Clinical trial results:
Phase II Trial of Plitidepsin (Aplidin®) in Combination with Bortezomib and Dexamethasone in Multiple Myeloma Patients Double Refractory to Bortezomib and Lenalidomide .

Summary

EudraCT number	2015-003486-29
Trial protocol	ES FR
Global end of trial date	30 July 2018

Results information

Result version number	v1 (current)
This version publication date	29 May 2019
First version publication date	29 May 2019

Trial information

Trial identification

Sponsor protocol code	APL-B-022-15

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03117361
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	15 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 July 2018
Global end of trial reached?	Yes
Global end of trial date	30 July 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of plitidepsin in combination with bortezomib and dexamethasone in patients with multiple myeloma (MM) double refractory to bortezomib and lenalidomide in terms of overall response rate (ORR), including stringent complete response (sCR), complete response (CR), very good partial response (VGPR) and partial response (PR).

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 patients had to receive the following i.v. prophylactic medication 30-60 minutes before each infusion of plitidepsin:
- Ondansetron 8 mg i.v. or equivalent,
- Diphenhydramine hydrochloride 25 mg i.v. or equivalent,
- Ranitidine 50 mg i.v. or equivalent.

If necessary, in addition to the above, 10 mg of metoclopramide every eight hours could be administered after the end of plitidepsin infusion or the duration of treatment with serotonin (5-HT3) antagonists and/or DXM could be extended.
Prophylactic antiemetic medication for BTZ was given according to the Investigator’s criteria. Herpes virus infection prophylaxis had to be given while the patients were on BTZ therapy.

Evidence for comparator:

-

Actual start date of recruitment	08 May 2017
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	Spain: 3
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Italy: 4
Worldwide total number of subjects	10
EEA total number of subjects	10

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)	8
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients participated between 15May2017-30Jul2018 (last follow-up cutoff date). The 1st dose/1st cycle was administered on 15May2017 and the last dose/last cycle on 23Jul2018. At cutoff date 10 patients had been included and treated with plitidepsin+BTZ+DXM and they were evaluable for safety. 8 of these were evaluable for the efficacy endpoint

Pre-assignment

Screening details:

IC signed;Age≥18 years;confirmed diagnosis of MM,ECOG PS≤2;LVEF≥45%;negative pregnancy test

Period 1

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

Blinding implementation details:

Not applicable

Arms

Arm title	Plitidepsin+BTZ+DXM

Arm description:

Plitidepsin was to be administered as a 3-hour (h) intravenous (i.v.) infusion at a dose of 5 mg/m2, on Day (D) 1 and 15, every four weeks (q4wk); BTZ was to be administered as a subcutaneous (s.c.) injection at a dose of 1.3 mg/m2 on D1, 4, 8 and 11, q4wk and DXM was to be taken orally at a dose of 40 mg/day on D1, 8, 15 and 22, q4wk. A cycle was defined as 28 days, plus any additional days required for dosing delays due to any reason. Treatment cycles were repeated q4wk.

Arm type	Experimental
Investigational medicinal product name	Plitidepsin
Investigational medicinal product code	Plitidepsin
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

3-hour i.v. infusion at a dose of 5 mg/m2 on Days 1 and 15 every four weeks (q4wk)

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

Dosage and administration details:

3-5-second bolus s.c. injection at a dose of 1.3 mg/m2 on Days 1, 4, 8 and 11 q4wk, one minute after the end of the plitidepsin infusion

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

Dosage and administration details:

at least one hour before the administration of plitidepsin infusion at a dose of 40 mg/day on Days 1, 8, 15 and 22 q4wk.

