CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 206256
Supplement #:	000
Drug Name:	Belinostat
Indication(s):	Relapsed or refractory peripheral T-cell lymphoma
Applicant:	Spectrum Pharmaceuticals
Date(s):	Submission Date: December 9, 2013 PDUFA due Date: August 9, 2014 Review Completion Date: May 6, 2014
Review Priority:	Priority
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Erik Bloomquist, PhD
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Keywords: PTCL, peripheral T-cell lymphoma, Overall Response Rate, Duration of Response

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1 EXECUTIVE SUMMARY

In NDA 206256, Spectrum Pharmaceuticals is seeking accelerated approval of belionstat for the treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL). This review is for an NME.

The sponsor relied on a single-arm, phase 2, pivotal study to support their NDA submission (Study PXD101-CLN-19). Study CLN-19 examined 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. 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 confirmed that 120 out of 129 patients had PTCL.

Study CLN-19 showed an overall response rate (ORR) of 25.8% (95% CI [18.3%, 34.6%]). The median duration of response, based on 31 responding patients, was 8.4 months (95% CI, 4.5-29.4).

Study CLN-19 was designed as a nonrandomized study. Therefore, all statistical analyses were descriptive and no formal statistical comparisons were performed.

In summary, the study appears to demonstrate a good response to belionstat and a durable duration of response to support an accelerated approval. However, the final decision on the benefit-risk evaluation of belinostat is deferred to the clinical review team.

2 INTRODUCTION

2.1 Overview

Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of clinically aggressive hematologic malignancies that represent approximately 10% of all non-Hodgkin's lymphomas (NHL) in Western populations, and are associated with a poorer outcome and survival compared to the B-cell lymphomas. The majority of patients with PTCL relapse after initial treatment with cytotoxic agents or alternative modalities such as immunomodulators, and 5-year survival is less than 32%.

Currently, physicians treat most subtypes of CTCL using anthracycline-based chemotherapy regimens, predominantly the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), adopted from the management of B cell NHL. But, with the exception of anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL), patients with PTCL subtypes respond poorly to CHOP regimens.

Belinostat is a hydroxamic acid-derived potent pan-inhibitor of HDAC enzymes that alters the acetylation levels of histone and non-histone proteins and, in turn, modulates the expression of various cellular genes and pathways. HDACs regulate numerous cellular processes involved in differentiation, proliferation, migration, and survival, and have been shown to play multiple roles

in cancer pathogenesis. Through their pleiotropic effects, HDAC inhibitors may simultaneously target multiple signal transduction pathways crucial for tumor cell survival.

The proposed indication submitted in this NDA application is for the treatment of patients with relapsed/refractory PTCL (b) (4)

Study CLN-19 was a single-arm, phase 2, open-label, nonrandomized, and multicenter study designed to evaluate the efficacy and safety of belinostat monotherapy (1,000 mg/m^2 /day) relapsed or refractory PTCL after failure of at least 1 line of prior systemic therapy. The primary efficacy endpoint was overall response rate (ORR) based on independent review (IRC). The secondary efficacy endpoints were duration of response (DOR), time to response (TTR), time to progression (TTP), progression-free survival (PFS), 1-year progression-free rate, overall survival (OS), and 1-year survival rate.

A total of 129 patients with investigator assessed PTCL were enrolled. The first patient was enrolled on May 4, 2009, and the last patient was enrolled on August 2, 2011. The database was locked on March 1, 2013 for data up to August 31, 2012. Of the 129 patients enrolled 120 patients had IRC (Independent Review Committee) confirmed PTCL diagnosed. The 120 patients made up the primary efficacy analysis dataset. Throughout this review, the total sample sizes refer to the efficacy analysis dataset, unless otherwise noted.

The sponsor obtained a special protocol agreement (SPA) for CLN-19 in September 2008. A summary of study design is shown below:

2.2 Data Sources

Analysis datasets, SDTM tabulations, and software codes are located on network with network path: \\CDSESUB1\evsprod\NDA206256\0010

TABLE 1: LIST OF ALL STUDIES INCLUDED IN ANALYSIS

Study	Phase and Design	Treatment Period	Follow-up Period	# of Subjects	Enrollment period Geographic region
CLN-19	A Multicenter, Open-Label Trial of Belinostat in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma	Belinostat Was administered for 5 consecutive days every 21 days on Days 1-5 of the 21-day treatment cycle. Treatment until progressive disease (PD), death, or any other reason listed in the protocol for mandatory withdrawal.	All patients who received at least 1 dose of belinostat were to be followed for safety for 30 days after the last dose of belinostat.	N=120	08 February 2011 – 21 March 2012 62 sites in the US, Canada, Europe, Israel, and Africa

3 STATISTICAL EVALUATION

This statistical evaluation is based on data from the Study CLN-19. There were five versions of protocol with the first version dated 4/25/08 and the last version (V. 5) dated 1/4/2010. No patients were enrolled under protocol versions 1, 2 and 4. The first patient was enrolled under protocol version 3.0. The original SAP was dated 4/11/2008 and the final SAP was signed off on 1/30/2013. The SAP was amended twice during the course of the study, on 7/16/2008 and 2/11/2011, in order to align with amendments to the protocol. The only change in the SAP that may affect the efficacy evaluation is the addition of the duration of response calculated per IWG criteria.

3.1 Data and Analysis Quality

The overall response data for CLN-19 were derived and saved in analysis dataset "ADXR" for both IRC and investigator assessments. This NDA application provided the datasets in ADaM format along with SAS programs used for the analysis. The data quality was acceptable for review.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

3.2.1.1 Study Design

Study CLN-10 was a phase 2, open-label, nonrandomized, and multicenter study designed to evaluate the efficacy and safety of belionstat monotherapy. The study was based upon Simon's Two-stage optimal design, where one futility analysis is built in. The sponsor hypothesized an ORR of p_1=20% for belinostat and a minimal or "uninteresting" ORR of p_0=9%. Based upon these numbers, if there were fewer than 5 objective responses in the first 41 evaluable patients (based on IRC), the trial would have been discontinued for futility. Otherwise, the trial will continue until there are at least 100 evaluable patients for the primary efficacy analysis. If the trial continued on pass the futility look, 120 total subjects would be enrolled assuming 15% attrition rate.

Sample Size Calculation

This sample size was calculated assuming that at least 14 objective responses in 100 evaluable patients were required to confirm the 20% target response rate with an alpha of 0.05 assuming a power of 90%. With a total sample size of 100 patients, the half width of the 95% confidence interval for ORR would be approximately 7.8% based on a normal approximation. Assuming 15% attrition rate, 120 total subjects would be enrolled.

Interim Analysis

DMC (Data Monitoring Committee) meetings were conducted twice in the study, one after the first cohort of 41 evaluable patients enrolled and a final review at the end of enrollment. There was no change to the protocol at either of the 2 DMC meetings.

3.2.1.2 Efficacy Endpoints

The primary efficacy endpoint analysis was pre-defined to be based on response as assessed by the IRC.

As defined by the international working group (IWG), the duration of response was measured from the date that 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.

The duration of response was also measured by the SAP-defined criteria that expanded the IWG criteria by including death in addition to relapse or progression (i.e. based on the International

Harmonization Project [IHP] revision of IWG criteria). The SAP-defined criteria were used in the labelling.

For the SAP-defined criteria, the duration of response was measured from the date that measurement criteria were first met for CR or PR (whichever status was recorded first) until the first subsequent date of relapse, progressive disease, or death was documented. Patients who neither progressed nor died at the time of the last tumor assessment were censored at that time point for both of the above measurements.

Time-to-event endpoints (TTP, PFS, and OS) were calculated from the time of first administration of belinostat (Day 1) until the stated event or end of study. Patients receiving subsequent therapy before PD was documented were censored.

