Clinical trial results:
A Phase II Study of Plitidepsin in Patients with Relapsed or Refractory Angioimmunoblastic T-cell Lymphoma.

Summary

EudraCT number	2015-001909-14
Trial protocol	ES CZ IT
Global end of trial date	02 July 2018

Results information

Result version number	v1 (current)
This version publication date	10 August 2019
First version publication date	10 August 2019

Trial information

Trial identification

Sponsor protocol code	APL-B-021-13

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03070964
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 91846 60 00, clinicaltrials@pharmamar.com
Scientific contact	Clinical Developtment, Department of PharmaMar´s Oncology., Business Unit., Pharmamar, S.A., 34 91846 60 00, 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	11 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 July 2018
Global end of trial reached?	Yes
Global end of trial date	02 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 on the basis of overall response rate (ORR) in patients with relapsing/refractory angioimmunoblastic T-cell lymphoma (AITL).

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 prophylactic medication 30-60 min before infusion of plitidepsin.
• Dexamethasone (8 mg i.v. or equivalent).
• Ondansetron (8 mg i.v.) or equivalent (granisetron 3 mg i.v. preferred when available), and
• Diphenhydramine hydrochloride (25 mg i.v.) or equivalent, and
• Ranitidine (50 mg i.v.) or equivalent.
Oral metoclopramide and/or extended oral ondansetron (or their equivalents) could be used as per Investigator’s criteria/institutional guidelines. Additional dexamethasone only could be used as an antiemetic in the event that alternative antiemetics could not be used; and only if the Investigator had considered the options above as insufficient.

Evidence for comparator: -

Actual start date of recruitment	25 October 2016
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	Italy: 3
Country: Number of subjects enrolled	United States: 1
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Czech Republic: 1
Worldwide total number of subjects	14
EEA total number of subjects	13

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)	9
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first IC was signed on 25Oct2016 and the first study treatment administration was on 9Nov2016. The cutoff date was 2Jul2018 (date of last follow-up, clinical cutoff). At cutoff date, 14 patients had been included, of whom 13 were treated and evaluable for safety, and 12 were evaluable for the primary efficacy endpoint.

Pre-assignment

Screening details:

Age≥18 years;signed IC;ECOG PS≤2;Life expectancy≥3 months;Histologically confirmed diagnosis of R/R AITL;At least a two-week washout period;Adequate bone marrow (BM), renal, hepatic, and metabolic function;LVEF within normal range

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

Arm description:

Plitidepsin was administered i.v. as a 1-hour infusion (fixed rate) via central or peripheral venous catheter. Patients received plitidepsin at a starting dose of 3.2 mg/m2 on Day 1, 8 and 15 every four weeks (q4wk). A 1-day window is allowed for plitidepsin administration. A cycle is defined as a four-week period. A 1-day window was allowed for plitidepsin administration.

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:

Plitidepsin was administered i.v. as a 1-hour infusion (fixed rate) via central or peripheral venous catheter. Patients received plitidepsin at a starting dose of 3.2 mg/m2 on Day 1, 8 and 15 every four weeks (q4wk). A 1-day window is allowed for plitidepsin administration. A cycle is defined as a four-week period. A 1-day window was allowed for plitidepsin administration.

Number of subjects in period 1	Plitidepsin
Started	14
Completed	0
Not completed	14
Consent withdrawn by subject	1
Physician decision	1
Treatment-unrelated adverse event	2
Never treated	1

Treatment-related adverse event	1
Progressive disease	8

Baseline characteristics

Reporting groups	
Reporting group title	Plitidepsin
Reporting group description:	
Plitidepsin was administered i.v. as a 1-hour infusion (fixed rate) via central or peripheral venous catheter. Patients received plitidepsin at a starting dose of 3.2 mg/m2 on Day 1, 8 and 15 every four weeks (q4wk). A 1-day window is allowed for plitidepsin administration. A cycle is defined as a four-week period. A 1-day window was allowed for plitidepsin administration.	