Number of subjects in period 1	Plitidepsin+BTZ+DXM
Started	10
Completed	0
Not completed	10
Physician decision	2
Death	1
Progressive disease	5
Treatment-related adverse event	1
On study treatment at the end of study	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall period

Reporting group description: -

Reporting group values	Overall period	Total	
Number of subjects	10	10	
Age categorical Units: Subjects			
Adults (18-64 years)	8	8	
From 65-84 years	2	2	
Age continuous Units: years			
median	59		
full range (min-max)	43 to 72	-	
Gender categorical Units: Subjects			
Female	5	5	
Male	5	5	
Race Units: Subjects			
White	7	7	
Other	3	3	
ECOG PS			
ECOG PS, Eastern Cooperative Oncology Group performance status			
Units: Subjects			
PS 0	5	5	
PS 1	4	4	
PS 2	1	1	
MM type at diagnosis			
MM, multiple myeloma			
Units: Subjects			
Secretory IgA	2	2	
Secretory IgG	4	4	
Secretory Kappa light-chain disease	2	2	
Secretory Lambda light-chain disease	2	2	
Durie-Salmon stage and subclassification at diagnosis			
Four patients had missing data in stage and sub-classification: 2 patients had no Durie-Salmon stage and sub-classification data at diagnosis; and 2 patients were stage III, but had no Durie-Salmon sub-classification at diagnosis.			
Units: Subjects			
IIA	2	2	
IIIA	3	3	
IIIB	1	1	
Missing	4	4	
ISS stage at diagnosis			
ISS, International Staging System			

Units: Subjects			
ISS I	1	1	
ISS II	1	1	
ISS III	4	4	
Not done	4	4	
R-ISS stage at study entry			
ISS, International Staging System			
Units: Subjects			
II (Not R-ISS I stage or III)	3	3	
III (ISS stage III and either high-risk CA)	3	3	
Non available genetic results	4	4	
Cytogenetic at study entry			
Units: Subjects			
High risk	2	2	
Standard risk	4	4	
Non available genetic results	4	4	
Disease status with respect to last prior therapy			
Total refractory MM included 2 categories of refractory: - Primary Refractory: disease that was non-responsive in patients who had never achieved a MR or better, with any therapy. It included patients who never achieved MR or better, in whom there was no significant change in M-protein and no evidence of clinical progression, as well as primary, refractory PD where patients met criteria for true PD. - Relapsed and refractory: disease that was non-responsive while on salvage therapy, or progressed within 60 days of the last therapy in patients who had achieved MR or better at some point			
Units: Subjects			
Primary Refractory	7	7	
Relapsed and refractory	3	3	
Best response to last prior anticancer therapy			
MR, minimal response; PD, disease progression; PR, partial response; SD, stable disease			
Units: Subjects			
PR	2	2	
MR	1	1	
SD	2	2	
PD	5	5	
Prior HSCT			
HSCT, hematopoietic stem cell transplantation			
Units: Subjects			
Autologous	6	6	
Autologous and allogenic	2	2	
No	2	2	
Lines of prior chemotherapy			
Units: Subjects			
3 lines	1	1	
4 lines	2	2	
5 lines	4	4	
8 lines	2	2	
9 lines	1	1	
Weight			
Units: kg			
median	71.4		
full range (min-max)	51.0 to 105.3	-	

Height			
Units: cm			
median	167.1		
full range (min-max)	152 to 186	-	
BSA			
BSA, body surface area;			
Units: m2			
median	1.8		
full range (min-max)	1.5 to 2.2	-	
Time from diagnosis to first plitidepsin infusion			
Units: months			
median	70.7		
full range (min-max)	16 to 168	-	
Time from last progressive disease to first infusion			
Units: weeks			
median	5.3		
full range (min-max)	2 to 14	-	
Lines of prior chemotherapy			
Units: number of lines			
median	5		
full range (min-max)	3 to 9	-	
Agents of prior chemotherapy			
Units: number of agents			
median	9		
full range (min-max)	5 to 13	-	
TTP to last anticancer therapy			
TTP, time to progression			
Units: months			
median	3.4		
full range (min-max)	1.6 to 10.6	-	

End points

End points reporting groups

Reporting group title	Plitidepsin+BTZ+DXM

Reporting group description:

Plitidepsin was to be administered as a 3-hour (h) intravenous (i.v.) infusion at a dose of 5 mg/m2, on Day (D) 1 and 15, every four weeks (q4wk); BTZ was to be administered as a subcutaneous (s.c.) injection at a dose of 1.3 mg/m2 on D1, 4, 8 and 11, q4wk and DXM was to be taken orally at a dose of 40 mg/day on D1, 8, 15 and 22, q4wk. A cycle was defined as 28 days, plus any additional days required for dosing delays due to any reason. Treatment cycles were repeated q4wk.

Primary: Overall Response Rate

End point title	Overall Response Rate[1]

End point description:

The primary analysis should have been done once a total of 64 patients have received plitidepsin+BTZ+DXM, with one futility analysis planned after the inclusion of 20 evaluable patients that had completed two full treatment cycles. However, only a total of 10 patients were included and treated, of whom eight were evaluable for the primary efficacy endpoint (ORR including PR or better according to IMWG criteria). As a result of slow patient accrual, the study was closed before reaching the target enrollment of 20 patients for the first futility analysis. Therefore, the required sample size was not reached and only descriptive data in the population of patients evaluable for efficacy (no formal assessment) are provided.
MR,minimal response;ORR,overall response rate;PD,disease progression;PR,partial response;SD,stable disease
ORR (95%CI) = 12.5% (0.3-52.7%)
Clinical benefit rate (MR or better)[95%CI] = 25.0% [3.2-65.1%]
Disease control rate (SD or better)[95%CI] = 87.5% [47.3-99.7%]

End point type	Primary

End point timeframe:

Overall period

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The required sample size was not reached and only descriptive data in the population of patients evaluable for efficacy (no formal assessment) of the primary endpoint are provided

End point values	Plitidepsin+BTZ+DXM			
Subject group type	Reporting group			
Number of subjects analysed	8[2]			
Units: subjects				
PR	1			
MR	1			
SD	5			
PD	1			

Notes:

[2] - 1 died without any valid tumor assessment done
1 discontinued treatment-related AEs

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

End point type	Secondary

End point timeframe:

Overall period

End point values	Plitidepsin+BTZ+DXM			
Subject group type	Reporting group			
Number of subjects analysed	1[3]			
Units: months				
number (not applicable)	9.2			

Notes:

[3] - Only one patient achieved a partial response

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression

End point title	Time to Progression

End point description:

TTP, time to progression; 999, not reached.
Events: 6 (75.0%)
TTP at 3 months (95% CI) 37.5% (4.0-71.0%)
TTP at 6 months (95% CI) 25.0% (0-55.0%)
TTP at 12 months (95% CI) 25.0% (0-55.0%)

End point type	Secondary

End point timeframe:

Overall period

End point values	Plitidepsin+BTZ+DXM			
Subject group type	Reporting group			
Number of subjects analysed	8[4]			
Units: months				
median (confidence interval 95%)	2.7 (0.7 to 999)			

Notes:

[4] - 1 died without any valid tumor assessment done
1 discontinued treatment-related AEs

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival

End point title	Progression-free Survival

End point description:

PFS, progression-free survival; 999, not reached
Events 6 (75.0%)
PFS at 3 months (95% CI) 37.5% (4.0-71.0%)
PFS at 6 months (95% CI) 25.0% (0-55.0%)
PFS at 12 months (95% CI) 25.0% (0-55.0%)

End point type	Secondary

End point timeframe:

Overall period

End point values	Plitidepsin+BTZ+DXM			
Subject group type	Reporting group			
Number of subjects analysed	8[5]			
Units: months				
median (confidence interval 95%)	2.7 (0.7 to 999)			

Notes:

[5] - 1 died without any valid tumor assessment done
1 discontinued treatment-related AEs

Statistical analyses

No statistical analyses for this end point

Secondary: Event-free Survival

End point title	Event-free Survival

End point description:

EFS, Event-free survival; 999, not reached
Events 6 (75.0%)
EFS at 3 months (95% CI) 37.5% (4.0-71.0%)
EFS at 6 months (95% CI) 25.0% (0-55.0%)
EFS at 12 months (95% CI) 25.0% (0-55.0%)

End point type	Secondary

End point timeframe:

Overall period

End point values	Plitidepsin+BTZ+DXM			
Subject group type	Reporting group			
Number of subjects analysed	8[6]			
Units: months				
median (confidence interval 95%)	2.7 (0.7 to 999)			

Notes:

[6] - 1 died without any valid tumor assessment done
1 discontinued treatment-related AEs

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

OS, overall survival; 999, not reached
Events 2 (25.0%)
OS at 6 months (95% CI) 55.6% (6.9-100.0%)
OS at 12 months (95% CI) 55.6% (6.9-100.0%)

End point type	Secondary

End point timeframe:

Overall period

End point values	Plitidepsin+BTZ+DXM			
Subject group type	Reporting group			
Number of subjects analysed	8[7]			
Units: months				
median (confidence interval 95%)	999 (2.3 to 999)			

Notes:

[7] - 1 died without any valid tumor assessment done
1 discontinued treatment-related AEs

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall period

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Plitidepsin+BTZ+DXM

Reporting group description:

Plitidepsin was to be administered as a 3-hour (h) intravenous (i.v.) infusion at a dose of 5 mg/m2, on Day (D) 1 and 15, q4wk; BTZ was to be administered as a subcutaneous (s.c.) injection at a dose of 1.3 mg/m2 on D1, 4, 8 and 11, q4wk and DXM was to be taken orally at a dose of 40 mg/day on D1, 8, 15 and 22, q4wk. A cycle was defined as 28 days, plus any additional days required for dosing delays due to any reason. Treatment cycles were repeated every four weeks (q4wk).

Serious adverse events	Plitidepsin+BTZ+DXM		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 10 (50.00%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Sciatica			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Plitidepsin+BTZ+DXM		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Hypertension			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	3		
Surgical and medical procedures			
Intramedullary rod insertion			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia/Fatigue			
subjects affected / exposed	4 / 10 (40.00%)		
occurrences (all)	22		
Extravasation			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	7		
Peripheral swelling			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	4 / 10 (40.00%)		
occurrences (all)	6		
Respiratory, thoracic and mediastinal disorders			

Catarrh subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2		
Cough subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2		
Epistaxis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Respiratory failure subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Rhinorrhoea subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	4 / 10 (40.00%) 12		
Antithrombin III decreased subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Blood cholesterol subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Blood creatinine increased			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Neutrophil count decreased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Neuropathy peripheral			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	14		
Sciatica			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	4		
Seizure			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 10 (60.00%)		
occurrences (all)	25		
Neutropenia			

subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	5		
Thrombocytopenia			
subjects affected / exposed	4 / 10 (40.00%)		
occurrences (all)	35		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Eye disorders			
Cataract			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	7		
Gastric disorder			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Gingival bleeding			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Mouth haemorrhage			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	5 / 10 (50.00%)		
occurrences (all)	8		
Vomiting			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Renal and urinary disorders			

Renal failure			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	7		
Back pain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Muscular weakness			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	19		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Infections and infestations			
Folliculitis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Herpes zoster			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Influenza			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Respiratory tract infection			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	3		
Hypercalcaemia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Hyperglycaemia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Hyperuricaemia			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	3		
Hypocalcaemia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Hypokalaemia			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	4		
Hypomagnesaemia			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
29 May 2018	On 29 May 2018, the Sponsor informed to the study centers and Investigators regarding its decision to close the recruitment of the APL-B-022-15 study. The study was terminated before reaching the target enrollment due to the slow patient accrual. Furthermore, the negative opinion of the European Medicines Agency (EMA) recommending the refusal of the marketing authorization for plitidepsin for the treatment of MM reinforced this Sponsor decision.	-

Notes:

Limitations and caveats

None reported