Clinical trial results:
“Randomized, Multicenter, Open-label, Phase III Study of Plitidepsin in Combination with Dexamethasone vs. Dexamethasone Alone in Patients with Relapsed/Refractory Multiple Myeloma”.

Summary

EudraCT number	2009-016138-29
Trial protocol	FR GB ES AT NL DE BE CZ IT GR IE PT PL
Global end of trial date	20 November 2017

Results information

Result version number	v1 (current)
This version publication date	18 November 2018
First version publication date	18 November 2018

Trial information

Trial identification

Sponsor protocol code	APL-C-001-09

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01102426
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pharma Mar, S.A.
Sponsor organisation address	Avenida de los Reyes, 1 Polígono Industrial "La Mina", Colmenar Viejo, Madrid, Spain, 28770
Public contact	Clinical Developtment, Department of PharmaMar´s Oncology., Business Unit., Pharmamar, S.A. , 34 918466000, clinicaltrials@pharmamar.com
Scientific contact	Clinical Developtment, Department of PharmaMar´s Oncology., Business Unit., Pharmamar, S.A., 34 918466000, clinicaltrials@pharmamar.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	08 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 November 2015
Global end of trial reached?	Yes
Global end of trial date	20 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of plitidepsin in combination with dexamethasone vs. dexamethasone alone as measured by progression-free survival (PFS) in patients with relapsed/refractory multiple myeloma (MM).

Protection of trial subjects:

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

Background therapy:

All the patients have to receive DXM with or without Plitidepsin.
The administration of each study medication was as follows:
Arm A:
• DXM: 40 mg orally on Day 1, 8, 15 and 22 every four weeks (q4wk) at least one hour before plitidepsin infusion.
• Plitidepsin: 5 mg/m2 i.v. diluted to a total volume of 250 mL in 0.9% saline (or 5% glucose) via a central venous catheter (suggested) or diluted to a total volume of 500 mL in 0.9% saline (or 5% glucose) via a peripheral line.
Infusion was performed through a pump device over three hours (fixed rate) on Day 1 and 15 q4wk.
Arm B:
• DXM: 40 mg orally on Day 1, 8, 15 and 22 q4wk.
A cycle was defined as a four-week period

Evidence for comparator: -

Actual start date of recruitment	29 June 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	Austria: 28
Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Czech Republic: 33
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 9

Country: Number of subjects enrolled	Greece: 19
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Korea, Republic of: 12
Country: Number of subjects enrolled	New Zealand: 8
Country: Number of subjects enrolled	Australia: 37
Country: Number of subjects enrolled	United States: 7
Country: Number of subjects enrolled	Taiwan: 12
Worldwide total number of subjects	255
EEA total number of subjects	179

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)	124
From 65 to 84 years	129
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

A total of 255 patients were enrolled. 171 Group A (Plitidepsin in combination with DXM) and 84 Group B (DXM alone).
Enrolled patients between 29Jun10 and 19May15 (Last randomization). The first dose of the first patient was given on 19May15 and the last dose of the last patient was given on 07Aug17.

Pre-assignment

Screening details:

IC Signed,Age ≥18,ECOG PS≤2,Life expectancy≥3 mo,Previously diagnosed MM,Relapsed or relapsed and refractory MM between 3&6,Previous bortezomib-containing and lenalidomide containing regimens,Measurable disease,At least 2week washout period since end last therapy,Adequate BM,renal, hepatic&metabolic,Normal LVEF by ECHO/MUGA,negative pregnancy test

Period 1

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

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A (plitidepsin plus DXM)

Arm description:

Arm A (plitidepsin plus DXM)

Arm type	Experimental
Investigational medicinal product name	Aplidin
Investigational medicinal product code	
Other name	Plitidepsin
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

5 mg/m2 i.v. diluted to a total volume of 250 mL in 0.9% saline(or 5% glucose) via a central venous catheter (suggested) or diluted to a total volume of 500 mL in 0.9% saline (or 5% glucose) via a peripheral line.
Infusion was performed through a pump device over three hours (fixed rate) on Day 1 and 15 q4wk.