Reporting group values	Plitidepsin	Total	
Number of subjects	14	14	
Age categorical Units: Subjects			
Adults (18-64 years)	9	9	
From 65-84 years	5	5	
Age continuous Units: years			
median	61		
full range (min-max)	40 to 75	-	
Gender categorical Units: Subjects			
Female	6	6	
Male	8	8	
Race Units: Subjects			
White	13	13	
Hispanolatin	1	1	
ECOG PS			
ECOG PS, Eastern Cooperative Oncology Group performance status			
Units: Subjects			
PS 0	8	8	
PS 1	5	5	
PS 2	1	1	
Ann Arbor stage Units: Subjects			
III	1	1	
III-A	3	3	
III-B	3	3	
IV-A	3	3	
IV-B	4	4	
Extranodal disease at diagnosis Units: Subjects			
No	9	9	
Yes	5	5	
Bulky lesion at diagnosis Units: Subjects			
No	13	13	
Yes	1	1	

IPI score at diagnosis			
IPI, international prognostic index			
Units: Subjects			
Low risk (0-1 risk factors)	2	2	
Low-intermediate risk (2 risk factors)	2	2	
High-intermediate risk (3 risk factors)	2	2	
High risk (4-5 risk factors)	4	4	
NA	4	4	
PIT at diagnosis			
PIT, prognostic index for peripheral T-cell lymphoma			
Units: Subjects			
Group 1 (no adverse factors)	1	1	
Group 2 (1 risk factor)	1	1	
Group 4 (3-4 risk factors)	2	2	
NA	10	10	
PIAI score at diagnosis			
PIAI, prognostic index for angioimmunoblastic T-cell lymphoma			
Units: Subjects			
Low-risk group	3	3	
High-risk group	3	3	
NA	8	8	
IPI score at current disease			
IPI, international prognostic index			
Units: Subjects			
Low risk (0-1 risk factors)	3	3	
Low-intermediate risk (2 risk factors)	3	3	
High-intermediate risk (3 risk factors)	4	4	
High risk (4-5 risk factors)	4	4	
PIT at current disease			
PIT, prognostic index for peripheral T-cell lymphoma			
Units: Subjects			
Group 1 (no adverse factors)	2	2	
Group 2 (1 risk factor)	3	3	
Group 3 (2 risk factors)	1	1	
Group 4 (3-4 risk factors)	1	1	
NA	7	7	
PIAI score at current disease			
PIAI, prognostic index for angioimmunoblastic T-cell lymphoma			
Units: Subjects			
Low-risk group	5	5	
High-risk group	4	4	
NA	5	5	
Prior anticancer therapy lines Units: Subjects			
1 line	2	2	
2 lines	5	5	
3 lines	5	5	
4 lines	1	1	
5 lines	1	1	

Best response to last prior therapy			
CR, complete response; PD, disease progression; PR, partial response; SD, stable disease; UK, unknown			
Units: Subjects			
CR	4	4	
PR	4	4	
SD	1	1	
PD	3	3	
UK	2	2	
Prior stem cell transplantation Units: Subjects			
No	8	8	
Allogenic stem cell transplantation	1	1	
Autologous stem cell transplantation	5	5	
Weight Units: Kg			
median	72.5		
full range (min-max)	44.7 to 145.0	-	
Height Units: cm			
median	166.5		
full range (min-max)	152 to 190	-	
BSA			
BSA, body surface area			
Units: m2			
median	1.8		
full range (min-max)	1.4 to 2.8	-	
Time from diagnosis to first plitidepsin infusion Units: months			
median	24.1		
full range (min-max)	8.5 to 200.5	-	
Time from last progressive disease to first infusion Units: weeks			
median	6.9		
full range (min-max)	0.9 to 54.0	-	
Prior anticancer therapy lines Units: number			
median	2.5		
full range (min-max)	1 to 5	-	
TTP to last anticancer therapy			
TTP, time to progressions			
Units: months			
median	4.6		
full range (min-max)	1.5 to 92.5	-	

End points

End points reporting groups

Reporting group title	Plitidepsin

Reporting group description:

Plitidepsin was administered i.v. as a 1-hour infusion (fixed rate) via central or peripheral venous catheter. Patients received plitidepsin at a starting dose of 3.2 mg/m2 on Day 1, 8 and 15 every four weeks (q4wk). A 1-day window is allowed for plitidepsin administration. A cycle is defined as a four-week period. A 1-day window was allowed for plitidepsin administration.

Primary: Overall Response Rate by the Lugano Classification per Independent Review Assessment

End point title	Overall Response Rate by the Lugano Classification per Independent Review Assessment[1]

End point description:

The study protocol established that the analysis of the primary endpoint should have been done once a total of 60 patients have received plitidepsin, with two futility analyses planned after the inclusion of approximately 15 and 30 patients, respectively (see Section 9.5.1.5). However, only a total of 14 patients were included, of whom 13 were treated, and 12 were evaluable for the primary efficacy endpoint (ORR per IRC in the "Per Protocol Patients" population). As a result of slow patient accrual, the study was closed before reaching the target enrollment of 15 patients for the first futility analysis, and the primary endpoint (ORR according to the Lugano classification criteria and per IRC) was not assessed. Overall Response Rate by the Lugano Classification per Independent Review Assessment.

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 study was closed before reaching the target enrollment of 15 patients for the first futility analysis, and the primary endpoint (ORR according to the Lugano classification criteria and per IRC) was not assessed.

End point values	Plitidepsin			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate by Investigator's Assessment - Per Protocol Patients Population

End point title	Overall Response Rate by Investigator's Assessment - Per Protocol Patients Population

End point description:

CI, confidence interval; CR, complete response; NE, not evaluable; ORR, overall response rate; PD, disease progression; PR, partial response; SD, stable disease.
ORR (95% CI) = 16.7% (2.1-48.4%)

Clinical benefit rate (CR+PR+SD ≥ 6 months) (95% CI) = 25.0% (5.5-57.2%)

End point type	Secondary

End point timeframe:

Overall period

End point values	Plitidepsin			
Subject group type	Reporting group			
Number of subjects analysed	12[2]			
Units: subjects				
CR	1			
PR	1			
SD	1			
PD	7			
NE	2			

Notes:

[2] - A patient was never treated with plitidepsin
A patient due to lack of AITL diagnosis confirmation

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate by Investigator's Assessment - All Evaluable Patients Population

End point title	Overall Response Rate by Investigator's Assessment - All Evaluable Patients Population

End point description:

CI, confidence interval; CR, complete response; ORR, overall response rate; PD, disease progression; PR, partial response; SD, stable disease.
ORR (95% CI) = 20.0% (2.5-55.6%)
Clinical benefit rate (CR+PR+SD ≥ 6 months) (95% CI) = 30.0% (6.7-65.2%)

End point type	Secondary

End point timeframe:

Overall period

End point values	Plitidepsin			
Subject group type	Reporting group			
Number of subjects analysed	10[3]			
Units: subjects				
CR	1			
PR	1			
SD	1			
PD	7			

Notes:

[3] - Four patients were not evaluable for efficacy in the "All Evaluable Patients" population

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate by Investigator's Assessment - All Treated Patients Population

End point title	Overall Response Rate by Investigator's Assessment - All Treated Patients Population

End point description:

CI, confidence interval; CR, complete response; NE, not evaluable; ORR, overall response rate; PD, disease progression; PR, partial response; SD, stable disease.
ORR (95% CI) = 15.4% (1.9-45.4%)
Clinical benefit rate (CR+PR+SD ≥ 6 months) (95% CI) = 23.1% (5.0-53.8%)

End point type	Secondary

End point timeframe:

Overall period

End point values	Plitidepsin			
Subject group type	Reporting group			
Number of subjects analysed	13[4]			
Units: subjects				
CR	1			
PR	1			
SD	1			
PD	8			
NE	2			

Notes:

[4] - 1 patient was never treated

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Remission Rate by Investigator's Assessment

End point title	Complete Remission Rate by Investigator's Assessment

End point description:

CR rate in the "All Evaluable Patients" population was 10.0% (95% CI, 0.3-44.5%)
CR rate in the "All Treated Patients" population was 7.7% (95% CI, 0.2-36%)

