 gram per deciliter [g/dL]); Urine M component or (the absolute increase must be \geq 200 milligram per 24 hour. Only in participants without measurable serum and urine M-protein levels: the difference between involved and uninvolved free light chain levels. The absolute increase >10 mg/dL. Bone marrow plasma cell percentage $\geq 10\%$. Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing. Development of hypercalcemia. Participants who died or dropped out due to any reason without progression will be censored with the day of death or drop-out, respectively and who are alive at the end of the study without any progression was censored with the last available date.	
End point type	Primary
End point timeframe: From date of first participant randomization (20 December 2004) up to interim analysis cut-off date (28 April 2006).	

Notes:

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

Justification: Descriptive statistics were done, no inferential statistical analyses were performed

End point values	Velcade (Bortezomib) Monotherapy	Doxil/Caelyx Plus Velcade (Bortezomib)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	322	324		
Units: Months				
median (full range (min-max))	6.5 (5.6 to 7.1)	9.3 (8.2 to 11.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival
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End point description:

The overall survival is defined as the time from the date of first dose of study drug to date of death from any cause. If the participant is alive or the vital status is unknown, the participant will be censored at the date the participant will be last known to be alive.

End point type	Secondary
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End point timeframe:

From date of first participant randomization (20 December 2004) to cut-off date for final survival analysis (16 May 2014).

End point values	Velcade (Bortezomib) Monotherapy	Doxil/Caelyx Plus Velcade (Bortezomib)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	322	324		
Units: months				
median (full range (min-max))	30.8 (25.2 to 36.5)	33 (28.9 to 37.1)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 to follow up

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	9.0
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Reporting groups

Reporting group title	VELCADE
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Reporting group description:

bortezomib monotherapy

Reporting group title	DOXIL + VELCADE
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Reporting group description:

doxorubicin hydrochloride [HCl] liposome injection and bortezomib combination therapy

Serious adverse events	VELCADE	DOXIL + VELCADE	
Total subjects affected by serious adverse events			
subjects affected / exposed	105 / 322 (32.61%)	120 / 324 (37.04%)	
number of deaths (all causes)	12	12	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer Pain			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tumour Lysis Syndrome			
subjects affected / exposed	1 / 322 (0.31%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Colon Cancer			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep Vein Thrombosis			

subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 322 (0.62%)	4 / 324 (1.23%)	
occurrences causally related to treatment / all	2 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic Hypotension			
subjects affected / exposed	2 / 322 (0.62%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 322 (0.31%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter Related Complication			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest Pain			
subjects affected / exposed	3 / 322 (0.93%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chills			

subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 322 (0.00%)	3 / 324 (0.93%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hyperthermia			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General Physical Health Deterioration			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza Like Illness			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema Peripheral			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-Organ Failure			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pain			

subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	8 / 322 (2.48%)	15 / 324 (4.63%)	
occurrences causally related to treatment / all	5 / 8	14 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden Cardiac Death			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sudden Death			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign Prostatic Hyperplasia			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (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 Pulmonary Oedema			

subjects affected / exposed	1 / 322 (0.31%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	6 / 322 (1.86%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	5 / 6	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea Exertional			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial Lung Disease			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 322 (0.00%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	2 / 322 (0.62%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pulmonary Fibrosis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pulmonary Hypertension			

subjects affected / exposed	0 / 322 (0.00%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pulmonary Oedema			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Failure			
subjects affected / exposed	1 / 322 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed Suicide			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Nervousness			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal Ideation			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Blood Creatinine Increased subjects affected / exposed	2 / 322 (0.62%)	3 / 324 (0.93%)	
occurrences causally related to treatment / all	2 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Glucose Increased subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Troponin I Increased subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection Fraction Decreased subjects affected / exposed	0 / 322 (0.00%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Drug Toxicity subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall subjects affected / exposed	1 / 322 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skeletal Injury subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
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 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Thoracic Vertebral Fracture subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (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 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Pectoris subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Unstable subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation subjects affected / exposed	2 / 322 (0.62%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Flutter subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Arrest subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardiac Failure			

subjects affected / exposed	2 / 322 (0.62%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Chronic			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Congestive			
subjects affected / exposed	2 / 322 (0.62%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	1 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-Respiratory Arrest			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Infarction			
subjects affected / exposed	1 / 322 (0.31%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodal Arrhythmia			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right Ventricular Failure			
subjects affected / exposed	1 / 322 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Autonomic Neuropathy			

subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cauda Equina Syndrome			
subjects affected / exposed	2 / 322 (0.62%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Balance Disorder			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Haemorrhage			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Ischaemia			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
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	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coordination Abnormal			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 322 (0.31%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar Radiculopathy			

subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy Peripheral			
subjects affected / exposed	1 / 322 (0.31%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paralysis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	1 / 322 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Quadriparesis			

subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy in Malignant Disease			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (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	0 / 322 (0.00%)	3 / 324 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	4 / 322 (1.24%)	4 / 324 (1.23%)	
occurrences causally related to treatment / all	4 / 5	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 322 (1.24%)	3 / 324 (0.93%)	
occurrences causally related to treatment / all	2 / 4	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Neutropenia			
subjects affected / exposed	2 / 322 (0.62%)	5 / 324 (1.54%)	
occurrences causally related to treatment / all	0 / 3	11 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	0 / 322 (0.00%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 322 (0.00%)	9 / 324 (2.78%)	
occurrences causally related to treatment / all	0 / 0	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 322 (0.00%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	3 / 322 (0.93%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corneal Erosion			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diplopia			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal Vein Thrombosis			

subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	2 / 322 (0.62%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	6 / 322 (1.86%)	7 / 324 (2.16%)	
occurrences causally related to treatment / all	7 / 8	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 322 (0.00%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flatulence			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric Ulcer			
subjects affected / exposed	0 / 322 (0.00%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroduodenal Haemorrhage			

subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 322 (0.31%)	3 / 324 (0.93%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	2 / 322 (0.62%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus Paralytic			
subjects affected / exposed	1 / 322 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large Intestine Perforation			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mallory-Weiss Syndrome			
subjects affected / exposed	0 / 322 (0.00%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	3 / 322 (0.93%)	7 / 324 (2.16%)	
occurrences causally related to treatment / all	3 / 3	6 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Haemorrhage			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Prolapse			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small Intestinal Obstruction			
subjects affected / exposed	1 / 322 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 322 (0.00%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 322 (0.62%)	13 / 324 (4.01%)	
occurrences causally related to treatment / all	1 / 2	15 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Epidermal Necrosis			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palmar-Plantar Erythrodysaesthesia Syndrome			

subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jessner's Lymphocytic Infiltration			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling Face			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (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			
Calculus Bladder			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephritis Interstitial			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Colic			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
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	2 / 322 (0.62%)	3 / 324 (0.93%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal Failure Acute			
subjects affected / exposed	5 / 322 (1.55%)	4 / 324 (1.23%)	
occurrences causally related to treatment / all	5 / 6	4 / 5	
deaths causally related to treatment / all	0 / 0	1 / 1	
Renal Failure Chronic			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Impairment			
subjects affected / exposed	2 / 322 (0.62%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Bladder Haemorrhage			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Retention			
subjects affected / exposed	2 / 322 (0.62%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal Insufficiency			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercorticism			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inappropriate Antidiuretic Hormone Secretion			

subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 322 (0.62%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone Lesion			
subjects affected / exposed	1 / 322 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back Pain			
subjects affected / exposed	3 / 322 (0.93%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone Pain			
subjects affected / exposed	1 / 322 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint Instability			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal Chest Pain			

subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pain in Extremity			
subjects affected / exposed	2 / 322 (0.62%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological Fracture			
subjects affected / exposed	0 / 322 (0.00%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal Infection			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial Sepsis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis Acute			
subjects affected / exposed	2 / 322 (0.62%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis Chronic			

subjects affected / exposed	2 / 322 (0.62%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candidiasis			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 322 (0.31%)	3 / 324 (0.93%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter Related Infection			
subjects affected / exposed	0 / 322 (0.00%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea Infectious			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 322 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear Infection			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Furuncle			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	3 / 322 (0.93%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes Zoster			
subjects affected / exposed	3 / 322 (0.93%)	5 / 324 (1.54%)	
occurrences causally related to treatment / all	2 / 3	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genitourinary Tract Infection			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes Zoster Disseminated			
subjects affected / exposed	1 / 322 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 322 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella Sepsis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Respiratory Tract Infection			
subjects affected / exposed	3 / 322 (0.93%)	3 / 324 (0.93%)	
occurrences causally related to treatment / all	2 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar Pneumonia			

subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis Bacterial			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Opportunistic Infection			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic Sepsis			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Orchitis			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal Bacteraemia			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal Sepsis			
subjects affected / exposed	1 / 322 (0.31%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis JiroveCI Pneumonia			

subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	20 / 322 (6.21%)	16 / 324 (4.94%)	
occurrences causally related to treatment / all	13 / 21	11 / 17	
deaths causally related to treatment / all	3 / 4	1 / 3	
Pneumonia Aspergillus			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Legionella			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas Infection			
subjects affected / exposed	0 / 322 (0.00%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Pneumococcal			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection			
subjects affected / exposed	2 / 322 (0.62%)	3 / 324 (0.93%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory Tract Infection Bacterial			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic Embolus			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic Shock			
subjects affected / exposed	1 / 322 (0.31%)	3 / 324 (0.93%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Sinusitis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin Infection			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal Sepsis			
subjects affected / exposed	0 / 322 (0.00%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 322 (0.62%)	4 / 324 (1.23%)	
occurrences causally related to treatment / all	1 / 3	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	2 / 322 (0.62%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	0 / 322 (0.00%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	6 / 322 (1.86%)	6 / 324 (1.85%)	
occurrences causally related to treatment / all	5 / 8	6 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	0 / 322 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 322 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 322 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyperkalaemia			
subjects affected / exposed	1 / 322 (0.31%)	0 / 324 (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	1 / 322 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	1 / 322 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 322 (0.31%)	3 / 324 (0.93%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	VELCADE	DOXIL + VELCADE	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	298 / 322 (92.55%)	313 / 324 (96.60%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	17 / 322 (5.28%)	15 / 324 (4.63%)	
occurrences (all)	18	22	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	56 / 322 (17.39%)	70 / 324 (21.60%)	
occurrences (all)	84	138	
Fatigue			
subjects affected / exposed	88 / 322 (27.33%)	115 / 324 (35.49%)	
occurrences (all)	157	220	
Chills			
subjects affected / exposed	18 / 322 (5.59%)	25 / 324 (7.72%)	
occurrences (all)	19	44	
Influenza Like Illness			
subjects affected / exposed	13 / 322 (4.04%)	18 / 324 (5.56%)	
occurrences (all)	14	36	
Oedema Peripheral			
subjects affected / exposed	27 / 322 (8.39%)	32 / 324 (9.88%)	
occurrences (all)	34	38	
Pyrexia			

subjects affected / exposed occurrences (all)	67 / 322 (20.81%) 124	91 / 324 (28.09%) 154	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	38 / 322 (11.80%)	58 / 324 (17.90%)	
occurrences (all)	48	69	
Dyspnoea			
subjects affected / exposed	22 / 322 (6.83%)	32 / 324 (9.88%)	
occurrences (all)	35	40	
Epistaxis			
subjects affected / exposed	12 / 322 (3.73%)	18 / 324 (5.56%)	
occurrences (all)	12	22	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	43 / 322 (13.35%)	35 / 324 (10.80%)	
occurrences (all)	45	43	
Investigations			
Weight Decreased			
subjects affected / exposed	12 / 322 (3.73%)	37 / 324 (11.42%)	
occurrences (all)	15	43	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	9 / 322 (2.80%)	18 / 324 (5.56%)	
occurrences (all)	9	23	
Dizziness			
subjects affected / exposed	27 / 322 (8.39%)	32 / 324 (9.88%)	
occurrences (all)	43	45	
Headache			
subjects affected / exposed	56 / 322 (17.39%)	59 / 324 (18.21%)	
occurrences (all)	84	89	
Neuropathy			
subjects affected / exposed	38 / 322 (11.80%)	35 / 324 (10.80%)	
occurrences (all)	53	48	
Neuralgia			
subjects affected / exposed	63 / 322 (19.57%)	54 / 324 (16.67%)	
occurrences (all)	113	88	

Neuropathy Peripheral subjects affected / exposed occurrences (all)	46 / 322 (14.29%) 77	36 / 324 (11.11%) 60	
Paraesthesia subjects affected / exposed occurrences (all)	31 / 322 (9.63%) 41	41 / 324 (12.65%) 57	
Peripheral Sensory Neuropathy subjects affected / exposed occurrences (all)	42 / 322 (13.04%) 83	41 / 324 (12.65%) 69	
Polyneuropathy subjects affected / exposed occurrences (all)	27 / 322 (8.39%) 56	26 / 324 (8.02%) 63	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	67 / 322 (20.81%) 170	80 / 324 (24.69%) 236	
Leukopenia subjects affected / exposed occurrences (all)	23 / 322 (7.14%) 95	28 / 324 (8.64%) 152	
Thrombocytopenia subjects affected / exposed occurrences (all)	89 / 322 (27.64%) 379	104 / 324 (32.10%) 488	
Neutropenia subjects affected / exposed occurrences (all)	71 / 322 (22.05%) 270	113 / 324 (34.88%) 510	
Eye disorders			
Conjunctivitis subjects affected / exposed occurrences (all)	17 / 322 (5.28%) 21	24 / 324 (7.41%) 28	
Gastrointestinal disorders			
Abdominal Pain subjects affected / exposed occurrences (all)	23 / 322 (7.14%) 24	32 / 324 (9.88%) 41	
Abdominal Pain Upper subjects affected / exposed occurrences (all)	13 / 322 (4.04%) 14	24 / 324 (7.41%) 32	
Constipation			

