CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206256Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	Electronic Stamp
From	Virginia E. Kwitkowski, MS, RN, ACNP-BC
Subject	Cross-Discipline Team Leader Review
NDA #	206256
Applicant	Spectrum Pharmaceuticals, Inc.
Date of Submission	December 09, 2013
PDUFA Goal Date	August 08, 2014
Proprietary Name / Established (USAN) names	Beleodaq/ Belinostat
Dosage forms / Strength	500 mg single-use vial for reconstitution (50 mg/mL)
Proposed Indication(s)	Patients with relapsed or refractory peripheral T-cell lymphoma (PTCL)
Recommended:	*Accelerated Approval*

Cross Discipline Team Leader Review

1. Introduction

On December 9, 2013, Spectrum Pharmaceuticals submitted, New Drug Application (NDA) 206256 in accordance with 505(b)(1) of the Federal Food, Drug and Cosmetic Act and 21 CFR§314.50, for their histone deacetylase inhibitor, belinostat, to the Division of Hematology Products. The application cover letter requested accelerated approval and priority review designation. The application was complete upon submission. The proposed trade name is Beleodaq™. The recommended dose of belinostat is 1000 mg/m^2 by intravenous infusion administered over 30 minutes on Days 1-5 of a 21-day cycle. Beleodaq is available as a lyophilized powder for reconstitution in a single-use 30 mL clear glass vial containing 500 mg belinostat and 1000 mg L-Arginine, USP. The application was filed as a priority review because there are no available therapies for the proposed indication.

The Applicant proposed the following indication:
"*Patients with relapsed or refractory peripheral T-cell lymphoma (PTCL)*"

To support the proposed indication, Spectrum conducted CLN-19, a phase 2, single-arm, open-label, multicenter trial in patients with relapsed or refractory PTCL who had received at least one prior systemic therapy.

The Applicant included a Risk Management Plan in the application without a proposed REMS.

2. Background

Peripheral T Cell Lymphoma

Peripheral T-cell lymphoma (PTCL) represents a heterogeneous group of mature T and natural killer cell derived neoplasms. PTCL represents approximately 10-15% of all non-Hodgkin lymphomas in North America. At least 20 distinct histologic subtypes of PTCL have been identified. The most common types of PTCL worldwide are peripheral T cell lymphoma, not otherwise specified (NOS) at 25.9%, angioimmunoblastic T cell lymphoma (AITL) at 18.5%, and anaplastic large cell lymphoma (ALCL), which can be further subdivided by expression of the anaplastic lymphoma kinase (ALK) into ALK + versus ALK- ALCL, representing 6.6 and 5.5% of PTCL respectively. In North America, ALK+ ALCL is more common, representing 16% of PTCL. (Vose, 2008) PTCL has an aggressive clinical course with inferior outcomes compared to those of aggressive B-cell lymphomas. PTCL has an overall 5-year disease-free survival of <30% (with the exception of patients with ALK+ anaplastic large cell lymphoma). (Chen, 2008). PTCL is a rare malignancy with approximately 7000 cases per year in the US in 2013. (Intlekofer & Younes, 2014)

The standard first line therapy for PTCL is anthracycline-based combination chemotherapy. The most commonly used initial regimens include CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin), and Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone, alternating with high-dose methotrexate and cytarabine). These regimens provide inferior outcomes compared with those of patients with B cell lymphomas. A large meta-analysis on data from over 2800 patients with PTCL (excluding ALCL) who received up front therapy with anthracycline-based combination chemotherapy regimens resulted in a complete response (CR) rate of 52% and a 5-year overall survival of 35%. (Abouyabis, Shenoy, Sinha, Flowers, & Lechowicz, Epub 2011). Consolidation therapy is often considered for patients who enter remission following chemotherapy with the exception of patients determined to be at "low risk" of relapse/recurrence. Typical first-line consolidation regimens include high-dose chemotherapy followed by stem cell transplant. Stem cell transplant is generally limited to those who are fit enough for this intensive treatment.

Two drugs have previously received accelerated approval in the second line or later PTCL setting: pralatrexate and romidepsin. In 2009, Folotyn (pralatrexate) was granted accelerated approval for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) based upon a single-arm trial. In 2011, Istodax (romidepsin) was granted accelerated approval for the treatment of peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy. Both drugs have post-marketing requirements open to verify and describe the clinical benefit for each product and convert to regular approval. Both prior approvals have used Overall Response Rate (ORR) as the primary endpoint for the trials that led to accelerated approval in this indication. The Folotyn trial defined ORR as Complete Response (CR) + Complete Response Unconfirmed (CRu) + Partial Response (PR) while the Istodax trial included only CR + CRu in the ORR definition. The proposed endpoint of ORR is acceptable for accelerated approval in the relapsed/refractory PTCL indication.

There is no consensus on standard treatment for PTCL in the first-line and second-line settings and the approved therapies are not optimal (pralatrexate has an ORR of 27% while romidepsin has an ORR of 25%) [Source, Primary Review by Hyon-Zu Lee].

Regulatory Background*

(b) (4)

Pre-IND Meeting: On 10/15/04, a Type C pre-IND teleconference meeting was held between CuraGen (the Sponsor for PXD101 at that time) to discuss their proposed IND (b) (4)

Details of the discussion are omitted here because they are not relevant to the currently proposed indication.

Initial IND: On 11/15/04, the first US IND (#70789) was submitted for belinostat by CuraGen. (b) (4)

End of Phase 2 Meeting: On 11/29/07, a Type B End of Phase 2 meeting was held with CuraGen regarding their development plan in PTCL. (b) (4) At this meeting, the FDA agreed that objective response rate was an acceptable primary endpoint, and that the significance of ORR is assessed by its magnitude and duration, the percentage of complete responses, and an acceptable risk/benefit ratio. The Agency stated that the results of time-to-event endpoints, such as PFS or OS, in a single-arm study, are not interpretable and should be considered as exploratory. The FDA agreed that the trial may enroll based upon local institution pathology confirmation but that the protocol must include adequate minimum pathology evaluation parameters for the diagnosis of each patient. The FDA cautioned the Sponsor to capture these pathology evaluation parameters in Case Report Forms.

(b) (4)

Transfer of Ownership: In April 2008, IND 70789 was transferred to Topotarget. Topotarget A/S (Topotarget, Copenhagen, Denmark) initiated the trial CLN-19 in May 2009. With

Spectrum entering into a licensing and collaboration agreement with Topotarget for the development and commercialization of belinostat in patients with relapsed or refractory PTCL in February 2010, the IND was transferred to Spectrum on March 18, 2010.

Fast Track Request for PTCL Granted: On 05/28/08, FDA granted Fast Track Designation for "belinostat (PXD101) IV for relapsed or refractory PTCL after at least one prior systemic therapy".

(b) (4)

Special Protocol Assessment for PTCL Granted: On 09/04/08, a Special Protocol Assessment agreement was issued to Curagen for Protocol PXD101-CLN-19, titled "A Multicenter, Open-Label Trial of Belinostat in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma." This version of the protocol included at least 100 evaluable patients.

Type C Guidance meeting for PTCL July 20, 2011

The purpose of the meeting was to provide guidance for reporting and handling of cardiac, hepatic impairment, mass balance and baseline bone marrow evaluation data. The most clinically relevant discussion topics for this meeting were regarding the handling of missing bone marrow (BM) assessments. The initial protocol did not require baseline bone marrow assessments. During this meeting, the Sponsor stated that they had amended the trial to require bone marrow assessment going forward, but that there were now 12 patients without BM assessment at baseline. They proposed to handle the missing BM assessments as follows:

(b) (4)

The FDA did not agree that the Sponsor's proposal was a "worst case" handling and recommended the following handling of response determination for patients with missing baseline bone marrow assessments:

Alternative Method for Handling Missing Baseline Bone Marrow Assessments
(Assumes Negative Bone Marrow at Baseline)

	Radiology	Repeat Bone Marrow	Visit Response
Baseline bone marrow not done (Assume negative at baseline)	CR	Negative	CR
	CR	Not done or Positive	PD
	PR	Negative	PR
	PR	Not done	PD
	PR	Positive	PD

The following additional comments were also provided to the Sponsor:
1. Initial registration based on single arm clinical trials are generally considered under the accelerated approval mechanism. In February 2011, the Oncologic Drugs Advisory Committee (ODAC) recommended that randomized controlled trials should be the standard and that single arm trials should be the exception for accelerated approval. Committee members commented that single arm trials may be used for accelerated approval in the following situation: High level of activity of the agent or pronounced treatment effect.
2. Post-approval confirmatory clinical trials are required in order to be considered for accelerated approval. Discuss your development plan for Belinostat that may be used to satisfy the confirmatory requirements for accelerated approval.

