1 TITLE PAGE

Clinical Study Report: PXD101-CLN-19

Study Title:	**A Multicenter, Open-Label Trial of Belinostat in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma**
Study Number:	PXD101-**CLN-19**
Study Phase:	2
Study Design:	Open-label, non-randomized, multicenter
Product Name:	Belinostat
Indication:	Relapsed or refractory peripheral T-cell lymphoma (PTCL)
First Patient Dosed:	11-May-2009
Case Report Form Data Cut-off:	31-Aug-2012
Principal Investigator:	Owen O'Connor, MD, PhD (see Appendix 16.1.5)
Sponsor:	Spectrum Pharmaceuticals, Inc. 157 Technology Drive Irvine, CA 92618 949-788-6700
Responsible Medical Officer:	Shanta Chawla, MD
Final Date:	05-Nov-2013

This study was designed, conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) guidelines. These guidelines are stated in U.S. Federal regulations as well as "Guidance for Good Clinical Practice," International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

CLINICAL STUDY REPORT APPROVAL SIGNATURE PAGE

Protocol Title: A Multicenter, Open-Label Trial of Belinostat in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma

Protocol Number: PXD101-**CLN-19**

Reviewed and Approved by:

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Authorized Sponsor Representative Signature

Signature: _____ Date: 07 NOV 2013

Name: Lee F. Allen, MD, PhD
Title: CMO
Head of Medical Development

2 SYNOPSIS

NAME OF COMPANY Topotarget A/S and Spectrum Pharmaceuticals, Inc.	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT Belinostat Injection 50 mg/mL		
NAME OF ACTIVE INGREDIENT Belinostat (PXD101)		

TITLE OF STUDY:
A Multicenter, Open-Label Trial of Belinostat in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma

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PUBLICATION (REFERENCE):

1. S. Horwitz,O. O'Connor, W. Jurczak, A.Van Hoof, G. Hess, Z. Gasztonyi et al. Belinostat in Relapsed or Refractory Peripheral T-Cell Lymphoma-Cell Lymphoma (R/R PTCL) Subtype Angioimmunoblastic Subtype Angioimmunoblastic T-cell lymphoma (AITL): Results from the Pivotal BELIEF TRIAL. 12th International Conference on Malignant Lymphoma. 2013.
2. O. O'Connor, T. Masszi, K. Savage, L. Pinter-Brown, F. Foss, L. Popplewell, et al. Belinostat-A Novel Pan-histone Deacetylase Inhibitor (HDACi) in Relapsed or Refractory Peripheral T-cell Lymphoma (R/R PTCL): Results from the BELIEF trial. ASCO 2013.
3. O. O'Connor, S. Horwitz, T. Masszi, L. Pinter-Brown, S. Chawla, A. Shustov. Belinostat in Relapsed or Refractory Peripheral T-Cell Lymphoma (R/R PTCL): Preliminary Safety Results from the BELIEF Trial. T-Cell Forum 2013.

STUDY PERIOD:		**PHASE OF DEVELOPMENT:**
First patient enrolled:	04-May-2009	Phase 2 (Pivotal)
Last Patient enrolled:	02- Aug-2011	

OBJECTIVES:

The primary objectives of the study were:

- To determine the efficacy of belinostat monotherapy treatment as measured by Objective Response Rate (ORR), in patients with recurrent or refractory peripheral T-cell lymphoma (PTCL).

The secondary objectives for the PTCL population were:

- To determine duration of response
- Time to Response (TTR)
- Time to Progression (TTP)
- Progression-free Survival (PFS)
- 1-year Progression-free Rate
- Overall Survival (OS)
- 1-year Survival Rate following belinostat monotherapy.
- To assess safety following belinostat monotherapy

Additional objectives were to assess:

- Population pharmacokinetics (PK)
- Medical Care Utilization

METHODOLOGY:

This was a single arm, open-label, multicenter, Phase 2 study designed to determine the safety and efficacy

of belinostat monotherapy at a dose of 1,000 mg/m^2/day in the treatment of patients with relapsed or refractory PTCL after failure of at least 1 line of prior systemic therapy.

The study used the optimal 2-stage Simon design. Under this design, ≥5 objective responses (defined as complete response [CR] or partial response [PR] based on Independent Review Committee [**IRC**]) among the initial 41 evaluable patients who had received at least 1 dose of belinostat were required or the study would have been discontinued for futility. An independent Data Monitoring Committee (**DMC**) was charged with monitoring the safety of the study and was empowered to make recommendations to the Sponsor including halting the study or proposing an amendment to the protocol. The planned enrollment was approximately 120 patients to ensure a minimum of 100 evaluable patients at the conclusion of accrual. A total of 129 PTCL patients with PTCL diagnosis based on local pathology were treated in the study.

