Pharma Mar, S.A., Sociedad Unipersonal, Colmenar Viejo, Madrid, Spain
Pharma Mar USA, Inc., New York, U.S.A.

CLINICAL STUDY REPORT

APL-B-013-02

A PHASE II MULTICENTER, OPEN-LABEL, CLINICAL AND PHARMACOKINETIC STUDY OF APLIDIN® AS A 1-HOUR WEEKLY IV INFUSION, IN PATIENTS WITH RELAPSED OR REFRACTORY AGGRESSIVE NON-HODGKIN'S LYMPHOMA

Investigational Medicinal Product:	Plitidepsin
Name of Test Drug:	Aplidin®
Study Design:	Open-label, single-arm, multicenter, phase II clinical trial
Protocol Number:	APL-B-013-02
Study Start Date:	17 December 2004 (First consent signed)
Study Completion Date:	16 June 2010 (Date reported to the Competent Authorities)
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Responsible Medical Officer:	**Arturo Soto Matos-Pita, M.D.** Clinical Research and Development Associate Director Pharma Mar, S.A., Sociedad Unipersonal (abbreviated as PharmaMar S.A. in this report) Avenida de los Reyes, 1; Polígono Industrial La Mina-Norte 28770 Colmenar Viejo, Madrid, Spain Phone: +34 91 846 6053 Fax: +34 91 823 4504 E-mail: asoto@pharmamar.com
Earlier Approved Reports:	None
Version:	Final version
Approval Date:	30 November 2010

This study was conducted in compliance with Good Clinical Practice (GCP)

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2. SYNOPSIS

<table>
<tr><td>Name of Sponsor(s)/Company(ies):
PharmaMar, S.A.
PharmaMar USA, Inc.</td><td>Individual Study Table Referring to Part of the Dossier

Volume:

Page:</td><td>(For National Authority Use only)</td></tr>
<tr><td>Name of finished product:
Aplidin®</td><td></td><td></td></tr>
<tr><td>Name of active ingredient(s):
Plitidepsin</td><td></td><td></td></tr>
<tr><td>Protocol number</td><td colspan="2">APL-B-013-02</td></tr>
<tr><td>Title of the study</td><td colspan="2">A Phase II Multicenter, Open-Label, Clinical and Pharmacokinetic Study of Aplidin® as a 1-hour Weekly iv Infusion, in Patients With Relapsed or Refractory Aggressive Non-Hodgkin's Lymphoma.</td></tr>
<tr><td>Coordinating Investigator</td><td colspan="2">Vincent Ribrag, M.D.
Institut Gustave Roussy, Villejuif, France.</td></tr>
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<tr><td>Publication (references)</td><td colspan="2">At the time of this report no articles have been published on the study described herein.
Preliminary results of this study were presented at:
American Society of Hematology (ASH) 2008 Meeting. "Ferme C, Mateos MV, Szyldergemajn S, Zucca E, Espinoza J, Briones J, Morschhauser F, Gisselbrecht C, Ribrag V. Plitidepsin Is Active in Peripheral T-Cell Lymphoma (PTCL): A Subset Analysis from An Ongoing Multicenter Phase II Trial. Blood (ASH Annual Meeting Abstracts) 2008, 112(11): Abstract 1566".
2006-2009 Now we Know T-Cell Lymphomas Better. "Ferme C, Mateos MV, Szyldergemajn S, Zucca E, Extremera S, Briones J, Alessandro, G, Ribrag V. Plitidepsin is active in peripheral T-cell lymphoma: a subset analysis from an ongoing multicenter phase II trial. Hematology Meeting Reports 2009, 3(1):58-60".
T-Cell Lymphoma Forum 2010, Maui, HI, USA. "Ferme C, Mateos MV, Szyldergemajn S, Zucca E, Gianni AM, Ribrag V. Plitidepsin Activity in Peripheral T-Cell Lymphoma (PTCL)." Abstract Book, page 76.</td></tr>
<tr><td>Study period:
. First consent signed
. Last consent signed
. First infusion administered
. Last infusion administered
. Last follow-up
. Date of completion reported to authorities</td><td>
17 December 2004
14 September 2009

21 December 2004

22 January 2010
16 June 2010
16 June 2010</td><td>Phase of Development:

Phase II</td></tr>
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Study objectives	**Primary:** - To assess the antitumor activity of plitidepsin given as a 1-hour weekly i.v. infusion, in patients with relapsed or refractory aggressive non-Hodgkin's lymphoma (NHL). **Secondary:** - Evaluation of the pharmacokinetics (PK) of this schedule of plitidepsin in this patient population. - To further investigate the safety profile of plitidepsin given as 1-hour weekly i.v. infusion in this patient population.	
Methodology	This open-label, single-arm, multicenter, phase II clinical trial was designed to determine the efficacy, tolerability and PK profile of plitidepsin administered at 3.2 mg/m^2 as a 1-hour i.v. infusion on Days 1, 8 and 15 in 4-week cycles in adult patients with histologically confirmed aggressive NHL that had relapsed following response to standard chemotherapy or high-dose chemotherapy and stem cell transplantation, or that was refractory to its more recent chemotherapy. Initially, patients were to be recruited regardless of subtype of aggressive NHL. However, as four out of 12 patients with PTCL achieved objective responses [one complete response (CR) and three partial responses (PR)] to plitidepsin, the protocol was amended to further include only patients with non-cutaneous aggressive PTCL.	
Number of patients (planned and analyzed)	**Planned number of patients:** A two-stage phase II study design was used. After testing plitidepsin on 16 patients in the first stage, the trial was to be terminated if no responses were observed. If the trial proceeded on to the second stage, a total of 58 patients were to be studied; of these, a specific subset cohort of 28 evaluable patients with relapsed/refractory aggressive PTCL patients was to be enrolled. If seven or less patients in the cohort of 28 patients with relapsed/refractory aggressive PTCL were responders, the hypothesis that $P \geq 0.350$ for this indication would be rejected, with an actual error rate beta = 0.182, and this plitidepsin schedule would no longer be investigated in this setting. Otherwise, if eight or more responses were observed in this subset, the null hypothesis $P \geq 0.150$ would be rejected with an error rate alpha = 0.049, hence concluding that this plitidepsin schedule would deserve further investigation for this indication. **Patients analyzed:** Responses were found in two patients with angioimmunoblastic T-cell lymphoma among the 16 patients treated in the first stage of the study; therefore, the study proceeded onto the second stage. A total of 67 patients were enrolled at 14 investigational sites in Europe and Peru: 34 with non-cutaneous PTCL and 33 with other lymphomas. Sixty-four patients were treated with plitidepsin: 32 in each cohort. Five patients with non-cutaneous PTCL and three with other lymphomas were excluded from the primary analysis of efficacy. Therefore, 29 patients in the non-cutaneous PTCL cohort and 30 in the other lymphomas cohort were evaluable for efficacy, whereas 32 patients in each cohort were evaluable for safety.	
Diagnosis and main selection criteria	**<u>Inclusion Criteria</u>** 1. Written informed consent obtained before starting any study-specific procedure. 2. Histologically confirmed aggressive lymphomas, including the following: 2.1 B-Cell neoplasms. 2.1.1 Precursor B-cell neoplasm. 2.1.1.1.1 Precursor B-lymphoblastic lymphoma. 2.1.2 Mature (peripheral) B-cell neoplasms. 2.1.2.1.1 Follicular lymphoma (histological conversion). 2.1.2.1.2 Mantle-cell lymphoma (diffuse pattern or blastic variant). 2.1.2.1.3 Diffuse large B-cell lymphoma. 2.1.2.1.4 Mediastinal large B-cell lymphoma. 2.1.2.1.5 Burkitt's lymphoma/Burkitt cell leukemia. 2.2 T-cell and NK-cell neoplasms.	

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2.2.1 Precursor T-cell neoplasm.
2.2.1.1.1 Precursor T-lymphoblastic lymphoma.
2.2.2 Mature (peripheral) T-cell neoplasms.
2.2.2.1.1 Aggressive NK-cell leukemia.
2.2.2.1.2 Adult T-cell lymphoma/leukemia (HTLV1).
2.2.2.1.3 Extranodal NK/T-cell lymphoma, nasal type.
2.2.2.1.4 Enteropathy-type T-cell lymphoma.
2.2.2.1.5 Hepatosplenic gamma-delta T-cell lymphoma.
2.2.2.1.6 Subcutaneous panniculitis-like T-cell lymphoma.
2.2.2.1.7 Anaplastic large-cell lymphoma, T/null cell, primary cutaneous type.
2.2.2.1.8 Peripheral T-cell lymphoma, not otherwise characterized.
2.2.2.1.9 Angioimmunoblastic T-cell lymphoma.
2.2.2.1.10 Anaplastic large-cell lymphoma, T/null cell, primary systemic type.

3. Patient required treatment because of NHL relapse following response to standard chemotherapy or high-dose chemotherapy + stem cell transplantation (SCT), or NHL was refractory [i.e., failure to achieve al least CR, PR or stable disease (SD)] to its more recent chemotherapy.
4. Prior autologous and/or allogeneic SCT was allowed. In case of allogeneic hematopoietic SCT, the patient had to be off immunosuppressive agents before he could be enrolled.
5. Disease was measurable: existence of a bidimensional lesion greater than 2 cm in its longer diameter or malignant lymphocytosis greater than 5×10^9/l. Any other procedure for measurable disease in particular cases could be allowed upon PharmaMar's approval.
6. Recovery from any non-hematological toxicity derived from previous treatments. The presence of alopecia and National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade < 2 symptomatic peripheral neuropathy was allowed.
7. Age ≥ 18 years.
8. Performance status (ECOG) ≤ 2.
9. Adequate renal, hepatic, and bone marrow function (assessed ≤ 14 days before inclusion in the study):
   - Neutrophil count ≥ 1.5×10^9/l.
   - Platelet count ≥ 100×10^9/l.
   - Hemoglobin ≥ 8.0 g/dl.
   - Creatinine clearance ≥ 40 ml/min (calculated from the Cockcroft and Gault's formula).
   - Serum bilirubin ≤ 1.5 mg/dl and alkaline phosphatase (AP) ≤ 2.5 x the upper limit of normal (ULN) (≤ 5 x ULN in case of extensive bone involvement).
   - Aspartate aminotransferase (AST), alanine aminotransferase (ALT) ≤ 2.5 x ULN (≤ 5 x ULN in case of liver involvement).
   - Albumin ≥ 25 g/l.

   Lower hematological values due to bone marrow infiltration could be accepted upon PharmaMar's approval after clinical discussion between PharmaMar and the Investigator.
10. Left ventricular ejection fraction (LVEF) within normal limits.

<u>Histological Inclusion Criteria for the PTCL Expansion Cohort:</u>

1. Histologically confirmed relapsed/refractory aggressive PTCL, including the following:
   1.1 Mature (peripheral) T-cell neoplasms.
   1.1.1 Adult T-cell lymphoma/leukemia (HTLV1).
   1.1.2 Extranodal NK/T-cell lymphoma, nasal type.
   1.1.3 Enteropathy-type T-cell lymphoma.

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1.1.4 Hepatosplenic gamma-delta T-cell lymphoma.
1.1.5 Subcutaneous panniculitis-like T-cell lymphoma.
1.1.6 Peripheral T-cell lymphoma, not otherwise characterized.
1.1.7 Angioimmunoblastic T-cell lymphoma.
1.1.8 Anaplastic lymphoma kinase (ALK)- or Post-transplant refractory/relapsed ALK+ anaplastic large-cell lymphoma, T/null cell, primary systemic type.

Exclusion Criteria

1. Prior therapy with plitidepsin.
2. Concomitant therapy with any anti-lymphoproliferative agent, including glucocorticoids at a daily dose greater than 10 mg prednisone or equivalent, except when they were indicated for symptom control and disease progression was documented while on steroids.
3. Acute lymphoblastic leukemia.
4. Central nervous system (CNS) lymphoma.
5. Human immunodeficiency virus (HIV)-associated lymphoma.
6. Prior gene therapy with viral vectors.
7. More than three previous lines of systemic biological agents or chemotherapies. (Bone marrow or stem cell transplantation as consolidation therapy of a previous response was understood as one line of chemotherapy).
8. Washout periods since the end of the precedent therapy less than:
   - Six weeks for nitrosourea or high-dose chemotherapy.
   - Three weeks for other chemotherapies or biological agents.
   - Four weeks for radiation or radionuclide therapy (six weeks in case of prior extensive external beam radiation (more than 25% of bone marrow distribution).
   - Four weeks for major prior surgery.
   - Thirty days for any investigational product.
   - Four weeks for immunosuppressive therapy after allogeneic hematopoietic stem cell transplantation.
9. Pregnant or lactating women.
10. Men and women of reproductive potential who were not using effective contraceptive methods (one or more of the following):
    - Complete abstinence from intercourse from two weeks prior to administration of the study drug, throughout the study, and for at least six months after completion or premature discontinuation from the study to account for elimination of the investigational drug; or,
    - Patient or patient's partner physical sterilization; or,
    - One of the following, for female patients or female partner of male patients:
      - o Implants of levonorgestrel; or,
      - o Injectable progestogen; or,
      - o Oral contraceptive (combined or progestogen only; patients taking oral contraceptives had to have been on a stable regimen for at least two months prior to screening); or,
      - o Any intrauterine device (IUD) with published data showing that the lowest expected failure rate is less than 1% per year (not all IUDs meet this criterion); or,
      - o Double barrier method (two physical barriers or one physical barrier plus spermicide); or,
      - o Any other method with published data showing that the lowest expected failure rate for that method is less than 1% per year.
11. History of another neoplastic disease. The exceptions were:
    - Non-melanoma skin cancer.
    - Carcinoma in situ of any site.