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

Dosage and administration details:

40 mg orally on Day 1, 8, 15 and 22 every four weeks (q4wk) at least one hour before plitidepsin infusion.

Arm title	Arm B (DXM alone)

Arm description:

Arm B (DXM alone)

Arm type	Active comparator

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

Dosage and administration details:

DXM: 40 mg orally on Day 1, 8, 15 and 22 q4wk.

Number of subjects in period 1	Arm A (plitidepsin plus DXM)	Arm B (DXM alone)
Started	171	84
Completed	0	0
Not completed	171	84
Physician decision	7	4
Consent withdrawn by subject	24	6
Toxicity	15	3
Randomized but not treated	4	1
Death	20	5
Other	22	10
Progressive Disease	79	18
Transferred to other arm/group	-	37

Baseline characteristics

Reporting groups	
Reporting group title	Arm A (plitidepsin plus DXM)
Reporting group description: Arm A (plitidepsin plus DXM)	
Reporting group title	Arm B (DXM alone)
Reporting group description: Arm B (DXM alone)	

Reporting group values	Arm A (plitidepsin plus DXM)	Arm B (DXM alone)	Total
Number of subjects	171	84	255
Age categorical			
Years			
Units: Subjects			
Adults (18-64 years)	88	36	124
From 65-84 years	82	47	129
85 years and over	1	1	2
Age continuous			
Units: years			
median	64.0	65.0	
full range (min-max)	36 to 85	42 to 85	-
Gender categorical			
Units: Subjects			
Female	74	49	123
Male	97	35	132
ECOG PS			
PS Performance status			
Units: Subjects			
PS 0	68	31	99
PS 1	74	42	116
PS 2	28	11	39
PS 3	1	0	1
MM type at diagnosis			
Units: Subjects			
Non Secretory	6	1	7
Secretory IgA	35	21	56
Secretory IgD	1	1	2
Secretory IgG	101	51	152
Secretory IgM	1	0	1
Secretory Light chain disease	27	10	37
Durie-Salmon stage at diagnosis			
Units: Subjects			
Stage A	0	1	1
Stage IA	21	9	30
Stage IB	0	2	2
Stage II	3	1	4
Stage IIA	44	20	64

Stage IIB	1	0	1
Stage III	2	1	3
Stage IIIA	85	43	128
Stage IIIB	14	7	21
Not Durie-Salmon stage at diagnosis	1	0	1
ISS stage at diagnosis			
Units: Subjects			
Stage I	72	33	105
Stage II	41	18	59
Stage III	23	15	38
Not ISS stage at diagnosis	35	18	53
Cytogenetic risk group at diagnosis			
NA: not available; ND: not done; UK: unknown.			
Units: Subjects			
Standard risk	34	21	55
High risk	38	16	54
NA/ND/UK	99	47	146
Prior radiotherapy			
Units: Subjects			
Yes	68	35	103
No	103	49	152
Hb			
Units: g/dL			
median	10.4	10.1	
full range (min-max)	7.0 to 14.6	7.4 to 14.6	-
Platelets			
Units: 10^9/L			
median	140	154	
full range (min-max)	11.0 to 517.0	24.0 to 452.0	-
CrCL			
creatinine clearance			
Units: mL/min			
median	72.9	69.4	
full range (min-max)	21.9 to 252.2	23.0 to 137.0	-
Time from first diagnosis to randomization			
Units: months			
median	71.8	70.0	
full range (min-max)	0.1 to 277.2	19.5 to 178.9	-
Time from last PD/relapse to first study dose			
PD, Progressive disease			
Units: weeks			
median	6.1	6.4	
full range (min-max)	-0.4 to 83.1	1.0 to 101.7	-
Beta-2 microglobulin			
Units: mg/L			
median	4.1	4.2	
full range (min-max)	0.0 to 27.3	0.2 to 65.0	-
Number of lines of prior systemic therapy			

Units: Lines			
median	4	4	
full range (min-max)	2 to 6	3 to 7	-

End points

End points reporting groups

Reporting group title	Arm A (plitidepsin plus DXM)
Reporting group description: Arm A (plitidepsin plus DXM)	
Reporting group title	Arm B (DXM alone)
Reporting group description: Arm B (DXM alone)	

Primary: Progression-free Survival (Independent Review Committee)

End point title	Progression-free Survival (Independent Review Committee)

End point description:

The primary study analysis was based on externally assessed PFS data (An external IRC, blinded to treatment arm, assigned a progression or censoring date for each patient based on laboratory data and radiological and bone marrow assessments when required, and evaluation of all relevant clinical information, according to a predefined algorithm) in the ITT efficacy population, defined as all patients randomized to either treatment arm. PFS was calculated from randomization to the first evidence of PD (IMWG criteria) or death due to any cause.
If the patient received further antitumor therapy before PD, PFS was censored on the date of the last disease assessment prior to the administration.
If the patient was lost to follow-up , the PFS was censored at the date of last valid tumor assessment before the missing evaluations.
Event was assigned as the first time a PD is reported without the necessity of its confirmation.

End point type	Primary

End point timeframe:

Overall period - IRC-All Randomized Patients

End point values	Arm A (plitidepsin plus DXM)	Arm B (DXM alone)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	84		
Units: months				
median (confidence interval 95%)	2.6 (1.9 to 3.0)	1.7 (1.1 to 2.0)		

Statistical analyses

Statistical analysis title	Arm A compared to Arm B
Comparison groups	Arm B (DXM alone) v Arm A (plitidepsin plus DXM)

Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0054 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.477
upper limit	0.885

Notes:

[1] - PFS at 6 months (95% CI): Arm A: 20.0% (13.1-26.9%) vs Arm B: 10.0% (2.0-18.0%); p=0.0618

[2] - Cox regression: HR p=0.0062

Secondary: Progression-free Survival (Investigator assessment)

End point title	Progression-free Survival (Investigator assessment)

End point description:

The secondary study analysis was based on Investigator's assessment PFS data in the ITT efficacy population, defined as all patients randomized to either treatment arm. PFS was calculated from randomization to the first evidence of PD (IMWG criteria) or death due to any cause. If the patient received further antitumor therapy before PD and within the timeframe expected for first follow-up, PFS was censored on the date of the last disease assessment prior to the administration of this antitumor therapy. If the patient was lost to follow-up for the assessment of progression, or had more than one missing follow-up between the date of last tumor assessment and the date of progression, death or further antitumor therapy, the PFS was censored at the date of last valid tumor assessment before the missing evaluations. Event was assigned as the first time a PD is reported without the necessity of its confirmation.

End point type	Secondary

End point timeframe:

Overall period - IA - All Randomized Patients

End point values	Arm A (plitidepsin plus DXM)	Arm B (DXM alone)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	84		
Units: months				
median (confidence interval 95%)	2.9 (2.1 to 3.7)	1.1 (1.0 to 1.9)		

Statistical analyses

Statistical analysis title	Arm A compared to Arm B
Comparison groups	Arm A (plitidepsin plus DXM) v Arm B (DXM alone)

Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.512
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.382
upper limit	0.686

Notes:

[3] - PFS at 6 months (95% CI): Arm A: 26.4% (19.1-33.7%) vs Arm B: 8.1% (1.9-14.3%); p=0.0002

[4] - Cox regression HR: p<0.0001

Secondary: Best Overall Response (Independent Review Committee)

End point title	Best Overall Response (Independent Review Committee)

End point description:

CR; complete response; DXM, dexamethasone; MR; minor response; NE, not evaluable; ORR, overall response rate; P, plitidepsin; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD; stable disease; VGPR, very good partial response.

End point type	Secondary

End point timeframe:

Overall period

End point values	Arm A (plitidepsin plus DXM)	Arm B (DXM alone)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	84		
Units: subjects				
VGPR	2	0		
PR	15	1		
MR	22	2		
SD	43	21		
PD	41	35		
NE	48	25		

Statistical analyses

Statistical analysis title	Overall response rate
Comparison groups	Arm A (plitidepsin plus DXM) v Arm B (DXM alone)

Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.0001
Method	Fisher exact

Notes:

[5] - ORR (95% CI): Arm A: 22.8% (16.8-29.8%) vs Arm B: 3.6% (0.7-10.1%); p<0.0001
ORR (excluding MR) (95% CI): Arm A: 9.9% (5.9-15.4%) vs Arm B: 1.2% (0.03-6.5%); p=0.0085

Secondary: Duration of Response (Independent Review Committee)

End point title	Duration of Response (Independent Review Committee)

End point description:

DR was calculated from the date of first documentation of response to the date of disease progression or death. The same censoring rules described above for PFS calculation were also considered for DR.

End point type	Secondary

End point timeframe:

Overall period - IRC- All Responder Patients

End point values	Arm A (plitidepsin plus DXM)	Arm B (DXM alone)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39[6]	3[7]		
Units: months				
median (confidence interval 95%)	3.7 (2.7 to 10.5)	1.8 (1.8 to 5.5)		

Notes:

[6] - Responder Patients

[7] - Responder Patients

Statistical analyses

Statistical analysis title	Arm A compared to Arm B
Comparison groups	Arm A (plitidepsin plus DXM) v Arm B (DXM alone)
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.1015 [9]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.384
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.113
upper limit	1.303

Notes:

[8] - DR at 6 months (95% CI): Arm A: 41.2% (24.6-57.7%) vs 0.0% (0.0-.%)

[9] - Cox regression HR: 0.1247

Secondary: Overall survival

End point title	Overall survival

End point description:

OS was defined as the time from the date of randomization to the date of death or last contact

End point type	Secondary

End point timeframe:

Overall period - All Randomized Patients

End point values	Arm A (plitidepsin plus DXM)	Arm B (DXM alone)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	84		
Units: months				
median (confidence interval 95%)	11.6 (9.2 to 16.1)	8.9 (6.0 to 15.4)		

Statistical analyses

Statistical analysis title	Arm A compared to Arm B
Comparison groups	Arm A (plitidepsin plus DXM) v Arm B (DXM alone)
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.1261 [11]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.797
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.596
upper limit	1.067

Notes:

[10] - OS at 12 months (95% CI): Arm A: 48.3% (40.4-56.2%) vs Arm B: 42.1% (31.3-52.9%); p=0.3625
OS at 24 months (95% CI): Arm A: 30.8% (23.3-38.3%) vs Arm B: 21.0% (12.0-30.1%); p=0.1037
[11] - Cox regression HR: p=0.1273

Secondary: Best Overall Response (Investigator assessment)

End point title	Best Overall Response (Investigator assessment)

End point description:

CR; complete response; DXM, dexamethasone; MR; minor response; NE, not evaluable; ORR, overall response rate; P, plitidepsin; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD; stable disease; VGPR, very good partial resp

End point type	Secondary

End point timeframe:

Overall period

End point values	Arm A (plitidepsin plus DXM)	Arm B (DXM alone)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	84		
Units: subjects				
VGPR	4	0		
PR	16	1		
MR	31	0		
SD	61	31		
PD	37	39		
NE	22	13		

Statistical analyses

Statistical analysis title	Overall response rate
Comparison groups	Arm A (plitidepsin plus DXM) v Arm B (DXM alone)
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	< 0.0001
Method	Fisher exact

Notes:

[12] - ORR (95% CI): Arm A: 29.8% (23.1-37.3%) vs Arm B: 1.2% (0.03-6.5%); p<0.0001
ORR (excluding MR) (95% CI): Arm A: 11.7% (7.3-17.5%) vs Arm B: 1.2% (0.03-6.5%); p=0.0029

Secondary: Duration of Response (Investigator assessment)

End point title	Duration of Response (Investigator assessment)

End point description:

DR was calculated from the date of first documentation of response to the date of disease progression or death. The same censoring rules described above for PFS calculation were also considered for DR.

End point type	Secondary

End point timeframe:

Overall period

End point values	Arm A (plitidepsin plus DXM)	Arm B (DXM alone)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[13]	1[14]		
Units: months				
median (confidence interval 95%)	5.1 (3.2 to 6.2)	0.9 (-999 to 999)		

Notes:

[13] - Responder Patients

[14] - Responder Patients
-999,999 = Interval could not be calculated

Statistical analyses

Statistical analysis title	Arm A compared to Arm B
Comparison groups	Arm B (DXM alone) v Arm A (plitidepsin plus DXM)
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.0001 [16]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.043
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.004
upper limit	0.479

Notes:

[15] - DR at 6 months (95% CI): Arm A: 38.2% (23.7-52.8%) vs 0.0% (0.0-.%)

[16] - Cox regression HR: 0.0105

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Overall period	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	Arm A (plitidepsin plus DXM)
Reporting group description:	
Arm A (plitidepsin plus DXM)	
Reporting group title	Arm B (DXM alone)
Reporting group description:	
Arm B (DXM alone)	

Serious adverse events	Arm A (plitidepsin plus DXM)	Arm B (DXM alone)	
Total subjects affected by serious adverse events			
subjects affected / exposed	99 / 167 (59.28%)	26 / 83 (31.33%)	
number of deaths (all causes)	126	74	
number of deaths resulting from adverse events	23	5	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Oesophageal squamous cell carcinoma			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasmablastic lymphoma			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (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	1 / 167 (0.60%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (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	0 / 167 (0.00%)	1 / 83 (1.20%)	
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	4 / 167 (2.40%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	3 / 167 (1.80%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 167 (1.20%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			

subjects affected / exposed	2 / 167 (1.20%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pain			
subjects affected / exposed	2 / 167 (1.20%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	8 / 167 (4.79%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	2 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis in device			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 167 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 167 (1.20%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			

subjects affected / exposed	2 / 167 (1.20%)	2 / 83 (2.41%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Productive cough			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			

subjects affected / exposed	0 / 167 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	1 / 167 (0.60%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 167 (4.19%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	10 / 10	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 167 (3.59%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	12 / 12	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood creatine phosphokinase MB increased			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	6 / 167 (3.59%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	8 / 9	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	3 / 167 (1.80%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 167 (1.20%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme abnormal			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin I increased			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cells increased			
subjects affected / exposed	0 / 167 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Drug administration error			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sternal fracture			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion reaction			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	0 / 167 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 167 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Upper limb fracture			
subjects affected / exposed	0 / 167 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 167 (1.20%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	3 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 167 (1.20%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Cardiac failure			
subjects affected / exposed	3 / 167 (1.80%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systolic dysfunction			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			

subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Headache			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (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 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paresis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Quadriparesis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (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	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 167 (1.20%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic neuropathy			
subjects affected / exposed	0 / 167 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Memory impairment			
subjects affected / exposed	0 / 167 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 167 (1.80%)	3 / 83 (3.61%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperviscosity syndrome			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (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			
subjects affected / exposed	1 / 167 (0.60%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 167 (1.80%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	4 / 167 (2.40%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	1 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	6 / 167 (3.59%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	3 / 8	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	3 / 167 (1.80%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	4 / 167 (2.40%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	3 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal failure acute			
subjects affected / exposed	2 / 167 (1.20%)	3 / 83 (3.61%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Calculus urinary			

subjects affected / exposed	0 / 167 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure chronic			
subjects affected / exposed	0 / 167 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 167 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	3 / 167 (1.80%)	0 / 83 (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 / 167 (0.60%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mobility decreased			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			

subjects affected / exposed	2 / 167 (1.20%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myopathy			
subjects affected / exposed	2 / 167 (1.20%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Myopathy toxic			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteolysis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	2 / 167 (1.20%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Atypical pneumonia			

subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 167 (0.60%)	2 / 83 (2.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 167 (1.20%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	2 / 167 (1.20%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Device related infection			
subjects affected / exposed	2 / 167 (1.20%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			

subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	2 / 167 (1.20%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 167 (0.60%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung infection			

subjects affected / exposed	2 / 167 (1.20%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jiroveci pneumonia			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	15 / 167 (8.98%)	3 / 83 (3.61%)	
occurrences causally related to treatment / all	9 / 18	0 / 3	
deaths causally related to treatment / all	0 / 3	0 / 1	
Pneumonia fungal			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	2 / 167 (1.20%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pseudomonal bacteraemia			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas infection			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	3 / 167 (1.80%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Sepsis			
subjects affected / exposed	9 / 167 (5.39%)	2 / 83 (2.41%)	
occurrences causally related to treatment / all	3 / 9	2 / 2	
deaths causally related to treatment / all	0 / 5	0 / 0	
Septic shock			
subjects affected / exposed	4 / 167 (2.40%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	4 / 167 (2.40%)	2 / 83 (2.41%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 167 (0.60%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium colitis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			

subjects affected / exposed	0 / 167 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Clostridium difficile infection			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (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			
Decreased appetite			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	3 / 167 (1.80%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	6 / 167 (3.59%)	2 / 83 (2.41%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			

subjects affected / exposed	4 / 167 (2.40%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			
subjects affected / exposed	1 / 167 (0.60%)	0 / 83 (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 A (plitidepsin plus DXM)	Arm B (DXM alone)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	161 / 167 (96.41%)	80 / 83 (96.39%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	22 / 167 (13.17%)	0 / 83 (0.00%)	
occurrences (all)	48	0	
Aspartate aminotransferase increased			
subjects affected / exposed	11 / 167 (6.59%)	0 / 83 (0.00%)	
occurrences (all)	20	0	
Blood creatine phosphokinase increased			
subjects affected / exposed	28 / 167 (16.77%)	0 / 83 (0.00%)	
occurrences (all)	41	0	
Electrocardiogram QT prolonged			
subjects affected / exposed	15 / 167 (8.98%)	1 / 83 (1.20%)	
occurrences (all)	34	1	
Weight decreased			
subjects affected / exposed	12 / 167 (7.19%)	1 / 83 (1.20%)	
occurrences (all)	13	1	
Platelet count decreased			

subjects affected / exposed	7 / 167 (4.19%)	5 / 83 (6.02%)	
occurrences (all)	67	21	
Vascular disorders			
Hypertension			
subjects affected / exposed	14 / 167 (8.38%)	5 / 83 (6.02%)	
occurrences (all)	17	6	
Hypotension			
subjects affected / exposed	16 / 167 (9.58%)	1 / 83 (1.20%)	
occurrences (all)	17	1	
Nervous system disorders			
Headache			
subjects affected / exposed	18 / 167 (10.78%)	5 / 83 (6.02%)	
occurrences (all)	18	6	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	69 / 167 (41.32%)	34 / 83 (40.96%)	
occurrences (all)	203	97	
Neutropenia			
subjects affected / exposed	12 / 167 (7.19%)	2 / 83 (2.41%)	
occurrences (all)	26	3	
Thrombocytopenia			
subjects affected / exposed	15 / 167 (8.98%)	8 / 83 (9.64%)	
occurrences (all)	47	15	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	32 / 167 (19.16%)	9 / 83 (10.84%)	
occurrences (all)	60	11	
Chest pain			
subjects affected / exposed	9 / 167 (5.39%)	2 / 83 (2.41%)	
occurrences (all)	12	2	
Fatigue			
subjects affected / exposed	55 / 167 (32.93%)	18 / 83 (21.69%)	
occurrences (all)	95	22	
Oedema peripheral			
subjects affected / exposed	31 / 167 (18.56%)	5 / 83 (6.02%)	
occurrences (all)	45	6	

Pyrexia			
subjects affected / exposed	32 / 167 (19.16%)	11 / 83 (13.25%)	
occurrences (all)	50	14	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	16 / 167 (9.58%)	1 / 83 (1.20%)	
occurrences (all)	16	1	
Constipation			
subjects affected / exposed	21 / 167 (12.57%)	5 / 83 (6.02%)	
occurrences (all)	23	7	
Diarrhoea			
subjects affected / exposed	57 / 167 (34.13%)	8 / 83 (9.64%)	
occurrences (all)	80	10	
Dyspepsia			
subjects affected / exposed	9 / 167 (5.39%)	4 / 83 (4.82%)	
occurrences (all)	12	5	
Nausea			
subjects affected / exposed	76 / 167 (45.51%)	17 / 83 (20.48%)	
occurrences (all)	122	19	
Vomiting			
subjects affected / exposed	41 / 167 (24.55%)	3 / 83 (3.61%)	
occurrences (all)	57	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	31 / 167 (18.56%)	9 / 83 (10.84%)	
occurrences (all)	42	10	
Dyspnoea			
subjects affected / exposed	23 / 167 (13.77%)	3 / 83 (3.61%)	
occurrences (all)	36	3	
Epistaxis			
subjects affected / exposed	10 / 167 (5.99%)	6 / 83 (7.23%)	
occurrences (all)	11	8	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	18 / 167 (10.78%)	10 / 83 (12.05%)	
occurrences (all)	23	11	

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 167 (4.79%)	6 / 83 (7.23%)	
occurrences (all)	8	6	
Back pain			
subjects affected / exposed	16 / 167 (9.58%)	15 / 83 (18.07%)	
occurrences (all)	18	22	
Bone pain			
subjects affected / exposed	12 / 167 (7.19%)	15 / 83 (18.07%)	
occurrences (all)	13	17	
Muscular weakness			
subjects affected / exposed	21 / 167 (12.57%)	3 / 83 (3.61%)	
occurrences (all)	27	5	
Musculoskeletal pain			
subjects affected / exposed	12 / 167 (7.19%)	1 / 83 (1.20%)	
occurrences (all)	14	1	
Myalgia			
subjects affected / exposed	30 / 167 (17.96%)	3 / 83 (3.61%)	
occurrences (all)	47	3	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 167 (2.99%)	5 / 83 (6.02%)	
occurrences (all)	5	5	
Upper respiratory tract infection			
subjects affected / exposed	14 / 167 (8.38%)	5 / 83 (6.02%)	
occurrences (all)	19	5	
Urinary tract infection			
subjects affected / exposed	12 / 167 (7.19%)	2 / 83 (2.41%)	
occurrences (all)	13	2	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	34 / 167 (20.36%)	5 / 83 (6.02%)	
occurrences (all)	40	5	
Hypercalcaemia			
subjects affected / exposed	8 / 167 (4.79%)	7 / 83 (8.43%)	
occurrences (all)	9	11	