A central pathology review group (**CPRG**) confirmed the diagnosis of eligible PTCL histopathological subtypes. The primary study endpoint was ORR, defined as a CR or PR based on the independent central radiology and oncology clinical review by the **IRC**. Tumor assessments according to the International Harmonization Project (IHP) revision of the International Working Group (IWG) criteria [Cheson et al, 2007] were made by radiologic imaging using computerized tomography (CT) scans.

Radiology and oncology response assessments to assess on-study efficacy were performed by the **IRC**. Assessments were performed at Baseline (Day -28 [Screening] to Cycle 1, Day 1 prior to belinostat treatment) and every 6 weeks for the first 12 months, then every 12 weeks until 2 years from the start of study treatment. Radiological assessments were discontinued at the time of tumor progression or initiation of new anticancer therapy, after which survival data was collected every 3 months until 2 years from the start of study treatment or until study closure.

Adverse event (AE) assessments, physical examination, Eastern Cooperative Oncology Group (ECOG) performance status, electrocardiogram (ECG), vital signs, blood chemistry, clinical hematology, coagulation parameters, and urinalysis were used to assess on-study safety.

ECGs were assessed on each treatment day. ECG readings were performed by a central laboratory for analysis purposes but ECG interpretation for clinical management of patients was conducted by the treating physician.

NUMBER OF PATIENTS (PLANNED AND ANALYZED):

The planned number of patients was 120. The actual number of patients enrolled was 129.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

1. Male or female with age ≥18 years.
2. A histologically confirmed diagnosis of PTCL (based on histology and immunohistochemistry) by local pathology review, leading to the diagnosis of:
    - Anaplastic large-cell lymphoma (ALCL), anaplastic lymphoma kinase (ALK)-positive
    - ALCL, ALK-negative
    - Angioimmunoblastic T-cell lymphoma
    - Enteropathy-associated T-cell lymphoma
    - Extranodal natural killer (NK)/T-cell lymphoma, nasal type
    - Hepatosplenic T-cell lymphoma

- PTCL, not otherwise specified (NOS)
- Subcutaneous panniculitis-like T-cell lymphoma

3. Available pathology material for central review by the **CPRG**.
4. Relapsed or refractory disease after at least 1 prior systemic anti-lymphoma regimen.
5. At least 1 site of disease measurable in 2 dimensions by CT scans.
6. An absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L, platelets $\geq 50 \times 10^9$/L.
7. ECOG performance status 0-2.
8.
9. Estimated life expectancy greater than 3 months.
10. Negative pregnancy test for women of childbearing potential.
11. Signed an Informed Consent form approved by the local Ethics Committee (EC) or Institutional Review Board (IRB).

Key Exclusion Criteria

1. Any use of anticancer therapies within 2 weeks prior to initiation of study treatment.
2. Relapse within 100 days of autologous or allogeneic bone marrow transplant.
3. Prior histone deacetylase (HDAC) inhibitor therapy.
4. Patients with a diagnosis of:
   - Precursor T-cell lymphoma or leukemia
   - Adult T-cell lymphoma/leukemia
   - T-cell prolymphocytic leukemia
   - T-cell large granular lymphocytic leukemia
   - Primary cutaneous type anaplastic large cell lymphoma
   - Mycosis fungoides/Sezary syndrome
5. Baseline prolongation of QT/corrected QT (QTc) interval, i.e., demonstration of a QTc interval >450 msec; long QT Syndrome; the required use of a concomitant medication that may cause Torsades de Pointes.

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION; BATCH NUMBER:

Belinostat was administered at a dose of 1,000 mg/m^2 as a 30-minute IV infusion on Days 1-5 of a 21-day cycle.

The following belinostat batches were used: 07E24, 07H21, 09C06, 09J16, 10A28, 10C14, 11B04, 11H29.

DURATION OF TREATMENT:

All patients were to receive belinostat monotherapy unless a criterion for discontinuation occurred.

Patients were to be withdrawn from study drug treatment for the following reasons:

- Progressive Disease (PD)
- Unacceptable or recurrent toxicity despite optimal prophylaxis and appropriate dose modification
- Substantial non-compliance with the requirements of the study
- Positive pregnancy test
- Use of illicit drugs or other substances that may, in the opinion of the Investigator, have had a reasonable risk of contributing to toxicity or otherwise skewing results
- Development of an intercurrent illness or situation which, in the opinion of the Investigator, affected assessments of clinical status and study endpoints to a significant degree
- Interruption in study drug administration for >42 days since last study drug administration

The Investigator also could withdraw patients from study treatment, study-related procedures, or follow-up for the following reasons:

- In the Investigator's opinion, continuation would have been detrimental to the patient's well being
- The patient was lost to follow-up
- Patient withdrawal of consent

Patients who were withdrawn from study drug treatment were to continue study-related procedures and follow-up for toxicity, tumor assessments, and survival.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION; BATCH NUMBER:

No other therapy.