subjects affected / exposed	98 / 322 (30.43%)	99 / 324 (30.56%)	
occurrences (all)	132	141	
Dyspepsia			
subjects affected / exposed	13 / 322 (4.04%)	27 / 324 (8.33%)	
occurrences (all)	15	39	
Diarrhoea			
subjects affected / exposed	122 / 322 (37.89%)	142 / 324 (43.83%)	
occurrences (all)	237	295	
Nausea			
subjects affected / exposed	125 / 322 (38.82%)	152 / 324 (46.91%)	
occurrences (all)	231	303	
Stomatitis			
subjects affected / exposed	11 / 322 (3.42%)	55 / 324 (16.98%)	
occurrences (all)	12	75	
Vomiting			
subjects affected / exposed	67 / 322 (20.81%)	93 / 324 (28.70%)	
occurrences (all)	106	166	
Skin and subcutaneous tissue disorders			
Dry Skin			
subjects affected / exposed	7 / 322 (2.17%)	28 / 324 (8.64%)	
occurrences (all)	7	30	
Palmar-Plantar Erythrodysesthesia Syndrome			
subjects affected / exposed	1 / 322 (0.31%)	62 / 324 (19.14%)	
occurrences (all)	1	114	
Pruritus			
subjects affected / exposed	16 / 322 (4.97%)	20 / 324 (6.17%)	
occurrences (all)	25	25	
Rash			
subjects affected / exposed	29 / 322 (9.01%)	48 / 324 (14.81%)	
occurrences (all)	45	69	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	37 / 322 (11.49%)	38 / 324 (11.73%)	
occurrences (all)	49	43	
Arthralgia			

subjects affected / exposed occurrences (all)	27 / 322 (8.39%) 36	34 / 324 (10.49%) 50	
Bone Pain subjects affected / exposed occurrences (all)	25 / 322 (7.76%) 36	10 / 324 (3.09%) 10	
Musculoskeletal Chest Pain subjects affected / exposed occurrences (all)	12 / 322 (3.73%) 12	20 / 324 (6.17%) 24	
Pain in Extremity subjects affected / exposed occurrences (all)	47 / 322 (14.60%) 66	34 / 324 (10.49%) 40	
Myalgia subjects affected / exposed occurrences (all)	20 / 322 (6.21%) 27	10 / 324 (3.09%) 10	
Infections and infestations			
Herpes Zoster subjects affected / exposed occurrences (all)	26 / 322 (8.07%) 28	30 / 324 (9.26%) 32	
Bronchitis subjects affected / exposed occurrences (all)	14 / 322 (4.35%) 15	25 / 324 (7.72%) 32	
Herpes Simplex subjects affected / exposed occurrences (all)	18 / 322 (5.59%) 19	32 / 324 (9.88%) 39	
Nasopharyngitis subjects affected / exposed occurrences (all)	20 / 322 (6.21%) 23	25 / 324 (7.72%) 31	
Pneumonia subjects affected / exposed occurrences (all)	9 / 322 (2.80%) 11	18 / 324 (5.56%) 20	
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	32 / 322 (9.94%) 46	30 / 324 (9.26%) 52	
Metabolism and nutrition disorders			
Anorexia			

subjects affected / exposed	43 / 322 (13.35%)	58 / 324 (17.90%)
occurrences (all)	63	99
Decreased Appetite		
subjects affected / exposed	9 / 322 (2.80%)	30 / 324 (9.26%)
occurrences (all)	13	39
Hypocalcaemia		
subjects affected / exposed	9 / 322 (2.80%)	19 / 324 (5.86%)
occurrences (all)	11	32
Hypomagnesaemia		
subjects affected / exposed	12 / 322 (3.73%)	17 / 324 (5.25%)
occurrences (all)	21	35
Hypokalaemia		
subjects affected / exposed	15 / 322 (4.66%)	23 / 324 (7.10%)
occurrences (all)	22	31

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 September 2006	After the protocol-specified interim analysis, the Independent Data Monitoring Committee (IDMC) concluded that there was a significant benefit to subjects randomized to receive DOXIL/CAELYX and VELCADE regarding the primary endpoint, time to progression, as well as progression - free survival. While there was an increase in adverse events associated with the combination therapy, this increase was judged to be acceptable in the context of the benefits. The primary objective of this amendment is to communicate this result to the investigators, who can then offer the subjects who were randomized to VELCADE monotherapy and are still actively receiving study treatment the option to cross over to receive the combination therapy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Study stopped in terms of primary endpoint based on its results at planned interim analysis (28 Apr 2006). However, Long-term follow-up for survival continued until 2014.
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Notes: