Clinical trial results:
A PHASE III STUDY OF VELCADE (BORTEZOMIB) THALIDOMIDE DEXAMETHASONE (VTD) VERSUS VELCADE (BORTEZOMIB) CYCLOPHOSPHAMIDE DEXAMETHASONE (VCD) AS AN INDUCTION TREATMENT PRIOR TO AUTOLOGOUS STEM CELL TRANSPLANTATION IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA.

Summary

EudraCT number	2013-003174-27
Trial protocol	FR
Global end of trial date	12 August 2015

Results information

Result version number	v1 (current)
This version publication date	09 August 2022
First version publication date	09 August 2022

Trial information

Trial identification

Sponsor protocol code	RC13-0284

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01971658
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CHU de Nantes
Sponsor organisation address	5 allée de l'Ile Gloriette, Nantes, France, 44 093
Public contact	Département Promotion, CHU de Nantes, 033 253482835, Bp-prom-regl@chu-nantes.fr
Scientific contact	Département Promotion, CHU de Nantes, 033 253482835, Bp-prom-regl@chu-nantes.fr

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	18 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 August 2015
Global end of trial reached?	Yes
Global end of trial date	12 August 2015
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 compare the VGPR rate achieved with four courses of VTD with that achieved with four courses of VCD

Protection of trial subjects:

- Prophylaxis of opportunistic infections: Bactrim Forte, oral enicillin or macrolide (for cases of penicillin allergy), Acyclovir or Valacyclovir (for antiviral prophylaxis)
- Bisphosphonate (for bone lesions or osteopaenia), according to centre policy
- Recombinant erythropoietin (if haemoglobin levels <11g/dL), according to centre policy

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	06 November 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 358
Worldwide total number of subjects	358
EEA total number of subjects	358

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)	333
From 65 to 84 years	25

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

358 patients were included from 06/11/2013 to 18/02/2015 in 58 French centers / 60 open.
340 patients were randomized arm VCD 170 ans arm VTD 170 patients

Pre-assignment

Screening details:

inclusion criteria - Patients newly diagnosed with symptomatic Multiple Myeloma patient, must have measurable disease by serum M-protein ≥ 10 g/L and/or urine M-protein ≥200mg/day
or Serum Free Light Chain MM (Freelite)

Pre-assignment period milestones

Number of subjects started	358
Number of subjects completed	340

Pre-assignment subject non-completion reasons

Reason: Number of subjects	patient not having the inclusion criteria: 18

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	ARM VCD

Arm description:

For arm B:
1- Induction therapy : 4 cycles of VCD
Each cycle : 21 days
Each cycle comprises:
o Cyclophosphamide 500 mg/m²/d, PO D1, 8, 15
o Velcade® 1.3 mg/m²/d, SC D1, 4, 8 and 11
o Dexamethasone 40 mg/d, PO D1 to 4, D9 to 12

Arm type	Active comparator
Investigational medicinal product name	Velcade
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1.3 mg/m² subcutaneously on Days 1, 4, 8, and 11, followed by a 10-day rest period (Days 12 to 21)

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	Endoxan
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

CYCLOPHOSPHAMIDE 500 mg/m² orally on Days 1, 8 and 15

Investigational medicinal product name	Dexaméthasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Buccal tablet
Routes of administration	Oral use

Dosage and administration details:

DEXAMETHASONE 40 mg/day orally on Days 1-4 and 9-12

Arm title	ARM VTD

Arm description:

For arm A:
Induction therapy : 4 cycles of VTD
Each cycle : 21 days
Each cycle comprises:
o Thalidomide® 100 mg/d, PO D1 to J21
o Velcade® 1.3 mg/m²/d, SC D1, 4, 8 and 11
o Dexamethasone 40 mg/d, PO D1 to 4, D9 to 12

Arm type	Active comparator
Investigational medicinal product name	Thalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

100 mg/day orally on days 1 to 21

Investigational medicinal product name	Velcade
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1.3 mg/m² subcutaneously on Days 1, 4, 8, and 11, followed by a 10-day rest period (Days 12 to 21)

Investigational medicinal product name	Dexaméthasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Buccal tablet
Routes of administration	Oral use

Dosage and administration details:

DEXAMETHASONE 40 mg/day orally on Days 1 to 4 and 9 to 12

Number of subjects in period 1[1]	ARM VCD	ARM VTD
Started	170	170
Completed	154	157
Not completed	16	13
Physician decision	6	1
Consent withdrawn by subject	-	1
death	3	2
progression	-	3

Adverse event, non-fatal	3	5
Progreseion	1	-
Protocol deviation	3	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 358 people were included in the Research and 340 randomized