CRITERIA FOR EVALUATION:

EFFICACY: Tumor response was assessed by IWG criteria for patients with PTCL. The primary efficacy endpoint was ORR that included patients with CRs and PRs. In addition, the secondary endpoints of TTR, Duration of Response (IWG and Statistical Analysis Plan [SAP]-defined criteria), TTP, PFS, and OS. Time-to-event endpoints (TTR, TTP, PFS, and OS) were calculated from the time of first administration of belinostat (Day 1) until the stated event or end of study. The stated event for TTP included disease progression, for PFS included disease progression and death, for OS included death from all causes. Patients receiving subsequent therapy before PD was documented were censored. The Duration of Response was calculated by the **IRC** using IWG criteria as well as IWG criteria plus death.

Response was assessed both locally, on the basis of clinical and radiological criteria by the treating Investigator, as well as independently by the **IRC.** The primary analysis was pre-defined to be based on the **IRC** assessment.

SAFETY:

Safety assessments included analysis of AEs, clinical laboratory results (including hematology, coagulation parameters, and serum chemistry), vital signs, performance status, physical examination, urine analysis and ECG results. The Medical Dictionary for Regulatory Activities (MedDRA, version 14) was used for assigning System Organ Classes (SOC) and Preferred Terms. The summary of AEs was provided by SOC, Preferred Term, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE)

grade, and seriousness criteria.

STATISTICAL METHODS:

Descriptive statistics (incidence and confidence intervals [CI]) were used to summarize the number of patients exhibiting an ORR in this study. The significance level (alpha) for the primary efficacy analysis was set at 0.05; therefore, ORR was reported with a 95% CI estimated using 2-sided Clopper-Pearson method.

Similarly, secondary analyses are presented with 95% CIs.

Duration of Response by IWG criteria was measured from the date the measurement criteria were first met for CR or PR (whichever status was recorded first) until the first subsequent date that relapse or progression was documented. Per the SAP-defined criteria, Duration of Response was expanded from the IWG criteria by also adding the first subsequent date that death was documented. All other secondary efficacy endpoints were calculated from the time of first administration of belinostat (Day 1) until the stated event or the end of study. Time-to-event parameters were estimated using the Kaplan-Meier method.

All reported symptoms and AEs were graded for intensity using the NCI-CTCAE (v3.0) coding system. AEs were mapped to SOC and Preferred Term using MedDRA. Any AEs that occurred on or after administration of belinostat were considered as treatment-emergent AEs (TEAEs).

All vital signs and laboratory measurements were summarized and presented by time. For laboratory measurements, a summary based on the maximum CTCAE grades for each patient and each laboratory parameter is presented.

A shift analysis of all graded laboratory parameters was also performed. This analysis accounted for any laboratory abnormalities present at Baseline, and presented as the maximum grade shift during treatment (i.e., if a patient had Grade 2 decreased hemoglobin at Baseline and the worst grade during treatment was Grade 4, the resulting shift was a 2-grade shift).

All ECG data was summarized by time. ECG analyses were performed by an independent ECG laboratory (eRT).

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Of 129 patients enrolled with relapsed or refractory PTCL and treated with at least 1 dose of belinostat **(Full Analysis Dataset)**, 120 patients had a PTCL diagnosis confirmed by **CPRG** (**Efficacy Analysis Dataset**). **DMC** meetings were conducted at 2 time points in the study: an interim review of the data after the first cohort of 41 evaluable patients enrolled and results were available, and a final review at the end of enrollment. Upon completion of each of the reviews, the **DMC** recommended that the study continue. No changes to the protocol were recommended at either of the 2 **DMC** meetings.

IRC assessment of response by IWG criteria showed an ORR of 25.8% (31 patients), with 13 CRs and 18 PRs. Most patients (61.3% of responders) responded at the first scheduled tumor assessment within 30-45 days of the first dose, with a median TTR of 5.6 weeks. The ORR observed with belinostat was durable with a median Duration of Response by IWG criteria of 13.6 months. The median Duration of Response by expanded SAP-defined criteria and based on 31 responding patients was 8.4 months (95% CI, 4.5-29.4). Belinostat treated patients had a 63.5% probability of being in response at 6 months. The median PFS, based on response as assessed by the **IRC** and estimated by the Kaplan-Meier method, was 1.6 months (95% CI: