



## 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 Development, Department of PharmaMar's Oncology., Business Unit., Pharmamar, S.A., 34 91846 60 00, clinicaltrials@pharmamar.com |
| Scientific contact           | Clinical Development, 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 $\geq$ 18 years; signed IC; ECOG PS $\leq$ 2; Life expectancy $\geq$ 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m <sup>2</sup> 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 <sup>[1]</sup> |
|-----------------|---|

#### 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.

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | 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  $\geq$  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 <sup>[2]</sup> |  |  |  |
| 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  $\geq$  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 <sup>[3]</sup> |  |  |  |
| 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:<br>CI, confidence interval; CR, complete response; NE, not evaluable; ORR, overall response rate; PD, disease progression; PR, partial response; SD, stable disease.<br>ORR (95% CI) = 15.4% (1.9-45.4%)<br>Clinical benefit rate (CR+PR+SD $\geq$ 6 months) (95% CI) = 23.1% (5.0-53.8%) |  |
| End point type   | Secondary  |
| End point timeframe:<br>Overall period   |  |

| End point values            | Plitidepsin       |  |  |  |
|-----------------------------|-------------------|--|--|--|
| Subject group type          | Reporting group   |  |  |  |
| Number of subjects analysed | 13 <sup>[4]</sup> |  |  |  |
| 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:<br>CR rate in the "All Evaluable Patients" population was 10.0% (95% CI, 0.3-44.5%)<br>CR rate in the "All Treated Patients" population was 7.7% (95% CI, 0.2-36%) |  |
| End point type  | Secondary  |
| End point timeframe:<br>Overall period  |  |

| End point values                 | Plitidepsin       |  |  |  |
|----------------------------------|-------------------|--|--|--|
| Subject group type               | Reporting group   |  |  |  |
| Number of subjects analysed      | 12 <sup>[5]</sup> |  |  |  |
| 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 <sup>[6]</sup> |  |  |  |
| 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 <sup>[7]</sup> |  |  |  |
| 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   |  |

|                                  |                   |  |  |  |
|----------------------------------|-------------------|--|--|--|
| <b>End point values</b>          | Plitidepsin       |  |  |  |
| Subject group type               | Reporting group   |  |  |  |
| Number of subjects analysed      | 10 <sup>[8]</sup> |  |  |  |
| 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   |  |

|                                  |                   |  |  |  |
|----------------------------------|-------------------|--|--|--|
| <b>End point values</b>          | Plitidepsin       |  |  |  |
| Subject group type               | Reporting group   |  |  |  |
| Number of subjects analysed      | 13 <sup>[9]</sup> |  |  |  |
| 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

|                                  |                    |  |  |  |
|----------------------------------|--------------------|--|--|--|
| <b>End point values</b>          | Plitidepsin        |  |  |  |
| Subject group type               | Reporting group    |  |  |  |
| Number of subjects analysed      | 12 <sup>[10]</sup> |  |  |  |
| 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  |  |

|                                  |                    |  |  |  |
|----------------------------------|--------------------|--|--|--|
| <b>End point values</b>          | Plitidepsin        |  |  |  |
| Subject group type               | Reporting group    |  |  |  |
| Number of subjects analysed      | 10 <sup>[11]</sup> |  |  |  |
| 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       |           |

|                                  |                    |  |  |  |
|----------------------------------|--------------------|--|--|--|
| <b>End point values</b>          | Plitidepsin        |  |  |  |
| Subject group type               | Reporting group    |  |  |  |
| Number of subjects analysed      | 13 <sup>[12]</sup> |  |  |  |
| 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/m<sup>2</sup> 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          |  |  |
| <b>Infections and infestations</b>              |                |  |  |
| 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 %

|   |                   |  |  |
|---|-------------------|--|--|
| <b>Non-serious adverse events</b>                           | Plitidepsin       |  |  |
| Total subjects affected by non-serious adverse events       |                   |  |  |
| subjects affected / exposed                                 | 13 / 13 (100.00%) |  |  |
| <b>Vascular disorders</b>                                   |                   |  |  |
| Subclavian vein thrombosis                                  |                   |  |  |
| subjects affected / exposed                                 | 1 / 13 (7.69%)    |  |  |
| occurrences (all)   | 1                 |  |  |
| <b>General disorders and administration site conditions</b> |                   |  |  |
| Asthenia/Fatigue  |                   |  |  |
| subjects affected / exposed                                 | 4 / 13 (30.77%)   |  |  |
| occurrences (all)   | 6                 |  |  |
| Chills  |                   |  |  |

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

|  |                 |  |  |
|--|-----------------|--|--|
| 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                     | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Melaena   |                 |  |  |
| subjects affected / exposed                     | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Nausea  |                 |  |  |
| subjects affected / exposed                     | 6 / 13 (46.15%) |  |  |
| occurrences (all)                               | 7               |  |  |
| Rectal haemorrhage                              |                 |  |  |
| subjects affected / exposed                     | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Vomiting  |                 |  |  |
| subjects affected / exposed                     | 3 / 13 (23.08%) |  |  |
| occurrences (all)                               | 4               |  |  |
| Skin and subcutaneous tissue disorders          |                 |  |  |
| Night sweats                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Pruritus  |                 |  |  |
| subjects affected / exposed                     | 4 / 13 (30.77%) |  |  |
| occurrences (all)                               | 5               |  |  |
| Rash  |                 |  |  |
| subjects affected / exposed                     | 3 / 13 (23.08%) |  |  |
| occurrences (all)                               | 8               |  |  |
| Rash macular                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Renal and urinary disorders                     |                 |  |  |
| Renal failure                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 13 (7.69%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Renal impairment                                |                 |  |  |
| subjects affected / exposed                     | 2 / 13 (15.38%) |  |  |
| occurrences (all)                               | 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 | <p>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.</p> <p>Additionally, the following changes, corrections, and clarifications were also included in this substantial amendment:</p> <ul style="list-style-type: none"><li>- Clarifications to some of the parts of the text regarding the prior treatment, LVEF and hypersensitivity eligibility criteria were included to ensure patient safety</li><li>- Muscular toxicity criteria for treatment continuation and dose reduction were revised to ensure patient safety</li><li>- The list of excipients of plitidepsin was added to the study drug formulation information</li><li>- 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.</li><li>- 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.</li><li>- ICH Topic E6 Guideline for Good Clinical Practice reference to R1 was removed in anticipation of a revised version (R2).</li><li>- Study contact details were updated and some minor typographical errors were corrected</li></ul> |
| 09 June 2017 | <p>This substantial amendment was generated to:</p> <ul style="list-style-type: none"><li>- Implement additional information on imaging requirements and periods for radiological tumor assessment with PET-CT in combination with diagnostic quality CT.</li><li>- 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.</li><li>- 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).</li><li>- 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'.</li><li>- Update the study contacts and correct some minor typographical errors.</li></ul>   |

|             |  |
|-------------|--|
| 07 May 2018 | <p>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.</p> |
|-------------|--|

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date        | Interruption   | Restart date |
|-------------|--|--------------|
| 14 May 2018 | <p>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.</p> <p>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.</p> | -            |

Notes:

## Limitations and caveats

None reported