Baseline characteristics

Reporting groups	
Reporting group title	ARM VCD
Reporting group description:	
For arm B: 1- Induction therapy : 4 cycles of VCD Each cycle : 21 days Each cycle comprises: o Cyclophosphamide 500 mg/m²/d, PO D1, 8, 15 o Velcade® 1.3 mg/m²/d, SC D1, 4, 8 and 11 o Dexamethasone 40 mg/d, PO D1 to 4, D9 to 12	
Reporting group title	ARM VTD
Reporting group description:	
For arm A: Induction therapy : 4 cycles of VTD Each cycle : 21 days Each cycle comprises: o Thalidomide® 100 mg/d, PO D1 to J21 o Velcade® 1.3 mg/m²/d, SC D1, 4, 8 and 11 o Dexamethasone 40 mg/d, PO D1 to 4, D9 to 12	

Reporting group values	ARM VCD	ARM VTD	Total
Number of subjects	170	170	340
Age categorical Units: Subjects			
Adults (18-64 years)	155	161	316
From 65-84 years	15	9	24
Age continuous Units: years			
median	60	59	
full range (min-max)	26 to 65	34 to 65	-
Gender categorical Units: Subjects			
Female	61	67	128
Male	109	103	212

End points

End points reporting groups

Reporting group title	ARM VCD

Reporting group description:

For arm B:
1- Induction therapy : 4 cycles of VCD
Each cycle : 21 days
Each cycle comprises:
o Cyclophosphamide 500 mg/m²/d, PO D1, 8, 15
o Velcade® 1.3 mg/m²/d, SC D1, 4, 8 and 11
o Dexamethasone 40 mg/d, PO D1 to 4, D9 to 12

Reporting group title	ARM VTD

Reporting group description:

For arm A:
Induction therapy : 4 cycles of VTD
Each cycle : 21 days
Each cycle comprises:
o Thalidomide® 100 mg/d, PO D1 to J21
o Velcade® 1.3 mg/m²/d, SC D1, 4, 8 and 11
o Dexamethasone 40 mg/d, PO D1 to 4, D9 to 12

Primary: Compare the VGPR rate

End point title	Compare the VGPR rate

End point description:

The primary efficacy endpoint is VGPR rate obtained with VTD or VTC at the end of induction phase based on ITT population.
This analysis will use the Cochran-Mantel-Haenszel chi-square test, adjusted for the stratification factors.
The 2-sided 95% confidence intervals for the response rate for each treatment group, the 2-sided 95% confidence interval for the difference in response rate between the two groups, and the p-value will be presented.

End point type	Primary

End point timeframe:

5 months

End point values	ARM VCD	ARM VTD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169	169		
Units: percentage				
number (not applicable)	56.2	66.3		

Statistical analyses

Statistical analysis title	Compare the VGPR rate

Statistical analysis description:

The primary efficacy endpoint is VGPR rate obtained with VTD or VTC at the end of induction phase based on ITT population.

This analysis will use the Cochran-Mantel-Haenszel chi-square test, adjusted for the stratification factors.
The 2-sided 95% confidence intervals for the response rate for each treatment group, the 2-sided 95% confidence interval for the difference in response rate between the two groups, and the p-value will be presented.

Comparison groups	ARM VTD v ARM VCD
Number of subjects included in analysis	338
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.05 [2]
Method	Khi² Cochran-Mantel-Haenszel

Notes:

[1] - In the ITT population, 66.3% of patients in the VTD arm achieved at least one VGPR versus 56.2% in the VCD arm (P=0.05). The difference in VGRR rate (primary objective) between the VTD and VCD arms was 10.1% (95% CI, 1% to 18%)
In the PP per-protocol analysis, the VGPR rate was also significantly higher in the VTD arm (70.7% vs 60.4%, P 0.05, difference 10.3%, 95% CI 2% to 21%).
[2] - In the ITT population p=0.05
In the PP per-protocol analysis P=0.05

Secondary: Quality of stem cell collection

End point title	Quality of stem cell collection

End point description:

Stem cell collection, starting 1 week after cycle 3: cyclophosphamide 3 g/m² followed by G-CSF (5 µg/kg/day)

End point type	Secondary

End point timeframe:

3 cycle

End point values	ARM VCD	ARM VTD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	159		
Units: 10X6 cellules / kg				
number (not applicable)	9.2	10.7		

Statistical analyses

Statistical analysis title	Stem cell collection
Comparison groups	ARM VTD v ARM VCD
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.05 [3]
Method	Cochran-Mantel-Haenszel chisquare test,

Notes:

[3] - Le nombre médian de CD34+ collecté étaient de 10.7 X 106 cellules / kg dans le bras VTD versus 9.2 X 106 cellule/kg dans le bras VCD (P=0.05).

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 5 cycles	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	ARM VCD

Reporting group description:

For arm B:
1- Induction therapy : 4 cycles of VCD
Each cycle : 21 days
Each cycle comprises:
o Cyclophosphamide 500 mg/m²/d, PO D1, 8, 15
o Velcade® 1.3 mg/m²/d, SC D1, 4, 8 and 11
o Dexamethasone 40 mg/d, PO D1 to 4, D9 to 12

Reporting group title	ARM VTD

Reporting group description:

For arm A:
Induction therapy : 4 cycles of VTD
Each cycle : 21 days
Each cycle comprises:
o Thalidomide® 100 mg/d, PO D1 to J21
o Velcade® 1.3 mg/m²/d, SC D1, 4, 8 and 11
o Dexamethasone 40 mg/d, PO D1 to 4, D9 to 12

Serious adverse events	ARM VCD	ARM VTD	
Total subjects affected by serious adverse events			
subjects affected / exposed	63 / 167 (37.72%)	61 / 167 (36.53%)	
number of deaths (all causes)	3	2	
number of deaths resulting from adverse events	3	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Refractory anaemia with an excess of blasts			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			

subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic neoplasm			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parathyroid tumour benign			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	2 / 167 (1.20%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 167 (0.60%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			

subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cryoglobulinaemia			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Parathyroidectomy			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			
subjects affected / exposed	2 / 167 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site erythema			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
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	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Oral administration complication			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 167 (0.60%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	3 / 167 (1.80%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 167 (1.80%)	4 / 167 (2.40%)	
occurrences causally related to treatment / all	2 / 3	4 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Bronchial obstruction			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleural effusion			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
mania			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Lipase increased			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal myelogram abnormal			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Drug administration error			
subjects affected / exposed	2 / 167 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medication error			
subjects affected / exposed	2 / 167 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			

subjects affected / exposed	2 / 167 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug dose omission			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inappropriate schedule of drug administration			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incorrect dose administered			
subjects affected / exposed	0 / 167 (0.00%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incorrect drug administration duration			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional product misuse			
subjects affected / exposed	2 / 167 (1.20%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax traumatic			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural complication			

subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
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 / 167 (0.00%)	1 / 167 (0.60%)	
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	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive heart disease			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			

subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebellar syndrome			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extrapyramidal disorder			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (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	2 / 167 (1.20%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensorimotor neuropathy			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brown-Sequard syndrome			

subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperaesthesia			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle contractions involuntary			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (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	2 / 167 (1.20%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			

subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			
subjects affected / exposed	7 / 167 (4.19%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	7 / 7	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	4 / 167 (2.40%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 167 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic microangiopathy			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Ear and labyrinth disorders			
Ear pain			

subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal necrosis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal toxicity			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			

subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	0 / 167 (0.00%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Acute generalised exanthematous pustulosis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Toxic skin eruption			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Cystitis haemorrhagic			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	1 / 167 (0.60%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 167 (2.99%)	3 / 167 (1.80%)	
occurrences causally related to treatment / all	2 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 167 (0.60%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Spinal compression fracture			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sternal fracture			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacterial sepsis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	4 / 167 (2.40%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 167 (0.60%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic abscess			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			

subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	2 / 167 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jiroveci pneumonia			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia escherichia			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia haemophilus			

subjects affected / exposed	3 / 167 (1.80%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	2 / 167 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis Escherichia coli			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 167 (1.20%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	3 / 167 (1.80%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	2 / 2	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stenotrophomonas infection			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis septic			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			

subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	9 / 167 (5.39%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	8 / 9	2 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Anal fistula infection			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 167 (0.00%)	3 / 167 (1.80%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercreatinaemia			

subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ARM VCD	ARM VTD	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	167 / 167 (100.00%)	167 / 167 (100.00%)	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 167 (0.00%)	2 / 167 (1.20%)	
occurrences (all)	0	2	
Flushing			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences (all)	1	1	
Hypertension			
subjects affected / exposed	4 / 167 (2.40%)	7 / 167 (4.19%)	
occurrences (all)	4	8	
Hot flush			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	2 / 167 (1.20%)	1 / 167 (0.60%)	
occurrences (all)	2	1	
Orthostatic hypotension			
subjects affected / exposed	2 / 167 (1.20%)	0 / 167 (0.00%)	
occurrences (all)	2	0	
Phlebitis superficial			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	