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	• Any other cancer curatively treated and no evidence of disease for at least ten years. 12. Known cerebral or leptomeningeal involvement. 13. Other relevant diseases or adverse clinical conditions: • History or presence of unstable angina, myocardial infarction, valvular heart disease or congestive heart failure. • Previous mediastinal radiotherapy. • Uncontrolled arterial hypertension despite optimal medical therapy. • Previous treatment with doxorubicin at cumulative doses in excess of 400 mg/m^2. • Symptomatic arrhythmia requiring treatment. • Abnormal electrocardiogram (ECG). • History of significant neurological or psychiatric disorders. • Active infection; infection by HIV, hepatitis B virus (HBV) or hepatitis C virus (HCV). • Myopathy or any clinical situation that caused significant and persistent elevation of creatine phosphokinase (CPK) (>2.5 x ULN in two different determinations performed with one week apart). • Significant non-neoplastic liver disease (e.g., cirrhosis, active chronic hepatitis). • Uncontrolled endocrine diseases (e.g., diabetes mellitus, hypothyroidism or hyperthyroidism) (i.e. requiring relevant changes in medication within the last month, or hospital admission within the last three months). 14. Treatment with any investigational product in the 30-day period before inclusion in the study. 15. Known hypersensitivity to plitidepsin, mannitol, Cremophor® EL, or ethanol. 16. Limitation of the patient's ability to comply with the treatment or follow-up protocol. <u>Histological Exclusion Criteria for the PTCL Expansion Cohort:</u> 1. Histology different from mature PTCL: 1.1 Primary cutaneous type T-cell lymphoma (CTCL). 1.2 Precursor T-cell/NK cell lymphoma/leukemia. 1.3 Primary T-cell leukemic forms.	
Test product, dose and mode of administration	Plitidepsin was supplied by PharmaMar (Colmenar Viejo, Madrid, Spain) as a lyophilized powder for concentrate for solution for infusion, available in vials with two strengths: 0.5 mg or 2 mg. The 0. 5-mg and 2-mg vials had to be reconstituted by adding 1 ml (0. 5-mg vials) or 4 ml (2-mg vials) of reconstitution solution [Cremophor®/ethanol/Water for Injection, 15%/15%/70% (v/v/v). The reconstituted solution had to be clear, colorless and essentially clear from visible particles, and contained 0.5 mg/ml of plitidepsin. It then had to be immediately diluted with 0.9% w/v sodium chloride solution for infusion, at an allowed dilution range of 1:10 to 1:400 (v:v). The total volume of infusion was to be between 250 and 500 ml for administration through a central venous catheter, which was recommended. In cases where administration occurred through a peripheral line, the reconstituted drug was to be diluted to a total volume of 500 ml. Plitidepsin was administered **as a 1-hour intravenous (i.v.) infusion of 3.2 mg/m^2 weekly on Days 1, 8 and 15 in 4-week cycles**. The numbers of the plitidepsin batches were as follows: • **0.5-mg vial batches:** #01G02 and #04K25. • **2-mg vial batches:** #03D07, #03I25, #04H27, #05C10, #05E25, #06B15, #06K08, #07I27 and #08K20.	