End point type	Secondary

End point timeframe:

Overall period

End point values	Plitidepsin			
Subject group type	Reporting group			
Number of subjects analysed	12[5]			
Units: percentage				
number (confidence interval 95%)	8.3 (0.2 to 38.5)			

Notes:

[5] - A patient was never treated with plitidepsin
A patient due to lack of AITL diagnosis confirmation

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response by Investigator's Assessment

End point title	Duration of Response by Investigator's Assessment

End point description:

CI, confidence interval; DoR, duration of response
DoR (months) at 3 months (95% CI) = 100% (100-100%)
DoR (months) at 6 months (95% CI) = 50% (0-100%)

End point type	Secondary

End point timeframe:

Overall period

End point values	Plitidepsin			
Subject group type	Reporting group			
Number of subjects analysed	2[6]			
Units: months				
median (confidence interval 95%)	6.6 (3.7 to 9.4)			

Notes:

[6] - the two responders to plitidepsin

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response by Investigator's Assessment

End point title	Time to Response by Investigator's Assessment

End point description:

End point type	Secondary

End point timeframe:

Overall period

End point values	Plitidepsin			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: months				
median (full range (min-max))	2.9 (2.8 to 3.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival by Investigator’s Assessment - Per Protocol Patients Population

End point title	Progression-free Survival by Investigator’s Assessment - Per Protocol Patients Population

End point description:

CI, confidence interval; PFS, progression-free survival
Events = 10 (83.3%)
PFS at 6 months (95% CI) = 30.0% (1.6-58.4%)
PFS at 12 months (95% CI) = 10.0% (0-28.6%)

End point type	Secondary

End point timeframe:

Overall period

End point values	Plitidepsin			
Subject group type	Reporting group			
Number of subjects analysed	12[7]			
Units: months				
median (confidence interval 95%)	2.5 (0.9 to 6.4)			

Notes:

[7] - A patient was never treated with plitidepsin
A patient due to lack of AITL diagnosis confirmation

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival by Investigator’s Assessment - All Evaluable Patients Population

End point title	Progression-free Survival by Investigator’s Assessment - All Evaluable Patients Population

End point description:

CI, confidence interval; PFS, progression-free survival.
Events 10 (100%)
PFS at 6 months (95% CI) 30.0% (1.6-58.4%)
PFS at 12 months (95% CI) 10.0% (0-28.6%)

End point type	Secondary

End point timeframe:

Overall period

End point values	Plitidepsin			
Subject group type	Reporting group			
Number of subjects analysed	10[8]			
Units: months				
median (confidence interval 95%)	2.5 (0.9 to 6.4)			

Notes:

[8] - Four patients were not evaluable for efficacy in the "All Evaluable Patients" population

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival by Investigator's Assessment - All Treated Patients population

End point title	Progression-free Survival by Investigator's Assessment - All Treated Patients population

End point description:

CI, confidence interval; PFS, progression-free survival.
Events 11 (84.6%)
PFS at 6 months (95% CI) 27.3% (1.0-53.6%)
PFS at 12 months (95% CI) 9.1% (0-26.1%)

End point type	Secondary

End point timeframe:

Overall period

End point values	Plitidepsin			
Subject group type	Reporting group			
Number of subjects analysed	13[9]			
Units: months				
median (confidence interval 95%)	2.6 (1.6 to 6.4)			

Notes:

[9] - 1 patient was never treated

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival - Per Protocol Patients population

End point title	Overall survival - Per Protocol Patients population

End point description:

CI, confidence interval; 999, not reached; OS, overall survival
Events 7 (58.3%)
OS at 6 months (95% CI) 65.6% (38.1-93.1%)
OS at 12 months (95% CI) 29.2% (0-60.2%)

End point type	Secondary

End point timeframe:

Overall period

End point values	Plitidepsin			
Subject group type	Reporting group			
Number of subjects analysed	12[10]			
Units: months				
median (confidence interval 95%)	6.1 (3.4 to 999)			

Notes:

[10] - A patient was never treated with plitidepsin
A patient due to lack of AITL diagnosis confirmation