Thrombosis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Venous thrombosis			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences (all)	1	2	
Surgical and medical procedures			
Cementoplasty			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Oophorectomy			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Tooth extraction			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences (all)	1	1	
Vertebroplasty			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Phlebitis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	43 / 167 (25.75%)	35 / 167 (20.96%)	
occurrences (all)	49	38	
Chest discomfort			
subjects affected / exposed	1 / 167 (0.60%)	2 / 167 (1.20%)	
occurrences (all)	1	2	
Chest pain			
subjects affected / exposed	5 / 167 (2.99%)	5 / 167 (2.99%)	
occurrences (all)	5	5	
Chills			
subjects affected / exposed	3 / 167 (1.80%)	2 / 167 (1.20%)	
occurrences (all)	3	2	
Face oedema			

subjects affected / exposed	0 / 167 (0.00%)	3 / 167 (1.80%)	
occurrences (all)	0	3	
Fatigue			
subjects affected / exposed	1 / 167 (0.60%)	3 / 167 (1.80%)	
occurrences (all)	1	3	
Feeling jittery			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
General physical health deterioration			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Hyperthermia			
subjects affected / exposed	2 / 167 (1.20%)	3 / 167 (1.80%)	
occurrences (all)	2	3	
Inflammation			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Injection site erythema			
subjects affected / exposed	2 / 167 (1.20%)	1 / 167 (0.60%)	
occurrences (all)	2	1	
Injection site haemorrhage			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Injection site reaction			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Local swelling			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Localised oedema			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Malaise			

subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences (all)	1	1	
Mucosal dryness			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Mucosal inflammation			
subjects affected / exposed	2 / 167 (1.20%)	2 / 167 (1.20%)	
occurrences (all)	2	2	
Mucositis			
subjects affected / exposed	2 / 167 (1.20%)	0 / 167 (0.00%)	
occurrences (all)	2	0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Oedema			
subjects affected / exposed	2 / 167 (1.20%)	3 / 167 (1.80%)	
occurrences (all)	2	3	
Oedema peripheral			
subjects affected / exposed	18 / 167 (10.78%)	31 / 167 (18.56%)	
occurrences (all)	20	34	
Pain			
subjects affected / exposed	2 / 167 (1.20%)	6 / 167 (3.59%)	
occurrences (all)	2	6	
Pyrexia			
subjects affected / exposed	18 / 167 (10.78%)	11 / 167 (6.59%)	
occurrences (all)	19	11	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 167 (0.00%)	3 / 167 (1.80%)	
occurrences (all)	0	3	
Hypersensitivity			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Seasonal allergy			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	

Reproductive system and breast disorders			
Acquired phimosis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal discomfort			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Asthmatic crisis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Bronchospasm			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	11 / 167 (6.59%)	9 / 167 (5.39%)	
occurrences (all)	11	9	
Dysphonia			
subjects affected / exposed	4 / 167 (2.40%)	0 / 167 (0.00%)	
occurrences (all)	4	0	
Dyspnoea			
subjects affected / exposed	6 / 167 (3.59%)	8 / 167 (4.79%)	
occurrences (all)	7	10	
Dyspnoea exertional			
subjects affected / exposed	3 / 167 (1.80%)	2 / 167 (1.20%)	
occurrences (all)	3	2	
Epistaxis			
subjects affected / exposed	1 / 167 (0.60%)	2 / 167 (1.20%)	
occurrences (all)	1	2	

Hiccups			
subjects affected / exposed	4 / 167 (2.40%)	3 / 167 (1.80%)	
occurrences (all)	4	3	
Oropharyngeal pain			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Pleurisy			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Productive cough			
subjects affected / exposed	1 / 167 (0.60%)	2 / 167 (1.20%)	
occurrences (all)	1	2	
Pulmonary hypertension			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Pulmonary embolism			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Respiratory failure			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Tachypnoea			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Wheezing			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Aggression			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences (all)	1	1	
affective disorder			

subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Anxiety			
subjects affected / exposed	9 / 167 (5.39%)	12 / 167 (7.19%)	
occurrences (all)	9	12	
Confusional state			
subjects affected / exposed	0 / 167 (0.00%)	2 / 167 (1.20%)	
occurrences (all)	0	2	
Depression			
subjects affected / exposed	3 / 167 (1.80%)	3 / 167 (1.80%)	
occurrences (all)	3	3	
Hallucination, visual			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
hyperexcitation			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
hypomania			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	10 / 167 (5.99%)	7 / 167 (4.19%)	
occurrences (all)	11	8	
Mood altered			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
nervousness			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Nightmare			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Sleep disorder			
subjects affected / exposed	5 / 167 (2.99%)	3 / 167 (1.80%)	
occurrences (all)	5	3	
Logorrhoea			

subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Psychiatric symptom			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Investigations			
Lymphocyte count decreased			
subjects affected / exposed	2 / 167 (1.20%)	1 / 167 (0.60%)	
occurrences (all)	3	1	
Neutrophil count decreased			
subjects affected / exposed	6 / 167 (3.59%)	7 / 167 (4.19%)	
occurrences (all)	8	7	
Platelet count decreased			
subjects affected / exposed	2 / 167 (1.20%)	1 / 167 (0.60%)	
occurrences (all)	2	1	
White blood cell count decreased			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences (all)	1	1	
Angina pectoris			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Alanine aminotransferase decreased			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 167 (0.00%)	4 / 167 (2.40%)	
occurrences (all)	0	4	
Aspartate aminotransferase decreased			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Gamma-glutamyltransferase increased			

subjects affected / exposed	0 / 167 (0.00%)	3 / 167 (1.80%)	
occurrences (all)	0	5	
Blood creatinine increased			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences (all)	1	1	
Blood phosphorus decreased			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 167 (1.20%)	0 / 167 (0.00%)	
occurrences (all)	2	0	
C-reactive protein increased			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Staphylococcus test positive			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	5 / 167 (2.99%)	1 / 167 (0.60%)	
occurrences (all)	5	1	
Weight increased			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences (all)	1	1	
Injury, poisoning and procedural complications			
fall			
subjects affected / exposed	2 / 167 (1.20%)	2 / 167 (1.20%)	
occurrences (all)	2	2	
Intentional product misuse			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Fracture			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Subcutaneous haematoma			

subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Tooth fracture			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Bradycardia			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences (all)	1	1	
Palpitations			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences (all)	1	1	
Tachycardia			
subjects affected / exposed	1 / 167 (0.60%)	4 / 167 (2.40%)	
occurrences (all)	1	4	
Sinus tachycardia			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Chest pain			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Ageusia			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Cognitive disorder			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences (all)	1	1	
Dizziness			
subjects affected / exposed	2 / 167 (1.20%)	4 / 167 (2.40%)	
occurrences (all)	2	4	
Dysaesthesia			

subjects affected / exposed	4 / 167 (2.40%)	3 / 167 (1.80%)	
occurrences (all)	4	3	
Dysgeusia			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Extrapyramidal disorder			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	13 / 167 (7.78%)	9 / 167 (5.39%)	
occurrences (all)	14	10	
Hypoaesthesia			
subjects affected / exposed	3 / 167 (1.80%)	3 / 167 (1.80%)	
occurrences (all)	3	3	
Migraine			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Neuralgia			
subjects affected / exposed	0 / 167 (0.00%)	2 / 167 (1.20%)	
occurrences (all)	0	2	
Neuropathy peripheral			
subjects affected / exposed	40 / 167 (23.95%)	63 / 167 (37.72%)	
occurrences (all)	51	82	
Neurotoxicity			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Optic neuritis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	18 / 167 (10.78%)	25 / 167 (14.97%)	
occurrences (all)	18	28	
Peripheral motor neuropathy			
subjects affected / exposed	1 / 167 (0.60%)	2 / 167 (1.20%)	
occurrences (all)	1	2	
Peripheral nerve palsy			

subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences (all)	1	1	
Peripheral sensorimotor neuropathy			
subjects affected / exposed	0 / 167 (0.00%)	3 / 167 (1.80%)	
occurrences (all)	0	6	
Polyneuropathy			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Presyncope			
subjects affected / exposed	1 / 167 (0.60%)	2 / 167 (1.20%)	
occurrences (all)	1	2	
Radicular syndrome			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Sciatica			
subjects affected / exposed	4 / 167 (2.40%)	1 / 167 (0.60%)	
occurrences (all)	4	1	
Somnolence			
subjects affected / exposed	1 / 167 (0.60%)	3 / 167 (1.80%)	
occurrences (all)	1	3	
syncope			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
tremor			
subjects affected / exposed	2 / 167 (1.20%)	8 / 167 (4.79%)	
occurrences (all)	2	9	
Agitation			
subjects affected / exposed	6 / 167 (3.59%)	3 / 167 (1.80%)	
occurrences (all)	6	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	26 / 167 (15.57%)	22 / 167 (13.17%)	
occurrences (all)	37	22	
Bone marrow failure			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	

Febrile bone marrow aplasia			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Febrile neutropenia			
subjects affected / exposed	4 / 167 (2.40%)	1 / 167 (0.60%)	
occurrences (all)	4	1	
Leukopenia			
subjects affected / exposed	12 / 167 (7.19%)	5 / 167 (2.99%)	
occurrences (all)	16	5	
Leukocytosis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Lymphopenia			
subjects affected / exposed	53 / 167 (31.74%)	43 / 167 (25.75%)	
occurrences (all)	135	72	
Neutropenia			
subjects affected / exposed	42 / 167 (25.15%)	21 / 167 (12.57%)	
occurrences (all)	72	29	
Thrombocytopenia			
subjects affected / exposed	19 / 167 (11.38%)	11 / 167 (6.59%)	
occurrences (all)	30	11	
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Tinnitus			
subjects affected / exposed	2 / 167 (1.20%)	2 / 167 (1.20%)	
occurrences (all)	2	2	
Vertigo			
subjects affected / exposed	3 / 167 (1.80%)	4 / 167 (2.40%)	
occurrences (all)	3	4	
Acute vestibular syndrome			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Ear pain			

subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
hearing impaired			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Chalazion			
subjects affected / exposed	3 / 167 (1.80%)	1 / 167 (0.60%)	
occurrences (all)	3	1	
Chromatopsia			
subjects affected / exposed	0 / 167 (0.00%)	2 / 167 (1.20%)	
occurrences (all)	0	2	
Conjunctival haemorrhage			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Eyelid oedema			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Keratitis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Uveitis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Vision blurred			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences (all)	1	1	
Visual acuity reduced			
subjects affected / exposed	0 / 167 (0.00%)	2 / 167 (1.20%)	
occurrences (all)	0	2	
Visual impairment			
subjects affected / exposed	1 / 167 (0.60%)	2 / 167 (1.20%)	
occurrences (all)	1	2	
Eye pruritus			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	

Miosis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Photophobia			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 167 (1.20%)	1 / 167 (0.60%)	
occurrences (all)	2	1	
Abdominal pain			
subjects affected / exposed	4 / 167 (2.40%)	5 / 167 (2.99%)	
occurrences (all)	4	5	
Abdominal pain upper			
subjects affected / exposed	7 / 167 (4.19%)	5 / 167 (2.99%)	
occurrences (all)	7	5	
aphthous stomatitis			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences (all)	1	1	
Constipation			
subjects affected / exposed	35 / 167 (20.96%)	59 / 167 (35.33%)	
occurrences (all)	39	68	
Diarrhoea			
subjects affected / exposed	21 / 167 (12.57%)	8 / 167 (4.79%)	
occurrences (all)	21	8	
Dry mouth			
subjects affected / exposed	0 / 167 (0.00%)	2 / 167 (1.20%)	
occurrences (all)	0	2	
Dysgeusia			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences (all)	1	1	
Dyspepsia			
subjects affected / exposed	6 / 167 (3.59%)	5 / 167 (2.99%)	
occurrences (all)	6	5	
Diverticulum intestinal			

subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Duodenogastric reflux			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Flatulence			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorder			
subjects affected / exposed	4 / 167 (2.40%)	2 / 167 (1.20%)	
occurrences (all)	4	2	
dysphagia			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Eructation			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Gastrointestinal motility disorder			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Impaired gastric emptying			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Intestinal dilatation			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Mouth ulceration			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	2	0	
Nausea			

subjects affected / exposed	47 / 167 (28.14%)	39 / 167 (23.35%)	
occurrences (all)	54	43	
Oesophagitis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Oral discomfort			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Rectal haemorrhage			
subjects affected / exposed	1 / 167 (0.60%)	2 / 167 (1.20%)	
occurrences (all)	1	2	
Rectal prolapse			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Stomatitis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	16 / 167 (9.58%)	12 / 167 (7.19%)	
occurrences (all)	18	12	
Tongue discolouration			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Tooth demineralisation			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Hepatocellular injury			
subjects affected / exposed	0 / 167 (0.00%)	6 / 167 (3.59%)	
occurrences (all)	0	6	
Cholelithiasis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Drug-induced liver injury			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	

Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 167 (1.80%)	6 / 167 (3.59%)	
occurrences (all)	3	6	
Decubitus ulcer			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Dermatitis acneiform			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Dermatitis allergic			
subjects affected / exposed	0 / 167 (0.00%)	2 / 167 (1.20%)	
occurrences (all)	0	2	
Dermatitis contact			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Dry skin			
subjects affected / exposed	2 / 167 (1.20%)	3 / 167 (1.80%)	
occurrences (all)	2	3	
Ecchymosis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Eczema			
subjects affected / exposed	0 / 167 (0.00%)	3 / 167 (1.80%)	
occurrences (all)	0	3	
Erythema			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences (all)	1	1	
Hand dermatitis			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences (all)	1	1	
Hidradenitis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Hyperhidrosis			

subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Macule			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Mucocutaneous rash			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Nail disorder			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Night sweats			
subjects affected / exposed	2 / 167 (1.20%)	1 / 167 (0.60%)	
occurrences (all)	2	1	
Pruritus			
subjects affected / exposed	2 / 167 (1.20%)	4 / 167 (2.40%)	
occurrences (all)	2	4	
Rash			
subjects affected / exposed	12 / 167 (7.19%)	14 / 167 (8.38%)	
occurrences (all)	13	14	
Rash maculo-papular			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Rash papular			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Rash pruritic			
subjects affected / exposed	0 / 167 (0.00%)	2 / 167 (1.20%)	
occurrences (all)	0	2	
Skin disorder			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Skin reaction			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Swelling face			

subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences (all)	1	1	
Toxic skin eruption			
subjects affected / exposed	1 / 167 (0.60%)	2 / 167 (1.20%)	
occurrences (all)	1	2	
Urticaria			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Bladder discomfort			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Cystitis haemorrhagic			
subjects affected / exposed	2 / 167 (1.20%)	0 / 167 (0.00%)	
occurrences (all)	2	0	
Dysuria			
subjects affected / exposed	4 / 167 (2.40%)	1 / 167 (0.60%)	
occurrences (all)	4	1	
Haematuria			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Nocturia			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Oliguria			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Pollakiuria			
subjects affected / exposed	2 / 167 (1.20%)	0 / 167 (0.00%)	
occurrences (all)	2	0	
Proteinuria			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	

Renal failure			
subjects affected / exposed	1 / 167 (0.60%)	2 / 167 (1.20%)	
occurrences (all)	1	2	
Urinary incontinence			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Endocrine disorders			
Cushingoid			
subjects affected / exposed	2 / 167 (1.20%)	0 / 167 (0.00%)	
occurrences (all)	2	0	
Hyperthyroidism			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences (all)	1	1	
Hyperparathyroidism			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 167 (1.20%)	3 / 167 (1.80%)	
occurrences (all)	2	3	
back pain			
subjects affected / exposed	25 / 167 (14.97%)	22 / 167 (13.17%)	
occurrences (all)	25	22	
Bone lesion			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Bone pain			
subjects affected / exposed	8 / 167 (4.79%)	7 / 167 (4.19%)	
occurrences (all)	9	7	
Enthesopathy			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Groin pain			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences (all)	1	1	
Muscle spasms			

subjects affected / exposed	3 / 167 (1.80%)	3 / 167 (1.80%)	
occurrences (all)	3	3	
Musculoskeletal chest pain			
subjects affected / exposed	4 / 167 (2.40%)	7 / 167 (4.19%)	
occurrences (all)	4	7	
Musculoskeletal discomfort			
subjects affected / exposed	2 / 167 (1.20%)	0 / 167 (0.00%)	
occurrences (all)	2	0	
Myalgia			
subjects affected / exposed	5 / 167 (2.99%)	3 / 167 (1.80%)	
occurrences (all)	5	3	
Neck pain			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Osteoporosis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Osteonecrosis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	11 / 167 (6.59%)	9 / 167 (5.39%)	
occurrences (all)	11	11	
Pathological fracture			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Spinal pain			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Tendonitis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Synovial cyst			

subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Amnesia			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Aphonia			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Balance disorder			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Bacterial prostatitis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
BK virus infection cystitis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	13 / 167 (7.78%)	17 / 167 (10.18%)	
occurrences (all)	13	18	
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Cellulitis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Conjunctivitis			
subjects affected / exposed	3 / 167 (1.80%)	1 / 167 (0.60%)	
occurrences (all)	3	2	
Cystitis			
subjects affected / exposed	5 / 167 (2.99%)	1 / 167 (0.60%)	
occurrences (all)	5	1	

Cytomegalovirus infection			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Device related infection			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Ear infection viral			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Erysipelas			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	2	
Escherichia infection			
subjects affected / exposed	0 / 167 (0.00%)	3 / 167 (1.80%)	
occurrences (all)	0	3	
Escherichia vaginitis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Folliculitis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Fungal skin infection			
subjects affected / exposed	2 / 167 (1.20%)	0 / 167 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal candidiasis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Genital infection fungal			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Hordeolum			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Haemorrhoid infection			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	

Infected cyst			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
infection			
subjects affected / exposed	0 / 167 (0.00%)	3 / 167 (1.80%)	
occurrences (all)	0	4	
infectious colitis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	4 / 167 (2.40%)	2 / 167 (1.20%)	
occurrences (all)	4	2	
Laryngitis			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences (all)	1	1	
Localised infection			
subjects affected / exposed	2 / 167 (1.20%)	0 / 167 (0.00%)	
occurrences (all)	2	0	
Lung infection			
subjects affected / exposed	3 / 167 (1.80%)	0 / 167 (0.00%)	
occurrences (all)	3	0	
Nasal herpes			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	4 / 167 (2.40%)	8 / 167 (4.79%)	
occurrences (all)	4	8	
Oral candidiasis			
subjects affected / exposed	0 / 167 (0.00%)	2 / 167 (1.20%)	
occurrences (all)	0	2	
Oral fungal infection			
subjects affected / exposed	1 / 167 (0.60%)	4 / 167 (2.40%)	
occurrences (all)	1	4	
Osteitis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	

ophtalmic herpes zoster			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Orchitis			
subjects affected / exposed	3 / 167 (1.80%)	0 / 167 (0.00%)	
occurrences (all)	3	0	
Pharyngitis			
subjects affected / exposed	1 / 167 (0.60%)	2 / 167 (1.20%)	
occurrences (all)	1	2	
Pneumococcal sepsis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	2 / 167 (1.20%)	2 / 167 (1.20%)	
occurrences (all)	2	2	
PROSTATITIS			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences (all)	1	1	
Prostatitis Escherichia coli			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences (all)	1	1	
Puncture site infection			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	2 / 167 (1.20%)	4 / 167 (2.40%)	
occurrences (all)	2	4	
Salmonellosis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Sepsis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	0 / 167 (0.00%)	2 / 167 (1.20%)	
occurrences (all)	0	2	

Staphylococcal bacteraemia			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Subcutaneous abscess			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Streptococcal sepsis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Tongue fungal infection			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Tonsillitis			
subjects affected / exposed	1 / 167 (0.60%)	2 / 167 (1.20%)	
occurrences (all)	1	2	
Tooth abscess			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences (all)	1	1	
Tooth infection			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences (all)	1	1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	7 / 167 (4.19%)	1 / 167 (0.60%)	
occurrences (all)	7	1	
Vaginal infection			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 167 (0.00%)	2 / 167 (1.20%)	
occurrences (all)	0	2	

Thermal burn			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Alkalosis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Appetite disorder			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Cell death			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Decreased appetite			
subjects affected / exposed	3 / 167 (1.80%)	4 / 167 (2.40%)	
occurrences (all)	3	4	
Dehydration			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
gout			
subjects affected / exposed	1 / 167 (0.60%)	2 / 167 (1.20%)	
occurrences (all)	1	2	
Hypercalcaemia			
subjects affected / exposed	0 / 167 (0.00%)	4 / 167 (2.40%)	
occurrences (all)	0	4	
Hyperglycaemia			
subjects affected / exposed	2 / 167 (1.20%)	3 / 167 (1.80%)	
occurrences (all)	2	3	
Hyperphagia			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences (all)	1	1	
Hypertriglyceridaemia			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Hyperuricaemia			

subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 167 (0.60%)	1 / 167 (0.60%)	
occurrences (all)	1	1	
Hypocalcaemia			
subjects affected / exposed	4 / 167 (2.40%)	0 / 167 (0.00%)	
occurrences (all)	4	0	
Hypokalaemia			
subjects affected / exposed	2 / 167 (1.20%)	4 / 167 (2.40%)	
occurrences (all)	2	4	
Hypomagnesemia			
subjects affected / exposed	1 / 167 (0.60%)	3 / 167 (1.80%)	
occurrences (all)	1	3	
Hyponatraemia			
subjects affected / exposed	0 / 167 (0.00%)	4 / 167 (2.40%)	
occurrences (all)	0	5	
HYPOPHOSPHATEMIE			
subjects affected / exposed	2 / 167 (1.20%)	4 / 167 (2.40%)	
occurrences (all)	2	5	
Limb discomfort			
subjects affected / exposed	0 / 167 (0.00%)	2 / 167 (1.20%)	
occurrences (all)	0	2	
Musculoskeletal pain			
subjects affected / exposed	2 / 167 (1.20%)	5 / 167 (2.99%)	
occurrences (all)	2	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 July 2014	augmentation du nombre de centre, modification critère exclusion inclusion, précision sur le dose de G-CSF, ajout du droit de participer à l'étude AMG 162, précision sur la prise de Velcade en fonction du poids, sur les dispensations de Cyclophosphamide, mise à jour des toxicités du cyclophosphamide, précision sur les examens fait au screeninig, modification des données de rando, précision des délais pour réaliser les examens biologiques, modification de la quantité de sang à prélever pour analyses de cytogénétique et analyses bioschiliques, mise à jour de l'adresse de l'unité génomique de Toulouse
04 December 2014	prolongation de la période de recrutement
07 May 2015	prolongation de la période de suivi de l'étude (de 2 mois), changement de l'investigateur principal du centre de Poitiers

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27002117