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Duration of treatment	Treatment was to be administered until progressive disease, at first myocardial damage signal, unmanageable toxicity, withdrawal of patient's consent, treatment delay for more than two weeks (except in case of obvious patient's benefit). In addition, patients with CR were to discontinue therapy after receiving three additional cycles beyond the date of confirmation of CR. After the end of study treatment (regardless of the reason for discontinuation), patients had to undergo toxicity, hematology and biochemistry assessments within 30 days after the administration of the last plitidepsin dose and until the recovery/stabilization of all toxicities that occurred during protocol treatment. Beyond 30 days after the last administration of plitidepsin, only those procedures that were relevant to response assessment or any remaining toxicity needed to be performed. All serious adverse events (SAEs) occurring within 30 days of the last study drug administration had to be reported. Beyond this time limit, only plitidepsin-related SAEs were to be reported.	
Criteria for evaluation **Efficacy**	The primary efficacy endpoint was the objective response rate (ORR), defined as the combined rate of CR, unconfirmed complete response (CRu) and PR following the definition of response according to the International Working Group (IWG) criteria for NHL. All eligible patients who received at least one complete or incomplete treatment cycle and had at least one disease assessment were to be considered evaluable for efficacy. Secondary efficacy endpoints were time to response onset, duration of response, time to progression (TTP), time to subsequent chemotherapy, progression-free survival (PFS) and overall survival (OS).	
Safety	All patients who had received at least (part of) one plitidepsin infusion were evaluable for safety. Safety parameters included the description of toxic deaths, premature withdrawals from treatment due to toxicity, description of adverse events (AEs), description of SAEs, and evaluation of toxicity according to the NCI-CTC, version 3.0.	
Pharmacokinetics	All patients included in the cohort of patients with PTCL were to be sampled for PK. Blood samples were to be taken at specific times before, during and after administration of the first plitidepsin infusion.	
Pharmacogenomics	Paraffin-embedded tumor tissue samples were to be obtained from patients with T-cell lymphoma consenting for the pharmacogenomic (PGx) testing either at initial diagnosis (in the case of refractory patients) or after relapse (in the case of relapsed patients). However, samples for the PGx substudy were only collected from two patients. Due to this low number of samples, the PGx substudy was not conducted.	
Statistical methodology	The efficacy and safety analyses were to be performed separately for the subset of treated patients with non-cutaneous PTCL, and for the subset of treated patients with other lymphomas (including those with B-cell lymphoma and other types of T-cell lymphoma considered together). Summary tables, data listings and statistical analyses were to be generated using the SAS statistical package (version 8.2). Categorical variables were to be summarized in frequency tables; percentages in the summary table were to be rounded and could therefore not always add up to exactly 100%. Continuous variables were to be summarized and presented with summary statistics (i.e., mean, standard deviation, median and range). The demographics and baseline characteristics of all recruited patients were to be summarized. Age, sex, race, baseline weight, height, body mass index (BMI), performance status (PS) and body surface area (BSA) were to be summarized descriptively. For cancer history, histology diagnosis, number of organs involved and sites of disease were to be described following standard tables. A frequency tabulation of the number of patients with and the different types of previous cancer surgery, radiotherapy or chemotherapy and biological values was to be given. In addition, a summary of prior relevant history and signs and symptoms was to be presented per patient. For the evaluation of the primary endpoint, ORR, the percentage of patients with any	

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	response (PR or CR/CRu) and the percentages of patients with PR and CR/CRu separately were to be characterized using descriptive statistics (95% confidence interval, range of value). Time-dependent parameters were to be analyzed using the Kaplan-Meier method (duration of response, TTP, PFS, OS, time to subsequent chemotherapy) or calculating the median and range of values (time to response). If relevant efficacy data were observed, the efficacy parameters were to be subjected to further appropriate analysis, considering correlation with factors of probable prognostic value and using the Fisher's exact test or the Pearson χ^2 as appropriate. All AEs were to be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 5.0). Toxicities were to be coded using the NCI-CTC, version 3.0. All deaths, all SAEs and all events resulting in study discontinuation also were to be tabulated. Additional safety analyses could be determined at any time in order to most clearly enumerate the rates of toxicities and to further define the safety profile of plitidepsin. The PK results were to be obtained using standard non-compartmental methods, and then integrated in the general population database.	
Results (1): <u>Patient characteristics</u>	**<u>Non-cutaneous PTCL</u>** Of the 34 patients enrolled, 24 (70.6%) were male, most (n=29, 85.3%) were Caucasians, and their median age was 58 years (range, 22-80 years). Most patients (n=27, 79.4%) had ECOG PS score of 0 or 1. All had mature T-cell neoplasms, including PTCL (n=17, 50.0%), angioimmunoblastic T-cell lymphoma (n=9, 26.5%), anaplastic large-cell lymphoma (n=5, 14.7%), and extranodal NK/T-cell lymphoma (n=3, 8.8%). Most (n=23, 67.6%) had stage III-IV disease. Eighteen (52.9%) had refractory disease while the other 16 (47.1%) had relapsed. The median time from initial diagnosis to the first plitidepsin infusion was 17.7 months (range, 3.2-99.3 months). At study entry, 30 patients (88.2%) had sites of disease involving lymph nodes; the median number of these sites per patient was 3.5 (range, 0-10). Sixteen patients (47.1%) had extranodal sites of disease (median, 0; range, 0-3). Seven patients (20.6%) had bone marrow involvement. All 34 patients had received prior systemic anticancer therapy, with a median of 2 lines (range, 1-5 lines) and 9 agents (range, 4-16 agents). The most common agents were vinca alkaloids and analogues (n=34, 100%), anthracyclines and related substances (n=34, 100%), and nitrogen mustard analogues (n=33, 97.1%). Other prior anticancer therapies comprised radiotherapy (n=8, 23.5%) and autologous stem cell transplantation (ASCT) (n=9, 26.5%). **<u>Other Lymphomas</u>** Of the 33 patients enrolled, 22 (66.7%) were male, most (n=32, 97.0%) were Caucasians, and their median age was 63 years (range, 17-79 years). Most patients (n=24, 72.7%) had ECOG PS score of 0 or 1. Most patients had mature B-cell neoplasms, including diffuse large B-cell lymphomas (n=20, 60.6%), mantle-cell lymphoma (n=5, 15.2%), follicular lymphoma (n=3, 9.1%) and Burkitt's lymphoma (n=1, 3.0%), In addition, two patients (6.1%) had mature cutaneous T-cell neoplasms and two more (6.1%) had precursor T-cell lymphoblastic lymphomas. Most patients (n=24, 72.7%) had stage III-IV disease. Twenty-four (72.7%) had refractory disease, and nine (27.3%) had relapsed. The median time from initial diagnosis to the first plitidepsin infusion was 22.4 months (range, 2.2-119.1 months). At study entry, 27 patients (81.8%) had sites of disease involving lymph nodes; the median number of these sites per patient was 2 (range, 0-11). Eighteen (54.5%) had extranodal sites of disease (median, 1; range, 0-3). Seven patients (21.2%) had bone marrow involvement. All 33 patients had received prior systemic anticancer therapy, with a median of 3 lines (range, 1-10 lines) and 10 agents (range, 4-18 agents). The most common agents were vinca alkaloids and analogues (n=33, 100%), anthracyclines and related substances (n=33, 100%), and nitrogen mustard analogues (n=33, 100%). Other prior anticancer therapies comprised radiotherapy (n=11, 33.3%) and ASCT (n=7, 21.2%).	

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Results (2): Efficacy	**Non-cutaneous PTCL** - Primary efficacy endpoint: ORR. A total of six patients in this cohort were responders: two had CR and four had PR. Thus, the ORR was 18.8% (95% CI, 7.2%-36.4%) for the 32 treated patients, and 20.7% (95% CI, 8.0%-39.7%) for the 29 patients evaluable for efficacy. - Secondary efficacy endpoints. The median time to response onset in the six responders was 7.5 weeks (range, 6.9-7.9 weeks). The median duration of response among the six responders was 2.2 months (range, 0-27.9 months). The median TTP was 1.6 months (95% CI, 1.1-3.0 months). The median time to subsequent chemotherapy was 3.8 months (95% CI, 2.3-5.6 months). The median PFS was 1.6 months (95% CI, 1.1-2.7 months). The median OS was 10.2 months (95% CI, 4.4-24.3 months). **Other Lymphomas** - Primary efficacy endpoint: ORR. No patients in this cohort had CR, CRu or PR. Thus, the ORR was 0% (95% CI, 0%-10.9%) in the 32 treated patients, and 0% (95% CI, 0%-11.6%) in the 30 patients evaluable for efficacy. - Secondary efficacy endpoints. Neither the median time to response onset nor the median duration of response could be calculated for this cohort, owing to the lack of responses. The median TTP was 1.3 months (95% CI, 0.8-1.6 months). The median time to subsequent chemotherapy was 1.9 months (95% CI, 1.4-2.6 months). The median PFS was 1.3 months (95% CI, 0.8-1.6 months). The median OS was 4.5 months (95% CI, 2.7-6.4 months). Owing to the lack of objective responses, it was decided not to further investigate this plitidepsin schedule in B-cell lymphomas or in T-cell lymphomas other than non-cutaneous PTCL.	
Results (3): Safety	**Non-cutaneous PTCL** A total of 77 cycles of plitidepsin were administered to patients in this cohort. The median number of cycles per patient was 2 (range, 1-8) and the median relative dose intensity was 87.4% (range, 2.8%-101.8%). Most plitidepsin-related AEs were mild or moderate (grade 1 or 2) in severity. The most common were nausea (31.3% of patients/19.5% of cycles), fatigue (21.9% of patients/19.5% of cycles), vomiting (15.6% of patients/7.8% of cycles), myalgia (12.5% of patients/13.0% of cycles), muscle weakness (12.5% of patients/7.8% of cycles) and pyrexia (12.5% of patients/6.5% of cycles). Five of the 32 treated patients (15.6%) had severe plitidepsin-related AEs; these comprised grade 3/4 muscle weakness (n=2), grade 4 back pain, grade 4 Guillain-Barré syndrome, grade 3 cardiac troponin I increase, grade 3 ejection fraction decrease, grade 3 injection site reaction, grade 3 ECG QTc interval prolonged, grade 3 myalgia, grade 3 supraventricular arrhythmia and grade 3 tachycardia (n=1). Most patients were able to continue receiving this plitidepsin schedule. Only two patients discontinued the treatment due to plitidepsin-related AEs: grade 2 maculo-papular rash and grade 3 injection site reaction (n=1 each). In addition, one patient died due to grade 4 Guillain-Barré syndrome, which had an unknown relationship with plitidepsin. A total of 11 plitidepsin-related SAEs were reported in three patients (9.4%): one with grade 3 myalgia, grade 3 muscular weakness and grade 4 Guillain-Barré syndrome; one with grade 4 back pain, grade 3 injection site reaction, grade 2 hypotension and grade 2 chills; and one with grade 2 asthenia and grade 1 pyrexia, followed in the next cycle by grade 3 troponin I increase and grade 3 ejection fraction increase [which was considered a suspected unexpected serious adverse reaction (SUSAR)]. Most	

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plitidepsin-related SAEs resolved; the two exceptions were grade 4 Guillain-Barré syndrome (which had a fatal outcome) and grade 3 ejection fraction decrease (which was ongoing at the time of the patient's death due to disease progression).

Eleven patients (34.4%) died during the study period. Eight died due to disease progression, one due to the aforementioned episode of Guillain-Barré syndrome, and two due to septic shock unrelated to plitidepsin.

The most common grade 3/4 hematological abnormality was lymphopenia (37.5% of patients/22.4% of cycles), followed by grade 3/4 thrombocytopenia (15.6% of patients/9.2% of cycles), grade 3/4 neutropenia (15.6% of patients/7.9% of cycles), grade 3/4 leukopenia (9.4% of patients/6.6% of cycles) and grade 3 anemia (9.4% of patients/3.9% of cycles). Of note, all patients with severe anemia and two each of the patients with severe neutropenia and thrombocytopenia already had these hematological abnormalities at baseline. No dose delays, infusion omissions or dose reductions occurred as a result of anemia or lymphopenia episodes. Episodes of neutropenia and thrombocytopenia resulted in one dose delay each, while those of leukopenia caused two dose delays and two dose omissions. No cases of febrile neutropenia were found.

Most severe biochemical abnormalities did not reach grade 4. The most common was transient grade 3 ALT increase (25.8% of patients/12.0% of cycles), followed by transient grade 3 AST increase (16.1% of patients/6.7% of cycles); episodes of transaminase increases resulted in five dose omissions and two dose reductions. CPK increase reached grade 4 in 10.3% of patients/4.3% of cycles, and was the cause of three dose omissions and one dose reduction; in addition, two patients discontinued treatment due to grade 2 CPK increase related to plitidepsin. Other biochemical abnormalities (grade 3 AP increase, grade 3 amylase increase, and grade 3 total bilirubin increase) only occurred in one patient and one cycle each and had no effects on treatment. No cases of severe creatinine increases were found. Two patients each with grade 3 ALT and AST increase, and both single cases of grade 3 AP increase and grade 3 total bilirubin increase, occurred in patients who already had these biochemical abnormalities at baseline, although at grade < 3.

A total of nine dose delays occurred in this cohort. Five were due to reasons related to treatment: hematological toxicity (neutropenia; leukopenia; and thrombocytopenia (n=1 each)] and non-hematological toxicity (myalgia plus muscular weakness; and QTc increase (n=1 each)]. The other four were due to reasons unrelated to plitidepsin.

Fifteen dose omissions in this cohort were related to plitidepsin: 13 were due to non-hematological toxicity [ALT increase alone or concomitant with CPK increase (n=5), CPK increase alone (n=2), hypersensitivity reaction (n=2), maculo-papular rash (n=2), muscular weakness (n=1), and supraventricular arrhythmia and tachycardia (n=1)] and two were due to hematological toxicity (leukopenia concomitant with fatigue unrelated to plitidepsin).

A total of four dose reductions occurred in this cohort. Three were due to non-hematological toxicity: transaminase increase alone or concomitant with grade 4 CPK increase (n=2), and myalgia with muscular weakness (n=1). The other dose reduction was due to reasons unrelated to plitidepsin.

Other Lymphomas

A total of 57 cycles of plitidepsin were administered to patients in this cohort. The median number of cycles per patient was 1.5 (range, 1-4). The median relative dose intensity was 94.6% (range, 33.1%-102.3%).

Most treatment-related AEs were mild or moderate (grade 1 or 2) in severity. The most common were nausea (37.5% of patients/22.8% of cycles), myalgia (31.3% of patients/22.8% of cycles), fatigue (28.1% of patients/21.1% of cycles) and vomiting (12.5% of patients/7.0% of cycles). Overall, three patients (9.4%) had severe treatment-related AEs: grade 4 fatigue, grade 3 edema and grade 3 gamma-glutamyltransferase (GGT) increase (n=1 each).