Hyperglycaemia			
subjects affected / exposed	11 / 167 (6.59%)	3 / 83 (3.61%)	
occurrences (all)	16	3	
Hypokalaemia			
subjects affected / exposed	19 / 167 (11.38%)	5 / 83 (6.02%)	
occurrences (all)	23	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 December 2010	This protocol amendment included the following changes: -A retrospective analysis performed in all adult patients treated with single-agent plitidepsin in phase I (at the recommended dose) and phase II clinical trials showed plitidepsin administration through a peripheral vein safe enough to be considered in this q3wk schedule whenever a central venous line was deemed unsuitable for any reason (e.g., coagulation problems, technical difficulties, patient's refusal, etc.). Therefore, central venous catheter administration was suggested, but peripheral lines were also accepted. -The exact binomial 95% CI for RR was provided to clarify futility analysis rules, as requested by the IDMC. -Patient eligibility criteria were modified to allow inclusion of patients with stable atrial fibrillation, or patients with controlled infection on antibiotics. -Some assessment and procedures were modified: 1 To allow determination of direct bilirubin only if total bilirubin was above ULN. 2 To extend from 14 to 28 days the timeframe for some baseline disease evaluation assessments (bone marrow, serum and urinary protein determinations, and radiological assessment in case of plasmacytomas); to clarify X-ray as the myeloma skeletal evaluation method; 3 Following a request by the French Health Authorities as to be consistent with the information reported in the Investigator's Brochure of plitidepsin regarding coagulation tests monitoring, the sentence "close monitoring of patients taking oral anticoagulants is required" was added into the footnotes of the "Schedule of Assessments and Procedures" table and to the section "Concomitant Medication". 4 Corrected in this amendment: IVRS system was used always in this trial, but due to a mistake during writing, v 1.0 of the protocol referred in the Patient Registration Section to a manual model (fast fact sheet). -A clarification regarding the extraction of PK blood samples was made.

12 April 2013	This protocol amendment included the following changes: -An update of study contact details and study timelines. -The implementation of the determination of direct bilirubin only if total bilirubin was above the ULN. -An update of the instructions for the preparation (dilution) of plitidepsin, in order to make them consistent with the preparation guidelines and other related documents that allow dilution with 5% glucose. -The removal of the need for assessing the creatinine clearance (measured) at baseline and end of treatment, leaving just the calculated creatinine clearance included in Biochemistry A. -To allow skeletal evaluation at baseline and end of treatment or whenever required, by X-ray or CT-scan, as long as the same procedure is used throughout the study. -To allow phone contacts for patients during survival follow-up whenever the patient's disease was so serious that he/she was unable to attend the clinic. This only applied to patients who were followed up after discontinuing treatment due to PD. -The conduct of the QTc substudy to assess the potential effects of plitidepsin on the heart activity of patients enrolled in this clinical trial. In particular the QTc interval, based on electrocardiogram evaluation, was to be recorded and studied. -An update of the PK section of the protocol. -An update of the Safety section in accordance with current regulations. -An update of the telephone number used for reporting SAEs to the PV Service out of office hours. -The IMWG uniform criteria for MM were initially used to document disease progression or response to treatment. In the second study stage, this protocol amendment implemented the use of the updated IMWG criteria only, and to remove the Durie et al. IMWG version shown in App. 5. Therefore, the decision taken at that time was to not confirm PD in two assessments. Due to this reason, the analysis of the primary endpoint was to identify the first PD reported with no further confirmation

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

09 December 2012	An early futility analysis was performed when information from 40 patients in Arm A were evaluable for response. A response rate (IMWG criteria) of at least 30% (12 or more responses by IRC review) was taken as threshold for continuation of the study. A minimum response rate of 30% was considered as clinically significant in this setting. This result ensured that the lower limit of the exact binomial 95% CI for RR would be greater than 15% (95% CI in case of 12 responses would be 16.6%-46.5%). However, the information from all randomized patients in both arms at that time was used by the IDMC to evaluate the safety profile and to provide the Sponsor with a recommendation for the further study conduct. No claim for superiority in efficacy was to be formulated in this interim analysis and no alpha-spending for the analysis of PFS was foreseen. Accrual was to be on-hold while data for the futility analysis was assessed. For futility analysis based on objective RR, the All Evaluable Patients analysis dataset was used. On 9 December 2012, the evaluation by the IDMC of efficacy and safety data from the first 60 evaluable patients included in this study resulted in the recommendation to continue the trial unmodified, as the study met the established efficacy threshold of 30% response rate according to IMWG criteria pre-specified in the protocol (RR in Arm A, plitidepsin plus DXM, was 37.8%). No safety issues were reported. Therefore, patient accrual was resumed.	09 December 2012

Notes:

Limitations and caveats

None reported