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival - All Evaluable Patients Population

End point title	Overall Survival - All Evaluable Patients Population

End point description:

CI, confidence interval; 999, not reached; OS, overall survival
Events 5 (50.0%)
OS at 6 months (95% CI) 68.6% (38.9-98.3%)
OS at 12 months (95% CI) 36.6% (0-73.5%)

End point type	Secondary

End point timeframe:

Overall period

End point values	Plitidepsin			
Subject group type	Reporting group			
Number of subjects analysed	10[11]			
Units: months				
median (confidence interval 95%)	6.1 (3.7 to 999)			

Notes:

[11] - Four patients were not evaluable for efficacy in the “All Evaluable Patients” population

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival - All Treated Patients Population

End point title	Overall Survival - All Treated Patients Population

End point description:

CI, confidence interval; 999, not reached; OS, overall survival
Events 7 (53.8%)
OS at 6 months (95% CI) 68.4% (42.6-94.1%)
OS at 12 months (95% CI) 32.6% (0-65.1%)

End point type	Secondary

End point timeframe:

Overall period

End point values	Plitidepsin			
Subject group type	Reporting group			
Number of subjects analysed	13[12]			
Units: months				
median (confidence interval 95%)	6.1 (3.7 to 999)			

Notes:

[12] - 1 patient was never treated

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

Reporting group description:

Plitidepsin was administered i.v. as a 1-hour infusion (fixed rate) via central or peripheral venous catheter. Patients received plitidepsin at a starting dose of 3.2 mg/m2 on Day 1, 8 and 15 every four weeks (q4wk). A 1-day window is allowed for plitidepsin administration. A cycle is defined as a four-week period. A 1-day window was allowed for plitidepsin administration.

Serious adverse events	Plitidepsin		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 13 (69.23%)		
number of deaths (all causes)	7		
number of deaths resulting from adverse events	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Peripheral embolism			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac arrest			

subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Skin and subcutaneous tissue disorders			
Rash			

subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Rhinovirus infection			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin infection			
subjects affected / exposed	1 / 13 (7.69%)		
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		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 13 (100.00%)		
Vascular disorders			
Subclavian vein thrombosis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia/Fatigue			
subjects affected / exposed	4 / 13 (30.77%)		
occurrences (all)	6		
Chills			

subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	2		
Malaise			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	6 / 13 (46.15%)		
occurrences (all)	17		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Dyspnoea			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	3		
Nasal congestion			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 13 (30.77%)		
occurrences (all)	15		
Aspartate aminotransferase increased			

subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	2		
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	2		
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	6		
Weight decreased			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Dysaesthesia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Neuropathy peripheral			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Transient ischaemic attack			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Blood and lymphatic system disorders			

Anaemia				
subjects affected / exposed	3 / 13 (23.08%)			
occurrences (all)	13			
Eosinophilia				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Lymphadenopathy				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Neutropenia				
subjects affected / exposed	2 / 13 (15.38%)			
occurrences (all)	2			
Thrombocytopenia				
subjects affected / exposed	2 / 13 (15.38%)			
occurrences (all)	2			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	2 / 13 (15.38%)			
occurrences (all)	2			
Abdominal pain upper				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Diarrhoea				
subjects affected / exposed	5 / 13 (38.46%)			
occurrences (all)	7			
Dysphagia				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Epigastric discomfort				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Flatulence				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Gastric mucosa erythema				

subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Melaena subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Nausea subjects affected / exposed occurrences (all)	6 / 13 (46.15%) 7		
Rectal haemorrhage subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Vomiting subjects affected / exposed occurrences (all)	3 / 13 (23.08%) 4		
Skin and subcutaneous tissue disorders			
Night sweats subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Pruritus subjects affected / exposed occurrences (all)	4 / 13 (30.77%) 5		
Rash subjects affected / exposed occurrences (all)	3 / 13 (23.08%) 8		
Rash macular subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Renal and urinary disorders			
Renal failure subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Renal impairment subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 2		
Musculoskeletal and connective tissue disorders			

Joint swelling			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	3		
Myopathy			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Infections and infestations			
Candida infection			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Cytomegalovirus infection			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Herpes zoster			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Influenza			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Pharyngitis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Rhinovirus infection			

subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Hypomagnesaemia			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	3		
Hyponatraemia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 July 2016	This substantial amendment was generated to include dexamethasone as prophylactic medication required before infusion with plitidepsin. Therefore, standard premedication for hypersensitivity reactions with anti H1 and H2 receptor antagonists and glucocorticoids had to be given intravenously before each plitidepsin infusion; this is mandatory in all ongoing studies with plitidepsin as stated in the Investigator Brochure. In v.1.0 of this protocol, dexamethasone was not part of the premedication regimen due to an omission at the time of writing the document. Additionally, the following changes, corrections, and clarifications were also included in this substantial amendment: - Clarifications to some of the parts of the text regarding the prior treatment, LVEF and hypersensitivity eligibility criteria were included to ensure patient safety - Muscular toxicity criteria for treatment continuation and dose reduction were revised to ensure patient safety - The list of excipients of plitidepsin was added to the study drug formulation information - Clarifications to some assessments and procedures windows were included as follow: tumor assessment timing after Cycle 3 was changed to avoid delays in starting Cycle 4; the frequency of follow-up until disease progression during the first year of follow-up was corrected in line with standard clinical practice; laboratory analyses required in the event of grade 3/4 nausea/vomiting or a treatment-related SAE were corrected to require only biochemistry-A laboratory tests. - The use of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade 5 was revised to align with current Pharmacovigilance Department standard practice. - ICH Topic E6 Guideline for Good Clinical Practice reference to R1 was removed in anticipation of a revised version (R2). - Study contact details were updated and some minor typographical errors were corrected
09 June 2017	This substantial amendment was generated to: - Implement additional information on imaging requirements and periods for radiological tumor assessment with PET-CT in combination with diagnostic quality CT. - Modify the exclusion criterion #5 to allow the inclusion of patients concurrently treated with low doses of corticosteroids (an equivalent prednisone dose of ≤10 mg daily) for controlling symptoms derived from the disease. - Modify section referred to prohibited medications/therapies to clarify that patients were allowed to receive hydrocortisone treatment by any administration, not only by single bolus, and also to be consistent with the amended Exclusion criterion #5 (see above). - Simplify the follow-up procedures and periods for patients discontinuing treatment with or without disease progression, to be similar to the procedures used in clinical practice for monitoring these patients. Therefore, both groups of patients would be followed up ‘every four months during the first two years and then once every six months’. - Update the study contacts and correct some minor typographical errors.

07 May 2018	Additionally, according to an FDA request, a new Substantial Amendment No. 3 (7 May 2018) was issued to include several changes as additional precautionary measures to mitigate any likely rhythm abnormality. This amendment was based on the occurrence of one episode of grade 4 cardiac arrest due to Torsades de pointes (TdP) reported in one patient during Cycle 4 that resolved but led to treatment discontinuation. Precautionary measures to avoid TdP risk were to be implemented in this ongoing phase II study, including more stringent eligibility criteria, continuation of treatment criteria, prohibited medications (excluding prophylactic antiemetic ondansetron), and more extensive cardiac monitoring. Furthermore, as preliminary data from the APL-C-001-09 ADMYRE study showed that the greatest increases in QTcF, although being below the safety threshold of 20 milliseconds (ms), occurred 30 and 60 min after the end of infusion, thus the FDA requested that protocol of APL-B-021-13 study had to be modified to check ECGs 30 and 60 min post-infusion, timed with pharmacokinetic sample collections. Nevertheless, the study APL-B-021-13 was closed before this new substantial amendment was implemented.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
14 May 2018	On 14 May 2018, the Sponsor informed to the study centers and Investigators regarding its decision to close the recruitment of the APL-B-021-13 study. The study was terminated before reaching the target enrollment due to slow patient accrual, and the negative opinion of the European Medicines Agency recommending the refusal of the marketing authorization for plitidepsin for the treatment of MM; all together prompted this Sponsor decision.	-

Notes:

Limitations and caveats

None reported