Most patients were able to remain on treatment. Only one patient discontinued due to plitidepsin-related AEs (grade 2 muscular weakness and grade 4 fatigue).

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	Two plitidepsin-related SAEs occurred in one patient (3.1%). These consisted of two episodes of grade 3 and 4 fatigue that were concomitant with CPK increase (which was suggestive of muscular toxicity but was not considered a SAE). Both SAEs resolved, but the patient was hospitalized and later withdrawn from the study. Eleven patients died during the study period, all due to disease progression. The most common grade 3/4 hematological abnormality was lymphopenia (29.0% of patients/23.2% of cycles), followed by grade 3 anemia (21.9% of patients/12.3% of cycles), grade 3/4 thrombocytopenia (15.6% of patients/8.8% of cycles), grade 3 neutropenia (6.5% of patients/3.6% of cycles) and grade 3 leukopenia (3.1% of patients/1.8% of cycles). Of note, all patients with severe anemia or neutropenia, and three of the five patients with severe thrombocytopenia, already had these hematological abnormalities at baseline. No dose delays, infusion omissions or dose reductions occurred due to hematological abnormalities. No patients in this cohort had febrile neutropenia. Most severe biochemical abnormalities in this cohort did not reach grade 4. The most common was transient grade 3 ALT increase (18.8% of patients/15.8% of cycles), followed by transient grade 3 AST increase (6.3% of patients/3.5% of cycles) and grade 3/4 CPK increases (6.5% of patients/3.6% of cycles). These were the only biochemical abnormalities that had any effects on treatment: severe transaminase increases resulted in one dose delays, five dose omissions and three dose reductions, whereas severe CPK increases resulted in one dose delay and one dose reduction. Other biochemical abnormalities (grade 3 AP increase and grade 3 creatinine increase) only occurred in one patient and one cycle each, and had no effects on treatment. Of note, the case of grade 3 AP increase and one of the six cases of grade 3 ALT increase occurred in patients who already had these biochemical abnormalities at baseline, although at grade < 3. No cases of severe amylase or total bilirubin increase were found. A total of five dose delays occurred in this cohort. Two of them were due to plitidepsin-related reasons (increases in ALT and CPK levels), while the other three were due to reasons unrelated to plitidepsin. All seven dose omissions in this cohort were due to non-hematological toxicity related to plitidepsin: transaminase increases alone or with GGT increase (n=5, including one categorized as hepatic toxicity); muscular toxicity and asthenia; and gastric disorder (n=1 each). All four dose reductions were due to non-hematological toxicity: transaminase increase alone (n=3); and CPK increase (n=1).	
Results (4): Pharmacokinetics	The PK of plitidepsin was investigated in 23 evaluable patients after receiving the first infusion of plitidepsin as a 1-hour i.v. infusion at a dose of 3.2 mg/m². The mean (standard deviation, SDev) total body clearance of plitidepsin was 7.45 (3.44) l/h, the mean volume of distribution at steady-state (V_{ss}) was 355 (231) l and the mean terminal half-life was 36.5 (6.24). These values were in line with the results observed in patients with solid tumors who were treated with the same plitidepsin dose and schedule in another phase I study. A population PK model for plitidepsin consisting of an open, three-compartment model with linear elimination and distribution from the central compartment was found to be appropriate to describe the time course of i.v. plitidepsin whole blood concentrations in the lymphoma patients enrolled into this study. The univariate analysis of the relationship between baseline covariates and PK parameters after the first plitidepsin infusion showed that hemoglobin, serum albumin, BSA, creatinine, β2-microglobulin and weight had some effect on whole blood clearance, and while hemoglobin, serum albumin, BSA, creatinine and weight had some effect on whole blood V_{ss}, hemoglobin was the only one to maintain a statistically significant effect on these parameters in the multivariate analysis, although its significance vanished after serum albumin was added to the model.	

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Conclusions	Plitidepsin 3.2 mg/m^2 given as a 1-hour i.v. infusion on Days 1, 8 and 15 in 4-week cycles induced objective tumor response in 20.7% of patients with non-cutaneous PTCL, which included two CRs in previously transplanted patients; this response lasted for more than 27 months in one patient and was associated with complete remission of the bone marrow in the other patient. In contrast, no patients with B-cell lymphomas or cutaneous T-cell lymphomas responded to plitidepsin. The PK profile obtained for this single-agent plitidepsin schedule in patients with non-cutaneous PTCL was similar to that previously found in patients with solid tumors. The schedule was generally well tolerated both in patients with non-cutaneous PTCL and in those with other lymphomas. These results warrant the conduct of further clinical trials to evaluate plitidepsin combined with other chemotherapeutic drugs in the management of relapsed/refractory non-cutaneous PTCL.	
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