Evaluation of response was performed every 6 weeks for the first 12 months, then every 12 weeks until 2 years from the start of study treatment. These assessments were to be stopped at the time of PD or when the patient initiated new anti-cancer therapy, after which survival data was collected every 3 months until 2 years from the start of study treatment or until study closure. Local Investigator assessments were used to guide treatment decisions; while the independent central radiology and oncology review response assessment by the IRC was used for determination of the efficacy study endpoints.

3.2.2 Statistical Methodologies

Confidence intervals for ORR are exact confidence intervals. Median duration of response and its corresponding 95% CI are calculated using Kaplan-Meier method.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Analysis population

CLN-19 had two main populations. The full analysis set contained all individuals who received at least one dose of belinostat. The efficacy analysis population consisted of those individuals who had IRC confirmed PTCL. The full analysis set had 129 patients while the efficacy analysis set had 120.

Subject disposition

In study PCYC-1104-CA, at the time of study cutoff (8/31/2012), 7 out of 120 subjects remained on treatment in the study (Table 2). The most common reason for discontinuation was disease progression (63.3%). The second most common reason for treatment discontinuation was death (11.7% for all patients).

TABLE 2: SUBJECT DISPOSITION

	Full-Analysis Set N=129 n (%)	**Efficacy Analysis N=120 n (%)**
Subject still on treatment	7 (5.4)	7 (5.8)
Subject discontinued study treatments	122 (94.6)	113 (94.2)
Primary reason for treatment discontinuation		
Disease progression	82 (63.6)	76 (63.3)
Death	14 (10.9)	14 (11.7)
Adverse event	9 (7.0)	8 (6.7)
Stem Cell Transplant	4 (3.1)	3 (2.5)
Withdraw by patient	11 (8.5)	10 (8.3)
Physician's decision	1 (0.8)	1 (0.8)
Loss to follow-up	1 (0.8)	1 (0.8)

[Source: study CLN-19 CSR Table 14.1.1.2]

Subject demographics and baseline disease characteristics

Demographics and baseline characteristics for study CLN-19 are summarized in Table 3. Baseline disease characteristics for study PCYC-1104-CA are summarized in Table 4. Median agge was 63 years old with the youngest patient being 29 and the oldest being 81. The study had an even mix of males and females (51.7% male), and race was primarily white (87.5%). Most patients had an ECOG score less than 2 (77.5%). In terms of disease subtype, 64.2% of patients had peripheral T-cell lymphoma NOS, 18.3% had angioimmunoblastic T-cell lymphoma, 10.8% had anaplastic large cell lymphoma, ALK-negative, and 1.7% had anaplastic large cell lymphoma, ALK-positive.

TABLE 3: DEMOGRAPHICS AND BASELINE CHARACTERISTICS

	Full-Analysis N=129	**Efficacy Analysis N=120**
Age (years)		
Mean (SD)	62.0 (11.1)	62.5 (10.4)
Median (Min, Max)	63.0 (29, 81)	64 (29, 81)
Category, n (%)		
< 65	67 (51.9)	61 (50.8)
Sex, n (%)		
Male	69 (53.5)	62 (51.7)
Female	60 (46.5)	58 (48.3)
Race, n (%)		
White	111 (86.0)	105 (87.5)
Black or African American	9 (7.0)	7 (5.8)
Asian	3 (2.3)	3 (2.5)
Latino	3 (2.3)	3 (2.5)
Other	3 (2.3)	2 (1.7)
ECOG performance Status, n (%)		
0	44 (34.1)	41 (34.2)
1	57 (44.2)	52 (43.3)
≥ 2	28 (21.7)	27 (22.5)

SD: standard deviation; ECOG: Eastern Cooperative Oncology Group
[Source: Study CLN-19 CSR Table 14.1.2.1]

TABLE 4: BASELINE DISEASE CHARACTERISTICS

	Full Analysis N=129	Efficacy Analysis N=120
Months from first lymphoma diagnosis to study entry (Months)		
Mean (SD)	26.5 (39.45)	27.1 (40.73)
Median (Min, Max)	12.2 (2.6, 266.4)	12.0 (2.6, 266.4)
Primary lymphoma diagnosis (central pathology)		
Peripheral T-cell lymphoma, NOS	77 (59.7)	77 (64.2)
Angioimmunoblastic T-cell lymphoma	22 (17.1)	22 (18.3)
Anaplastic large cell lymphoma, ALK-negative	13 (10.1)	13 (10.8)
Anaplastic large cell lymphoma, ALK-positive	2 (1.6)	2 (1.7)
Other	15 (11.6)	6 (5%)
Bone marrow involvement		
No	68 (52.7)	65 (54.2)
Yes	39 (30.2)	35 (29.2)
Intermediate	9 (7.0)	8 (6.7)
Not assessed	13 (10.1)	12 (10.0)
Prior number of regimens		
Mean (SD)	2.4 (1.4)	2.3 (1.41)
Median (Min, Max)	2.0 (1.0, 8.0)	2.0 (1.0, 8.0)
Prior Therapy Received, n (%)		
Radiation Therapy	28 (21.7)	28 (23.3)
Systemic Therapy	129 (100.0)	120 (100.0)
Stem Cell Transplant	29 (22.5)	25 (20.8)
Autologous	27 (20.9)	23 (19.2)
Allogeneic	2 (1.6)	2 (1.7)

SD: standard deviation;
[Source: Study CLN-19 Table 14.1.2.3]

Protocol deviation

The sponsor identified a list of major protocol deviations based on standard protocol guideline:

1. One patient did not have signed the informed consent;
2. Thirteen patients did not meet the inclusion criteria #1 ((histologically confirmed diagnosis of PTCL based on local pathology review) due to absence of T-cell and/or B-cell markers. However, 12 of these 13 patients were found based on the central pathology review to meet the entry requirement for PTCL and were included in the efficacy analysis dataset.
3. Five patients received incorrect dose;
4. Three patients received prohibited medication.

3.2.4 Results and Conclusions

3.2.4.1 Results of Overall response

ORR by IRC was used as the primary endpoint. Based on FDA analysis, study CLN-19 had an overall response rate (ORR) of 25.8% (95% CI [18.3%, 34.6%]). The median duration of response per SAP defined criteria, based on 31 responding patients, was 8.4 months (95% CI, 4.5-29.4). The median duration of response per IWG (including death in the definition), based on 31 responding patients, was 13.6 months (95% CI, 4.5-29.4).

TABLE 5: RESULTS OF ORR

	Efficacy Analysis N=120 n (%)
Overall response rate (CR + PR), n (%)	31 (25.9)
Complete response (CR), n (%)	13 (10.8)
Partial Response (PR), n (%)	18 (15.0)
95% CI for ORR (%)	(18.3, 34.6)
Duration of response (DOR) per SAP	N=31
Median DOR (Months) (95% CI)	8.4 (4.5, 29.4)
Duration of response (DOR) per IWG	N=31
Median DOR (Months) (95% CI)	13.8 (4.5, 29.4)

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CI: confidence interval.
[Source: Statistical reviewer's analysis]

Reviewer's commenst:

- The ORR was 24% (95% CI=17%, 32%) based on all patients (n=129).

- The ORR assessed by the investigator was 22.5% (27 responders, 95% CI=15.4%, 31%.)
- The median Duration of Response by SAP –defined criteria by local

Investigator assessment, based on 27 responding patients, was 8.0 months (95% CI, 4.7,19.8).

3.2.4.2 Analysis results for other efficacy endpoints

The analysis results of PFS and OS endpoints are summarized in Table 7.

TABLE 6: SUMMARY OF OTHER EFFICACY ENDPOINTS

Endpoints	**Statistic**	**Efficacy Analysis N=120 n (%)**
PFS (Months)		
	Number of subjects progressed/died	88
	Median (95% CI)	1.6 (1.4, 2.7)
OS (Months)		
	Number of subjects died	74
	Median (95% CI)	7.9 (6.1, 13.9)

PFS: progression-free survival; OS: overall survival; CI: confidence interval;
[Statistical reviewer's analysis]

3.2.4.3 Conclusions for efficacy

Study CLN-19 demonstrated good response and duration of response for PTCL. The results of ORR result appears to be consistent with the result assessed by the investigators.

3.3 Evaluation of Safety

Please refer to clinical review of this application for safety results and conclusions for safety.

3.4 Benefit-risk assessment

Since the pivotal study supporting this NDA application was a single-arm study, the benefit/risk can not be assessed based on comparative analyses. Whether the submission demonstrated an overall favorable risk-benefit profile is deferred to the clinical team reviewing this submission.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Age, Race and Region

Table 9 summarizes the subgroup analyses of overall response rate by gender, age and region for the study PCYC-1104-CA. The ORR results by subgroups of gender, age and region are consistent with the ORR results for all patients. Due to the small sample sizes in the subgroup and non-randomized feature of the subgroup, the interpretation of these results should be taken with caution.

TABLE 7: ORR PER IRC – SUBGROUP ANALYSES BY GENDER, AGE, AND LYMPHOMA DIAGNOSIS

Subgroup	Efficacy Analysis N=129 r/n (%)
Gender	
Male	13/62 (21.0)
Female	18/58 (31.0)
Age	
< 65 yrs	10/61 (16.4)
≥ 65 yrs	21/59 (35.6)
Primary lymphoma diagnosis (central pathology)	
Peripheral T-cell lymphoma, NOS	18/77 (23.4)
Angioimmunoblastic T-cell lymphoma	10/22 (45.5)
Anaplastic large cell lymphoma, ALK-negative	2/13 (15.4)
Anaplastic large cell lymphoma, ALK-positive	0/2 (0.0)
Other	1/6 (16.6)
Region	
USA	6/34 (17.6)
Other	25/86 (29.6)

r: number of response, n: number of subjects in a subgroup; CI: confidence interval.
[Source: Statistical reviewer's analysis]

Reviewer's comments:

- Most patients in Study CLN-19 were white. Therefore, subgroup analyses of ORR by race were not performed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The study CLN-19 was a single-arm study, no comparative evaluation of treatment effect of belinostat can be performed.

5.2 Collective evidence

Study CLN-19 showed an overall response rate (ORR) of 25.8% (95% CI [18.3%, 34.6%]) based on the SAP defined criteria. The median duration of response, based on 31 responding patients, was 8.4 months (95% CI, 4.5-29.4). The ORR result appears to be confirmed by the results assessed by the investigators.

5.3 Conclusions and Recommendations

This NDA application was based on one pivotal multicenter phase II study (CLN-19) to evaluate the treatment effect of belinostat for patients with relapsed/refractory PTCL.

The study appears to demonstrate a good response to belionstat and a durable duration of response. The final decision on the benefit-risk evaluation of belinostat is deferred to the clinical review team.

5.4 Labeling recommendations

Reviewer's comment:

- Overall response results by disease subgroups should not be included in the labeling.
- Only include duration of response by the SAP in the labeling. The duration of response by the IWG should not be included.

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/s/

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NDA/BLA Number: **Applicant: Spectrum Pharm.** **Stamp Date: 12/9/2013**

NDA 206256

Drug Name: Beleodaq™ (Belinostat) **NDA/BLA Type: Priority**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	√			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	√			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	√			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	√			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? __Yes____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	√			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	√			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	√			Simon Two-Stage Design
Appropriate references for novel statistical methodology (if present) are included.			√	The analysis methods used in the analysis are not novel.
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	√			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	√			

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ERIK W BLOOMQUIST
01/23/2014

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