Type C Guidance Meeting Regarding Confirmatory Trial: On 02/07/13, DHP met with Spectrum to discuss their proposed post-marketing confirmatory trial plan. Spectrum stated that they plan to submit an NDA for the relapsed/refractory PTCL indication during the second half of 2013. They acknowledged the need for a confirmatory trial. The Sponsor proposed a (b) (4) During this meeting we agreed with the use of PFS as the primary endpoint in the trial, but discouraged the planned interim analysis of PFS. *Further discussion of this meeting is not relevant to the review because this trial will no longer be conducted (it is being replaced by a three-arm trial that will convert both Folotyn and belinostat to regular approval).*

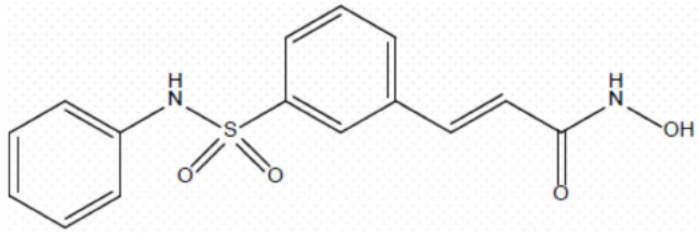
Type B, Pre-NDA Meeting: On 05/29/13, a Pre-NDA meeting was held with Spectrum Pharmaceuticals regarding their planned NDA for Belinostat "for the treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL) (b) (4) In addition to Clinical Pharmacology and Pharmacology/Toxicology topics, the clinical issues discussed were that we agreed with the proposed data cutoff of 08/31/12, requested that the Central Pathology Review Group forms be submitted in the NDA, and requested that the application contain both an SCE/SCS and ISE/ISS in accordance with the ICH M4E guidance and FDA ISE/ISS guidance.

3. CMC/Device

The primary Chemistry/Manufacturing/Controls (CMC) reviewer for the NDA was Xiao-Hong Chen, Ph.D. Janice Brown was the CMC lead for the application. The Branch Chief was Ali Al Hakin, Ph.D. There are no unresolved review issues with the CMC review. A high level summary of the CMC review is below.

Dosage Form: Lyophilized powder for Injection
Strength/Potency: 500 mg
Route of Administration: Intravenous
Name (USAN, INN): belinostat
Name (CAS): 2-Propenamide, *N*-hydroxy-3-[3-[(phenylamino)sulfonyl]phenyl]-,

(2*E*)-
IUPAC Name: (2E)-3-[3-(anilinosulfonyl)phenyl]-N-hydroxyacrylamide
Other Name: *N*-hydroxy-3-(3-phenylsulphamoylphenyl) acrylamide
Company code: PXD101
(CAS) Registry Number: 414864-00-9, 866323-14-0
Mol. Formula: $C_{15}H_{14}N_2O_4S$
Mol. Wt.: 318.35 g/mole
Structural Formula:



Drug Product
Belinostat for Injection is supplied as a sterile, yellow lyophilized (b) (4) The drug product contains belinostat (drug substance), 500 mg/vial, (b) (4) L-Arginine, 1000 mg/vial. (b) (4). All excipients comply with USP compendial standards.

The product is supplied in a 30 mL Type I clear glass vial closed with a (b) (4) -coated (b) (4) stopper. The vial is capped with an aluminum 'flip-off' seal. The primary container is enclosed in a carton. As indicated in the proposed labeling, the product is reconstituted in 9 mL Sterile Water for Injection. Prior to administration, the reconstituted belinostat (50 mg/mL) is admixed with 0.9% saline to the desired strength for infusion.
The pivotal clinical study was conducted using a (b) (4) formulation, Belinostat Injection (50 mg/mL). (b) (4) a lyophilized form of belinostat was developed as the commercial product. The lyophilized formulation, Belinostat for Injection (500 mg/vial), after reconstitution with 9 mL Sterile Water for Injection, is qualitatively and quantitatively identical to the (b) (4) formulation.

Three registration stability batches have been manufactured at (b) (4) representing (b) (4) of the proposed commercial scale, which is (b) (4). Clinical supplies have also been manufactured at a scale of (b) (4) vials per batch by (b) (4) The knowledge gained from manufacturing over 20 batches (16 clinical batches and 7 registration batches) with the impurity profile that meet the ICH guidance forms the basis for the commercial process. Stability studies conducted under the ICH Long-term (25°C/60% RH), intermediate (30°C/65% RH) and accelerated (40°C/75% RH) storage conditions demonstrated that the drug product is very stable under the intended storage conditions, i.e. *20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (between 59°F and 86°F).* The proposed 24 month shelf life is deemed acceptable.

Incompatibility was initially observed for the drug product diluted in saline, which showed that the level of particulate matter exceeds the USP<788> requirement for large parenteral products. In response to Agency's information request regarding particulates observed in the Belinostat diluted in 0.9% Sodium Chloride Injection in either (b) (4), the applicant carried out the multi-variable study to evaluate drug admixture conditions that would yield solutions that meet the USP <788> particulate matter specification. The results of these studies show that all samples met the USP <788> particulate matter specification through the (b) (4) hold time of the admixture solutions. The applicant recommends the use of an in-line 0.22 micron filter for administration as an additional safety measure.

Drug Substance
The drug substance is belinostat. The chemical name is 2-Propenamide, *N*-hydroxy-3-[3-[(phenylamino)sulfonyl]phenyl]-, (2*E*)-. It has a molecular formula of $C_{15}H_{14}N_2O_4S$ and it has a molecular weight is 318.35. Complete CMC information has been submitted in the Type 2 DMF #026926. The DMF that was referenced by the applicant has been reviewed and was found to be adequate. Refer to the review conducted by this reviewer dated Apr. 23, 2014.

Description of How the Drug Product is Intended to be Used
Beleodaq® is administered by intravenous infusion at the dose of 1000 mg/m$_2$ daily using an infusion set with an in-line filter. Prior to IV infusion, the drug product is reconstituted with 9 mL of sterile water for injection followed by dilution in 250 mL of 0.9% sterile saline solution.

Basis for Approvability Recommendation
From a CMC perspective, Spectrum Pharmaceuticals, Inc. has submitted sufficient CMC information to support the approval of the drug. Spectrum Pharmaceuticals has adequately addressed the CMC comments/deficiencies identified in the review. There are no outstanding deficiencies with the application. The referenced Type II DMF #26926 for the belinostat drug substance has been reviewed and is found to be adequate to support the NDA. An overall "Acceptable" recommendation was made by the Office of Compliance for the pre-approval inspection of the NDA.

From a CMC perspective, this application is recommended for Approval.
EES has an overall "Acceptable" recommendation for this NDA.

Review of the package insert labeling and container/carton labels is under way. The following comment should be included in the action letter:
An expiration dating period of 24-months is granted for Beleodaq(belinostat) for Injection when stored at 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (between 59°F and 86°F).

There are no CMC-specific post-marketing requirements or commitments.

4. Nonclinical Pharmacology/Toxicology

The primary pharmacology/toxicology review was conducted by Pedro L. Del Valle, PhD and M. Stacey Ricci, M.Eng., ScD. There are no outstanding review issues from Pharmacology/Toxicology and no recommended Pharm/Tox-specific post-marketing requirements or commitments. The high-level findings from their review are presented below.

Approvability Recommendation:
The Pharmacology/Toxicology reviewers recommend approval. The submitted pharmacology and toxicology studies using belinostat support the safety of its use in patients with relapsed or refractory peripheral T-cell lymphoma (PTCL).

Introduction
Belinostat (PDX101) is an intravenously administered histone deacetylase (HDAC) inhibitor that can alter acetylation levels of histone and non-histone proteins. HDAC enzymes catalyze the removal of acetyl groups from the lysine residues of histones leading to condensed chromatin and prevention of binding of transcription factors that can result in gene silencing.

Brief Discussion of Nonclinical Findings
Genotoxicity: Yes. Three assays tested were positive.

Reprotoxicity/Developmental Toxicity: Not tested. Expected to cause teratogenicity and/or embryo-fetal lethality. Assigned a pregnancy Category D.

Carcinogenicity: Not tested.

Mechanism of Action:
The proposed mechanism of action of belinostat is that upon inhibition of HDAC enzymes, (b) (4) occurs resulting in cell cycle arrest and apoptosis. In vitro results using cultured cells, demonstrated that belinostat treatment results in cytotoxic activity towards both transformed and normal cells, but transformed cells undergo greater cell cycle arrest and/or apoptosis on a percentage basis. Aberrant expression of HDACs in a wide variety of human tumor types and selective inhibition HDAC isoforms using gene silencing techniques demonstrated cell cycle arrest or cytotoxicity in both in vitro and in vivo models.

Pharmacology studies of belinostat were conducted using in vitro, cell based and in vivo assays by Spectrum Pharmaceuticals, Topotarget, commercial vendors or academic laboratories. Results that explored the mechanism of belinostat action include:

- Belinostat inhibits HDAC1, HDAC2, HDAC3, and HDAC8 (Class I), and HDAC4, HDAC6, HDAC7 and HDAC9 (Class II) enzymes at concentrations < 250 nM using purified recombinant human proteins.
- Belinostat treatment of cultured human tumor or normal cells, or peripheral blood cells collected from mice treated with belinostat showed a rapid increase of acetylated histone proteins.
- Belinostat treatment of cultured tumor cells results in reduced cell viability that

correlates with cleavage of poly (ADP-ribose) polymerase (PARP1; a marker of apoptosis), and induced expression of cyclin-dependent kinase inhibitor p21 (CDKN1A; a marker of G1-phase cell cycle arrest).

- Cultured human cancer cells were more sensitive to belinostat-induced cytotoxicity than the cultured normal human cells used.

Safety pharmacology studies conducted included a cardiovascular and respiratory evaluation in anesthetized dogs, an in vitro hERG channel assay and an observational study (Irwin test) in rats. Increased heart rates were observed in the dog cardiovascular study; there were no other findings of toxicity to the cardiovascular, respiratory or central nervous system. Cardiovascular toxicities also were observed in repeat-dose toxicology studies: microscopic findings of cardiomyopathy in the rat and increased heart weight in the dog were observed.

Plasma concentrations showed roughly dose proportional Cmax and AUC exposures in both rats and dogs. Exposures were typically higher in male rats compared to females, without gender differences noted in dogs. The half-life was between 0.35-1.2 hours in rats and 0.45-1.6 hours in dogs. The major pathway of belinostat metabolism is glucuronidation, with the formation of belinostat glucurounide as the primary metabolite and other metabolites which do not have an in vitro cytotoxic effect.

Single and repeat-dose general toxicology studies using IV administered belinostat were conducted in rats and dogs. Repeat-dose toxicology studies with oral administration in rats and dogs (twice daily for 4 weeks) were also conducted. Five-day and 28-day IV studies were conducted using a vehicle/formulation that differed from that used in clinical studies and the to-be-marketed formulation (L-arginine). These studies were supplemented with 7-day repeat-dose bridging studies in rats and dogs using the different formulations. Twenty-four week studies using the L-arginine vehicle/formulation were conducted according to a schedule of 5 days of daily belinostat IV administration followed by 16 days off for 8 cycles (for a total of 24 weeks) with controls and the high dose group containing recovery groups of 2 week duration.

In the 24-week intravenous studies, rats administered doses of 10, 25 or 100 mg/kg (60,150 or 600 mg/m2) experienced more severe toxicities than dogs that received 10, 25 or 50 mg/kg (200, 500 or 1000 mg/m2). Toxicities observed following belinostat administration were primarily related to the gastrointestinal system, hematopoietic system, lymphoid system, genitourinary system and the site of injection.

In dogs, vomiting occurred during or immediately after IV belinostat dosing; other clinical signs included soft feces, salivation, impaired mobility and subdued behavior. Changes in hematological parameters were limited to decreased leukocyte counts, shorter prothrombin times, and slightly higher red cell distribution widths that were also present at the end of the recovery period. Clinical chemistry changes included decreases in alkaline phosphatase levels in all dose groups, and increases in glucose, inorganic phosphorus and urea; the significance of these findings is unclear. Lymphoid atrophy was observed at the highest dose tested in mesenteric, mandibular, spleen, ileum and cecum tissues at the high dose tested. Male dogs

from all treatment groups had reduced organ weights of the testes/epididymides that correlated with delayed testicular maturation in all treatment groups. A dose-dependent increase in mean heart:body weight ratio in males was observed at terminal sacrifice with no microscopic correlates.

Belinostat was positive for genotoxicity in the three assays used: the bacterial reverse mutational test (Ames assay), the in vitro mouse lymphoma cell mutagenesis assay, and in vivo clastogenicity assay in mouse bone marrow cells (micronucleus assay). Animal studies to evaluate the reproductive, developmental and carcinogenic potential of belinostat were not conducted because belinostat is genotoxic and targets rapidly dividing cells and, therefore, is expected to cause teratogenicity and/or embryo-fetal lethality.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology and Pharmacometrics reviews were conducted by Bahru Habtemarium, PharmD (DCP5). The Clinical Pharmacology Team Leader is Julie Bullock, PharmD. The Pharmacometrics Team Leader is Nitin Mehrotra, Ph.D. The Genomics reviewer was Sarah Dorff, Ph.D. and Rosane Charlab Orbach, Ph.D. was her Team Leader.

There are no outstanding approvability issues for Clinical Pharmacology.

There are six proposed Post-Marketing Requirements pertinent to Clinical Pharmacology:

1. Submit the final clinical trial report for the ongoing human mass balance trial (protocol NCT01583777) designed to evaluate the excretion route of belinostat in humans.
2. Submit the final clinical trial report for the ongoing hepatic impairment trial that is designed to evaluate the influence of hepatic impairment on the PK and safety of belinostat.
3. Conduct a clinical trial evaluating the influence of strong UGT1A1 inhibitors on the pharmacokinetics of belinostat in patients with cancer.
4. Evaluate the safety and pharmacokinetics of belinostat in patients with wild-type, heterozygous, and homozygous UGT1A1*28 genotypes. The evaluations should be conducted for sufficient duration in order to evaluate safety following multiple dose administration.
5. Conduct a clinical trial in patients with varying degrees of renal impairment to evaluate the pharmacokinetic and safety of belinostat patients with impaired renal function. The trial should be conducted for sufficient duration in order to evaluate safety following multiple dose administration.
6. Conduct an in vitro study to determine the exact contributions of UGT1A1, CYP3A4, CYP2C9, and CYP2A6 in the biotransformation of belinostat.

Summary of Important Clinical Pharmacology Findings (Source: Dr. Habtemarium's review)

Pharmacokinetic sampling was collected from 187 patients who received belinostat monotherapy in studies (301G, CLN19, CLN20, and TT2).

The dose for the pivotal phase 2 trial was chosen using data from two phase 1 dose escalation trials; one in patients with solid tumors and another in patients with advanced hematological malignancies. The agency's dose response analyses for safety and efficacy showed overlapping rates for clinical response and grade 3+ adverse events at all of the studied dose levels (150 to 1200 mg/m2 given on days 1 to 5 of a 21-day cycle). Dose-dependent acetylation (a PD marker for HDAC enzymatic activity), was observed after the first dose and appeared to plateau at doses of 900 mg/m^2 and above. The 1000 mg/m^2 given on days 1 to 5 of a 21-day cycle, was determined to be the MTD dose in these phase 1 studies and this dose was used for the pivotal phase 2 trial. It was shown that the body surface are (BSA) based dosing provides consistent exposure across all body sizes.

The exposure-response analyses for efficacy (ORR) and safety (fatigue and overall grade 3/4 adverse events) from the pivotal phase 2 trial showed no trends over the exposures seen following a 1000 mg/m^2 dose.

In vitro, belinostat is primarily (≈ 80-90%) metabolized by UGT1A1 and to a lesser extent by CYP2A6, CYP2C9, and CYP3A4. However, the exact contribution of each enzyme in the biotransformation of belinostat has not been determined. The sponsor did not conduct human drug-drug interaction studies to evaluate the influence of liver enzyme inhibitors of UGT1A1, CYP2A6, CYP2C9, and CYP3A4 on the systemic exposure of belinostat. Available data indicate UGT1A1 inhibitors will likely produce meaningful belinostat exposure increases that could lead to dose limiting toxicities. Since the proposed starting dose (1000 mg/m^2) is also the MTD and 3 out of 5 patients treated with 1200 mg/m^2 developed dose limiting toxicities (including grade 3 fatigue, atrial fibrillation, and diarrhea), even modest exposure increases due to a DDI could lead to dose limiting toxicities.

UGT1A1 is a known polymorphic enzyme with allelic variants that influence enzymatic activity. The influence of UGT1A1 polymorphism on belinostat exposure has not been characterized by the applicant. However, a recent study by Wang et al. (PMID: 23382909) in human liver microsomes found that subjects homozygous for UGT1A1*28 had a 53% reduction in the production of the main metabolite (belinostat glucuronide). Since UGT1A1 metabolizes up to 90% of belinostat, patients homozygous for UGT1A1*28 could have belinostat systemic exposures greater than those seen at doses of 1000 mg/m^2. Results from simulations using physiological based pharmacokinetic (PBPK) modeling methods suggest that subjects with UGT1A1*28 may have up to 20% greater belinostat exposure than subjects with UGT1A1*1. *In vitro*, belinostat inhibited CYP2C8 and 2C9. A human PK study was conducted in patients following the administration of the CYP2C9 substrate warfarin in the absence and presence of belinostat. The exposure of S-warfarin was not increased to a meaningful extent.

The sponsor did not conduct a human ADME study to determine the excretion routes of belinostat. Human urinary excretion of belinostat and its metabolites were measured in study CLN20 following treatment with 1000 mg/m2 doses of belinostat. The urinary excretion assessment indicated less than 1% of unchanged belinostat was excreted in the urine. Belinostat glucuronide and 3-ASBA had the highest fractions of the belinostat dose excreted in urine, representing 30.5% and 4.6% of the administered dose, respectively. In total, it appears about 40% of the administered dose is excreted in urine, primarily in the form of metabolites.

Since the renally excreted metabolite, belinostat glucuronide is an active metabolite with cell killing activities, very high accumulation of this metabolite in patients with renal impairment may produce non-specific adverse events. The sponsor stated that human mass balance and hepatic impairment studies are ongoing. A post-marketing trial in patients with renal impairment will be requested.

Pharmacokinetics

In study TT20, single and multiple dose PK samples were collected following treatment with belinostat doses of 150 to 600 mg/m^2. Day 1 and day 5 AUCs belinostat were similar, indicating the absence of meaningful drug accumulation following repeated doses. Such a finding is expected because belinostat has a very short half-life of 1 to 2 hours.

Drug Distribution

The plasma protein binding characteristics of belinostat were evaluated in two in vitro studies and the average level of protein binding was around 94%, which is considered a moderate level of protein binding. This level of protein binding is consistent with mean steady-state volume of distribution (Vss) of 11 to 15 L as determined using non-compartmental analysis in study CLN4.

Intrinsic Factors

Dosage regimen adjustments for belinostat are not recommended for any specific population.

Age: In the population PK analysis, age (range: 28 to 81) was not shown to influence the disposition of belinostat. The Applicant has not conducted pediatric trials. None are required by PREA because belinostat has Orphan Drug designation for the proposed indication.

Gender: Population PK analysis showed that gender has no influence on belinostat PK.

Race: Population PK analysis showed that race has no influence on PK. However, because the population PK dataset contained small (<8%) number of non-Caucasian patients, the effect of race on belinostat PK could not reliably be determined.

Renal Impairment: The sponsor did not conduct a renal impairment study. The population PK analysis, included patients with mild (n = 31) to normal (n = 217) creatinine clearance (range of 36 to 236 mL/min). There was no relationship found between creatinine clearance and belinostat PK. Since a mass balance study was not conducted in humans, it is not clear what percent of belinostat is excreted in the urine. Whether moderate (CrCL 20-39 mL/min) or severe (CrCL < 20 mL/min) renal impairment would influence exposure to belinostat is

unknown, which supports the proposed PMR to evaluate the impact of renal impairment on the PK and safety of belinostat.

Hepatic Impairment: The sponsor did not conduct a study in subjects with impaired hepatic function. The sponsor also did not conduct a human ADME study. The sponsor stated that a hepatic impairment trial is currently ongoing. The population PK analysis, which included 59 patients with mild hepatic impairment, showed that mild hepatic impairment does not influence the PK of belinostat.

Pharmacogenetics: Belinostat is metabolized primarily by UGT1A1 (80 - 90%), a known polymorphic enzyme with allelic variants that influence enzymatic activity. UGT1A1 alleles that reduce enzyme activity are expected to decrease the metabolism of belinostat, thereby increasing belinostat exposure. The applicant cited a literature reference (PMID: 23382909) that showed in vitro formation of belinostat glucuronide was reduced by 26% and 53% in subjects heterozygous and homozygous for UGT1A1*28 (a reduced function allele), respectively. Among Caucasians, approximately 40% and 10% of individuals are heterozygous and homozygous for UGT1A1*28, respectively (PMID: 18518849). However, the applicant did not conduct any clinical studies to assess the influence of UGT1A1*28 or other known reduced function alleles on the systemic exposure of belinostat. The FDA PBPK reviewer conducted physiologically-based pharmacokinetic modeling and simulations to assess the impact of UGT1A1 polymorphism on the exposure of belinostat. The simulations suggest that subjects homozygous for UGT1A1*28 may have 20% higher belinostat AUC than subjects homozygous for UGT1A1*1.

Extrinsic Factors*:*
The sponsor did not submit results of specific studies or analyses designed to evaluate the effects of extrinsic factors such as herbal products, diet, smoking or alcohol use on the PK, safety, or efficacy of belinostat.

Impact of Belinostat on CYP Enzymes
In vitro studies suggest that belinostat and three of its metabolites were shown to inhibit human CYP2C8 and CYP2C9. The pending clinical DDI study using warfarin as a substrate of CYP2C9 will provide definitive information on the effect of belinostat and its metabolites on the metabolic activity of CYP2C9. Belinostat is a weak inducer of CYP1A2. Belinostat is likely a substrate of P-gp, however since the route of administration for belinostat is intravenous, P-gp inhibitors are not likely to have a clinically relevant influence on the exposure of belinostat.

Drug-Drug Interactions
Since in vitro drug- drug interaction (DDI) studies indicated belinostat and its metabolites inhibit CYP2C9 and CYP2C8, the sponsor conducted an in vivo DDI study in patients by administrating the known CYP2C9 substrate warfarin in the absence and presence of belinostat as outlined below. Since the IC50s for the inhibition of CYP2C9 and CYP2C8 were similar, in vivo evaluation of CYP2C9 will provide information regarding the magnitude of in vivo inhibition of CYP2C8. The AUC of S-warfarin was increased by about 10% in the presence of belinostat while the Cmax of S-warfarin was reduced by the same magnitude.

Although warfarin has a very narrow therapeutic window, coadministration with belinostat is unlikely to produce clinically meaningful drug-drug interaction when given in combination with belinostat.

Impact of Belinostat on the QTc:
The review division consulted the QT-Interdisciplinary Review Team on January 17, 2014. In the consult, they state:
"In this integrated cardiac safety report, an effect-exposure analysis of the potential effect of belinostat on cardiac repolarization from 8 clinical studies (N=380), and analyses of ECG information across the 13 clinical studies (N=529) were submitted."

Their consultation concludes that "based on information available, QT prolongation with belinostat cannot be confirmed or excluded. However, large QT prolongation (e.g., > 20 ms) with belinostat seems unlikely."

Preclinical experience showed that no significant risk of QT prolongation based on in vitro biological findings from the hERG (IC20 of 270 μM) or Purkinje fiber study.

They suggested the following slight edits to the sponsor's proposed labeling in section 12.3:

Cardiac Electrophysiology
Multiple clinical trials have been conducted with Beleodaq, in many of which ECG data were collected and analyzed by a central laboratory. Analysis of clinical ECG and belinostat plasma concentration data demonstrated no signal or meaningful effect of Beleodaq on cardiac repolarization. None of the trials showed any clinically relevant changes caused by Beleodaq on heart rate, PR duration or QRS duration as measures of autonomic state, atrio-ventricular conduction or depolarization; there were no cases of *Torsades de Pointes*.

6. Clinical Microbiology

- *Not relevant to oncology indications.*

7. Clinical/Statistical- Efficacy

The clinical review was conducted by Hyon-Zu Lee, PharmD. I was the clinical team leader and cross-discipline team leader (CDTL) for the application. The statistical review was conducted by Erik Bloomquist, PhD (Division of Biometrics V). His team leader was Yuan Li Shen, Dr. P.H. There are no outstanding clinical or statistical issues that would preclude an approval action.

Clinical Review Summary and Conclusion (Source: Hyon-Zu Lee's review):

Review Strategy:
As CLN-19 was the pivotal trial for efficacy and safety, the clinical review was primarily based on the CLN-19 (n=129) trial data to support the proposed indication. Supportive information was provided by the results of CLN-6, which enrolled 24 patients with PTCL.

Trial ID and Title:
PXD101-CLN-19 (referred to as CLN-19 throughout this review): A Multicenter, Open Label Trial of Belinostat in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma.

This was an open-label, multicenter, single-arm phase 2 trial in patients with relapsed or refractory peripheral T-cell lymphoma after at least one prior systemic therapy.

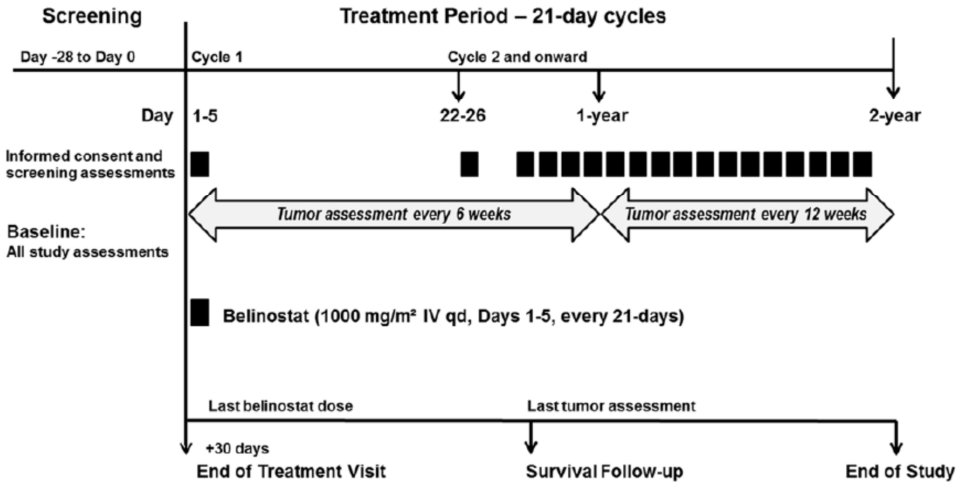
For patient enrollment into the trial, PTCL diagnosis was by local site pathology laboratory provided pathology material was available for central pathology review. A Central Pathology Review Group (CPRG) was to provide secondary assessment to confirm the local site assessment and the diagnosis of eligible PTCL histopathological subtypes. To be included in the evaluable population, the patients were to have a diagnosis of PTCL confirmed by the CPRG and received at least one dose of belinostat. Local investigator evaluations of tumor assessments were to be used to guide treatment decisions, including decisions to stop study treatment due to progressive disease. Central blinded review by an Independent Review Committee (IRC) was to be used for assessments for determination of efficacy variables.

Tumor assessments were to be evaluated according to the International Harmonization Project (IHP) revision of the International Working Group (IWG) criteria (Cheson 2007) by radiologic imaging using computerized tomography (CT). Assessments were to be performed at baseline and using the same techniques every 6 weeks for the first 12 months, then every 12 weeks until 2 years from the start of study treatment. Radiological assessments were to be discontinued at the time of tumor progression (as evaluated by investigator) or initiation of new anti-cancer therapy, after which survival were to be evaluated every 3 months until 2 years from the start of study treatment or until study closure.

If baseline bone marrow assessment was positive for lymphoma, a bone marrow biopsy was mandatory to confirm a complete response (i.e., after radiographic CR assessment). CT scan of the neck, chest, abdomen and pelvis, and other necessary investigations (i.e., documentation of skin lesions was to be done by PI using a ruler) to assess tumor status. The same techniques as utilized at baseline were to be 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 disease progression or when patient initiates new anti-cancer therapy.

Safety was to be monitored during belinostat treatment and 30 days following the last dose. Adverse events and laboratory results were to be graded according to NCI CTCAE version 3.0.

Figure 1 CLN-19 Trial Design and Assessments



Source: ISE pg. 18

Trial Objectives:

The primary objective was to determine the objective response rate (ORR). The secondary objectives were to determine the safety, time to response, duration of response, time to progression (TTP), progression free survival (PFS), one-year progression free rate, one-year survival rate and overall survival (OS). Additional objectives were to assess population pharmacokinetics and medical care utilization during belinostat treatment.

Trial Population:

Inclusion Criteria:

1. A histologically confirmed diagnosis of PTCL based on local pathology review and most recent edition of the WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues, leading to diagnosis of:
    - Anaplastic large cell lymphoma, ALK-positive
    - Anaplastic large cell lymphoma, ALK-negative
    - Angioimmunoblastic T-cell lymphoma (AITL)
    - Enteropathy-associated T-cell lymphoma
    - Extranodal natural killer (NK)/T-cell lymphoma, nasal type
    - Hepatosplenic T-cell lymphoma
    - Peripheral T-cell lymphoma, not otherwise specified (NOS)
    - Subcutaneous panniculitis-like T-cell lymphoma

    Diagnosis of PTCL was to be based on biopsy specimens characterized by positivity in the malignant cell population of at least 3 of the following T-cell markers: βF1, CD2, CD3, CD4, CD5, CD7, CD8, and negativity of at least 2 of the following B-cell markers CD19, CD20, CD79alpha and Pax-5. CD56 was to be used for the diagnosis of the nasal type, while CD30, ALK-1 and Pax-5 (negative) were to be required for the anaplastic type. CD10, CXCL13, PD-1 and CD 21 were warranted for the diagnosis of

angioimmunoblastic T-cell lymphoma along with EBER in situ hybridization. Determination of Mib-1/Ki-67 was to be performed. Additional markers for anaplastic large cell lymphoma, extranodal NK/T-cell lymphoma and subcutaneous panniculitis-like T-cell lymphoma were TIA-1, granzyme B and Perforin. It was acknowledged that no marker has absolute lineage specificity, and that immunophenotypic studies were to be performed with panels of monoclonal antibodies. Final diagnoses containing caveats such as "suspicious of" or "presumably" were to be considered inadequate for a patient to be enrolled in the trial.

2. Pathology material was to be available at the site for each patient before enrollment to be sent to the Sponsor (or designee) for central pathology review.
3. Relapsed or refractory disease after at least one prior systemic anticancer regimen. Systemic anticancer therapy was defined as chemotherapy or immunotherapy administered systemically.
4. At least one site of disease measurable in two dimensions by computed tomography (CT).
5. Age ≥ 18 years.
6. Laboratory status:
    a. Absolute neutrophil count ≥ 1.0 x 10^9/L, platelets ≥ 50 x 10^9/L.
    b. Total bilirubin ≤ 1.5 x upper limit normal (ULN), or ≤ 3 x ULN if documented hepatic involvement with lymphoma, or ≤ 5 x ULN if history of Gilbert's Disease.
    c. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN (≤ 5 x ULN if documented hepatic involvement with lymphoma).
    d. Serum potassium within normal range.
    e. Calculated creatinine clearance ≥ 45 mL/min /1.73 m^2 based on Cockcroft and Gault's method.
    f. PT or INR, and APTT ≤ 1.5 x ULN unless patient is receiving anticoagulants. If patient is on anticoagulation therapy, levels should be within therapeutic range.
7. Eastern Cooperative Oncology Group (ECOG) performance status 0-2.
8. Estimated life expectancy > 3 months.
9. Negative pregnancy test for women of childbearing potential.
10. Signed informed consent form approved by the local Ethics Committee or Institutional Review Board.

Exclusion Criteria:

1. Any use of anticancer therapies within 2 weeks prior to initiation of study treatment; patients were to have recovered from prior treatment-related toxicities and meet laboratory and ECOG criteria for inclusion.
2. Any use of investigational therapies within 3 weeks prior to initiation of study treatment.
3. Major surgery within 2 weeks of study drug administration.
4. Relapse within 100 days of autologous or allogeneic bone marrow transplant.
5. Prior HDAC inhibitor therapy.
6. Patients with a diagnosis of:
    - Precursor T-cell lymphoma or leukemia
    - Adult T-cell lymphoma/leukemia (ATLL)

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- Primary cutaneous type anaplastic large cell lymphoma
- Mycosis fungoides/Sezary syndrome

7. Co-existing active infection or any medical condition likely to interfere with trial procedures.
8. Significant cardiovascular disease (New York Heart Association Class III or IV cardiac disease), myocardial infarction within the past 6 months, unstable angina, unstable arrhythmia or a need for anti-arrhythmic therapy (use of frequency adjusting medication for atrial fibrillation was allowed, if stable medication for at least last month prior to enrollment and medication not listed as causing Torsade de Pointes), or evidence of acute ischemia on ECG.
9. Baseline prolongation of QT/QTc interval, i.e., demonstration of a QTc interval > 450 msec; Long QT Syndrome; the required use of concomitant medication that may cause Torsade de Pointes.
10. Clinically significant central nervous system disorders with altered mental status or psychiatric disorders precluding understanding of the informed consent process and/or completion of the necessary studies.
11. Active concurrent malignancy (except adequately treated non-melanoma skin cancer or carcinoma in situ of the cervix). If there was a history of prior malignancy, the patient was to be disease free for greater than or equal to 2 years (except carcinoma in situ of breast, prostate cancer, or superficial bladder cancer).
12. Symptomatic or untreated central nervous system (CNS) metastases. Patients with previously treated CNS metastases which were asymptomatic at baseline were permitted.
13. Pregnant or breast-feeding women.
14. Women of childbearing age and potential who were not willing to use effective contraception during the study and until 30 days after last dose of study drug. Male patients or male patients who have female partners of childbearing age and potential who were not willing to use effective contraception during the study and until 30 days after last dose of study drug. Highly effective methods of birth control were defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some IUDs, sexual abstinence or vasectomised partner.
15. Known infection with HIV, hepatitis B or hepatitis C.
16. Patients that were not affiliated with social security (study centers in France only).

No other anti-cancer therapy including chemotherapy, radiation therapy, hormonal cancer therapy and immunotherapy, or experimental medications were permitted during the trial.

Treatment:

Patients were to receive belinostat 1000 mg/m^2 by intravenous (IV) infusion over 30 minute on days 1 to 5 every 3 weeks until disease progression or unmanageable treatment related toxicities.

The infusion time could be extended to 45 minutes if patients experienced infusion site pain or other symptoms potentially attributable to the infusion. Prophylactic anti-emetics were recommended as belinostat is associated with a moderate risk of emesis. In general, anti-emetic administration was according to the American Society of Clinical Oncology guidelines for anti-emetics in oncology (Kris, 2006); however local institutional standards or guidelines were also acceptable. The dose of belinostat was determined using the body surface area (BSA) based on baseline actual body weight of the patient. The dose was to be recalculated at subsequent cycles with body weight changes by more than 10% compared to baseline.

Belinostat treatment could be delayed to recover from toxicities. Patients were to be evaluated at weekly intervals (or less) and toxicities improved to grade ≤ 2 prior to re-treatment. A patient who had not received study drug for > 42 days since the last dose was to be discontinued from further treatment. Any patient who required a dose reduction was to continue to receive the reduced dose for the remainder of the trial. A maximum of two dose reductions were allowed and if the specified toxicities were still observed after two dose reductions, belinostat administration was to be discontinued.

Belinostat dose modifications for hematologic toxicities were based on platelet and neutrophil nadir counts in the preceding treatment cycle. The criteria for resuming treatment following toxicity were as follows: absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L and platelet count ≥ 50 x 10^9/L. Treatment was to be resumed according the table below.

Table 1 CLN-19 Dose Adjustments Based on Nadir Hematologic Values

Platelets (x 10^9/L) nadir		**ANC (x 10^9/L) nadir**	**Daily dose**
≥ 25	and	≥ 0.5	No change
Any	and	< 0.5	Decrease dose by 25%
< 25	and	Any	Decrease dose by 25%

Source: Protocol CLN-19, pg. 23

Belinostat administration was to be withdrawn permanently in patients who had recurrent platelet count nadir of < 25 x 10^9/L and/or recurrent ANC nadir of < 0.5 x 10^9/L after two dose reductions.

Dose modifications for non-hematologic toxicities were conducted according to Table 2 below.

The belinostat dose was to be decreased by 25% at the first two occurrences of a grade 3 or 4 non-hematologic AEs (for nausea, vomiting, and diarrhea, only if duration > 7 days with supportive management) and discontinued permanently with the recurrence of grade 3 or 4 toxicity after that. Belinostat was to be discontinued permanently with a single occurrence of grade 4 QTc prolongation.

Nausea, vomiting, and diarrhea were to be treated maximally prior to implementing dose modifications. When possible, supportive medical measures were to be used to potentially

reduce the need for dose modifications. Anti-emetics, anti-diarrheals, laxatives, non-steroidal anti-inflammatory agents, and adequate pain medication could be used prophylactically or symptomatically, as per local practice. Non-hematological toxicities were to have improved to grade ≤ 2 prior to re-treatment.

Table 2 CLN-19 Dose Adjustments Based on Non-Hematologic Toxicities

CTCAE grade	Daily dose
Any grade 3 or 4 AE [a,b]	Decrease dose by 25%
Recurrence of grade 3 or 4 AE after 2 dose reductions	Discontinue belinostat permanently

a For nausea, vomiting, and diarrhea, only if duration > 7 days with supportive management.
b Discontinue belinostat permanently if there is a single occurrence of grade 4 QTc prolongation per Fridericia's formula for QTc interval correction (QTcF).
Source: Protocol CLN-19, page 24.

Source: Dr. Lee's Review
The efficacy of belinostat was evaluated in a single-arm phase 2 trial of 120 patients who had relapsed or refractory disease after at least one prior systemic anticancer therapy. The primary efficacy endpoint was ORR based on central radiology and clinical review by the IRC. Secondary efficacy endpoints included time to response, duration of response, time to progression (TTP), progression-free survival (PFS), one-year PFS, one-year survival rate, and OS.

At the database cutoff date of August 31, 2012, seven patients remained on treatment. The key efficacy results were:

- The IRC assessed ORR was 25.8% (31/120 patients, 95% CI: 18.3-34.6). The CR rate was 10.8% (13/120 patients, 95% CI: 5.9-17.8) and the PR rate was 15.0% (18/120 patients, 95% CI: 9.1-22.7).

- The median duration of response based on the 31 responding patients by the SAP-defined criteria was 8.4 months (95% CI: 4.5-29.4).

- The investigator assessed ORR was 22.5% (27/120 patients, 95% CI: 15.4-31.0). The CR rate was 9.2% (11/120 patients, 95% CI: 4.7-15.8) and the PR rate was 13.3% (16/120 patients, 95% CI: 7.8-20.7).

Efficacy results are summarized in the table below. There were no multiplicity adjustments for the secondary efficacy endpoints.

Table 3 CLN-19 Summary Efficacy Results

	Efficacy Analysis Set (n=120)
Primary endpoint	
ORR by IRC	31 (25.8%)
95% CI	18.3-34.6
Complete response	13 (10.8%)
Partial response	18 (15.0%)
Secondary endpoints	
Median duration of response (by SAP)	8.4 months
95% CI	4.5-29.4
Median time to response	5.6 weeks
Range	4.3-50.4
Median time to progression	2 months
95% CI	1.5-2.8
Median PFS	1.6 months
95% CI	1.4-2.7
Median OS	7.9 months
95% CI	6.1-13.9

For further details, the reader is referred to the Clinical Review by Dr. Hyon-Zu Lee.

Statistics Review Summary and Conclusion *(Source: Dr. Bloomquist's review):*

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.

Trial Design

The study was based upon Simon's Two-stage optimal design, where one futility analysis is built in. The sponsor hypothesized an ORR of p1=20% for belinostat and a minimal or "uninteresting" ORR of p0=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

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.

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 two DMC meetings.

Trial 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.

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.

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/m2 /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 belinostat 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.

CDTL Comment: The clinical and statistical reviewers did not disagree on the primary efficacy findings. There are no outstanding issues for the clinical or statistical reviewers. Their recommendation is accelerated approval.

Post Marketing Requirement Issues

Spectrum presented an overview of NDA 206256 at an Application Orientation Presentation at FDA on January 6, 2014. There were ongoing trials to confirm the clinical benefit of Folotyn (Spectrum) and Istodax (developed by Celgene). During the meeting, the Agency expressed concern about the feasibility of completing accrual to so many trials in PTCL, a rare disease

(b) (4)

[redacted]

In the February 5, 2014 Filing Communication Letter, the Agency also requested that Spectrum submit a formal meeting request to discuss this alternate post-marketing commitment study for Beleodaq.

On April 11, 2014, DHP met with Spectrum to discuss the post-marketing commitment study for belinostat. (b) (4)

[redacted] The Agency agreed that Spectrum should move forward with a three-arm post-marketing trial that includes belinostat and pralatrexate. The Agency preferred that the trial be conducted in a front-line setting comparing belinostat+CHOP or Folotyn + CHOP vs CHOP regimen alone (a single comparator).

(b) (4)

[redacted]

(b) (4)

In conjunction with the reauthorization of the Prescription Drug User Fee Act of 1992 (PDUFA) in November 1997, FDA agreed to specific performance goals (PDUFA goals) for special protocol assessment and agreement. The PDUFA goals for special protocol assessment and agreement provide that, upon request, FDA will evaluate within 45 days certain protocols and issues relating to the protocols to assess whether they are adequate to meet scientific and regulatory requirements identified by the sponsor. Under new sections 505(b)(4)(B) and (C) of the Act, if a sponsor makes a reasonable written request to meet with the Agency for the purpose of reaching agreement on the design and size of a clinical trial, the Agency will meet with the sponsor. If an agreement is reached, the Agency will reduce the agreement to writing and make it part of the administrative record. An agreement may not be changed by the sponsor or FDA after the trial begins, except (1) with the written agreement of the sponsor and FDA, or (2) if the director of the FDA reviewing division determines that "a substantial scientific issue essential to determining the safety or effectiveness of the drug" was identified after the testing began (section 505(b)(4)(C) of the Act). (Food and Drug Administration, 2002) CLN-19 was under Special Protocol Agreement with FDA at the time of the NDA submission.

8. Safety

Source: Dr. Lee's review

The safety review of belinostat was primarily based on the 129 patients enrolled in the CLN-19 trial. Data from the pooled IV belinostat monotherapy trials, CLN-6 and CLN-20 (n=80) were also evaluated to support the safety. In addition, cardiac safety data from IV belinostat monotherapy trials (TT-20, TT-30, 301-G) were reviewed.

The safety findings from the CLN-19 trial are summarized below:

- The median duration of belinostat treatment was 7 weeks (range 3-135), the median number of cycles was 2 (range (1-33), and the median number of belinostat dose received by patients was 10 (range 1-165).

- The most common treatment-emergent adverse events (TEAEs) of belinostat (>25%) included nausea, fatigue, pyrexia, anemia and vomiting.

- The most frequently reported grade 3/4 TEAEs (>5.0%) were anemia (10.9%), thrombocytopenia (7.0%), dyspnea (6.2%), neutropenia (6.2%), fatigue (5.4%), pneumonia (5.4%) and hypokalemia (5.4%).

- Nine patients (7.0%) died during the trial or within 30 days of the last dose of belinostat due to an adverse event: multi-organ failure (2 patients), cardiac failure (2 patients), hepatic failure (1 patient), lung infection (1 patient), gastrointestinal hemorrhage (1 patient), euthanasia (1 patient) and shock (1 patient).

- A total of 55 patients (43%) experienced AEs indicative of myelosuppression with the highest overall incidence in hemoglobin decreased/anemia (33.3%) and the highest grade 4 incidence in platelet count decreased/ thrombocytopenia (9.3%).

- A total of 13 patients (10.1%) experienced cardiac AEs. Grade 3 and grade 5 AEs occurred in two patients each (1.6%).

- Thirteen patients (10.1%) experienced QT prolongation as assessed as treatment-related by the investigators. Two patients (1.6%) had confirmed grade 3 QT prolongation (by (b) (4)) and no grade 4 or 5 cases were reported.

- Tumor lysis syndrome occurred in 4 patients (3.1%). No cases of grade 5 were reported.

In the pooled analysis of CLN-6 and CLN-20, three patients (3.8%) died due to an AE (1 patient each due to ventricular fibrillation, pneumonia, and sepsis).

In the pooled analysis of IV belinostat monotherapy trials (TT-20, TT-30, CLN-6, CLN20, 301-G), a total of 35 patients (21.0%) reported treatment emergent cardiac AEs. Three patients (1.8%) experienced grade 3 AEs. One patient (CLN6-005-001) died due to ventricular fibrillation. In these trials, QT/QTc prolongation occurred in 4 patients (2.4%) with one case of grade 3 QTc prolongation.

In the pooled analysis of CLN-6 and CLN-20, a total of 79 patients (99%) had at least one TEAE. Thirty patients (38%) experienced grade 3 or 4 TEAEs and 3 patients (4%) had a fatal outcome.

Belinostat is a histone deacetylase (HDAC) inhibitor. Romidepsin is another HDAC inhibitor indicated for the treatment of PTCL in patients who have received at least one prior therapy. The main toxicities of romidepsin include hematologic toxicities, infection, ECG changes and tumor lysis syndrome. Most of these toxicities were also observed with belinostat. Belinostat has not been studied in patients with hepatic or renal impairment.

In the CLN-19 trial, patients with hepatic and renal impairments were officially to be excluded however, some patients with baseline grade 1-2 liver or renal function test abnormalities were enrolled in the trial (see section 7.4.2 under liver and renal function).

Belinostat is predominantly eliminated through hepatic metabolism and renal excretion does not have a major role. In the CLN-19 trial, there was one patient with a history of hepatitis A and on diclofenac that died from hepatic failure after receiving 10 cycles of belinostat therapy. In addition, there was one patient that experienced treatment related increased AST and ALT

in cycle 1. In the CLN-19 trial, hepatic and renal functions were routinely monitored and had to be ≤ grade 2 prior to treatment and dose reduced by 25% up to first two occurrences of grade 3 or 4. As such, liver and renal function should be routinely monitored and dose should be held or adjusted until recovery or discontinued.

Since belinostat was shown to inhibit CYP2C9 and CYP2C8 *in vitro*, CLN-20 trial was conducted to evaluate if belinostat would alter the metabolism of a sensitive CYP2C9 substrate (S-warfarin). Belinostat was administered at a dose of 1,000 mg/m^2 as a 30 minute daily IV infusion on Days 1 through 5 of Cycle 1 and warfarin 5 mg PO on Day 3, two hours before the administration of belinostat. There was a slight increase (3%-18%) of R-warfarin and slight decrease of S-warfarin (10%-17%) plasma concentrations. These results were within the pre-specified boundaries indicating no significant drug-drug interaction that would require any dose adjustment. There was no major effect of belinostat on warfarin metabolism and plasma concentration as assessed by the International Normalized Ratio (INR), which was the primary pharmacodynamic endpoint.

Belinostat was shown to be genotoxic *in vitro* and *in vivo*. Carcinogenicity, reproductive and developmental toxicity for belinostat have not been assessed.

Human carcinogenicity could not be adequately evaluated in CLN-19 since it was a single-arm trial with a small safety population of 129 subjects. However, the following malignancies were reported in CLN-19 (in preferred term): lung neoplasm, lung squamous cell carcinoma, keratoacanthoma, skin cancer, neoplasm skin, and mycosis fungoides. These patients have a background increased rate of malignancies.

There are no clinical trials of belinostat in pregnant women. HDAC inhibitors are known to cause fetal harm and belinostat is a genotoxic agent that targets rapidly dividing cells.

The applicant submitted the 120-day safety report on April 3, 2014. The updated data cut-off date was December 9, 2013. Overall, no new safety signals were identified in the safety update report.

Since the pivotal trial (CLN-19) for the proposed indication was a single-arm trial, the safety profile of belinostat could not be adequately evaluated. The safety profile of belinostat will be further evaluated in the post-marketing confirmatory randomized trial.

Source REMS Review by Carolyn Yancey (5/8/14)

At this time, the DRISK and DHP do not believe that belinostat, proposed for the treatment of PTCL, is associated with serious risks that exceed the benefits. If belinostat is approved for PTCL, the DRISK and DHP agree that a REMS is not necessary if belinostat is approved. The rationale for this conclusion follows:

- The most likely prescribers for belinostat will be hematologists who are familiar with the other treatment options for PTCL, experienced in the management of adverse events associated with chemotherapeutic agents in oncology patients, and the management of the reported serious risks with use of belinostat in this application.
- The DRISK and the DHP acknowledge that this NDA has limited clinical duration in

the Phase 2, open label safety data. Under accelerated approval for subpart H, the DHP is requiring the applicant to submit a proposal for a trial to evaluate belinostat, as a single active-control treatment, compared with 3-treatment arms with CHOP, CHOP + belinostat, and CHOP + pralatrexate, respectively.

- The class of HDAC inhibitors in the treatment of PTCL has a well characterized safety profile that includes the risks of myelosuppression, cardiac risk of QT prolongation, gastrointestinal events (i.e., bleeding, elevation of AST/ALT), Tumor Lysis Syndrome, and the potential to cause embryo-fetal toxicity. The adverse events reported for belinostat are comparable to those seen with the approved HDAC inhibitors. The labeling for vorinostat and romidepsin does not include a Box Warning or a Medication Guide and neither product has a REMS.

9. Advisory Committee Meeting

This application was not considered for presentation at an Advisory Committee for the following reasons:

- The primary trial was under Special Protocol Assessment Agreement
- The primary trial was a positive trial
- The Division is familiar with the primary endpoint and trial design

10. Pediatrics

Pediatric patients were not enrolled in the CLN-19 trial. Belinostat was granted orphan product designation for the treatment of PTCL on 9/3/09 under the provision of section 526 of the Federal Food, Drug, and Cosmetic Act. Therefore, belinostat is exempt from the Pediatric Research Equity Act (PREA) requirement.

11. Other Relevant Regulatory Issues

Financial Disclosures: None of the 118 clinical investigators that enrolled to CLN-19 (the main trial supporting the indication) had financial interests or agreements that require disclosure. None of the investigators were employees of Spectrum. The results of CLN-19 do not appear to have been impacted by any financial interests.

Exclusivity Issues: Belinostat is not presently marketed in the United States, therefore there are no exclusivity issues with this application.

Submission Quality and Integrity: The overall quality and integrity of this NDA were adequate to allow review.

Compliance with Good Clinical Practices: Trial CLN-19 enrolled 129 patients from 62 sites in 16 countries. Patients from the United States constituted 29% of the enrolled patients while

61% of the patients enrolled were from Europe. We consulted the Office of Scientific Integrity and recommended inspections for sites 907 (Shustov/Seattle) and 914 (Horwitz/New York).

On 6/04/14, Dr. Orencia entered the results of the Horwitz/New York site inspection. His notes to the Division regarding the inspection state …
"At this clinical study site, nine subjects were screened and six subjects were enrolled. Six subjects completed one cycle and four of these subjects completed two cycles of treatment. An audit of the enrolled subjects' records was conducted. A 100% verification of the informed consent documents of the enrolled subjects was done. A complete audit of the enrolled subjects' records was conducted.

Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Specific records were reviewed for study participants' inclusion or exclusion criteria, drug accountability, adverse events, monitoring, IRB approval, and overall protocol compliance. There was no evidence of under-reporting of significant adverse events. No significant regulatory violations were noted during the FDA inspection and a Form FDA 483 was not issued."

The Shustov/Seattle site inspection was issued a preliminary VAI rating.

The study appears to have been conducted adequately and the data generated by this site appear acceptable in support of the respective indication.

From OSI's consult review, in addition to the above two sites, the applicant site (Spectrum Pharmaceuticals, Inc.) in Irvine, CA was also inspected from March 17 to 21, 2014. The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, training of staff and site monitors. OSI's conclusion was that the applicant generally maintained adequate oversight of the clinical trial. There was no evidence of under-reporting of adverse events. There were no GCP noncompliant sites reported. The monitoring appeared reliable. Data submitted by the applicant appeared acceptable in support of the respective indication. The findings from the inspections indicate that the trial was conducted within the principles of good clinical practice.

There are no outstanding regulatory issues for this application.

12. Labeling

Proprietary Name: On 03/16/14, the proprietary name, "Beleodaq", was found acceptable by DMEPA.

A consult was issued to the Patient Labeling group in the Division of Medical Policy Programs (DMPP). Their review was archived on 5/16/14. They concluded that the Applicant's

proposed label was acceptable with their recommended changes. The Division incorporated the comments in the draft labeling exchanges with the Applicant.

A consult was issued to the Office of Prescription Drug Promotion (OPDP) to review the Product Insert. Their consultative review was archived on 5/12/14 and their comments were included in the draft labeling exchanges with the Applicant.

Final labeling negotiations are nearly complete at this time.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Accelerated Approval with post-marketing requirement to verify and describe the clinical benefit of belinostat treatment in patients with relapsed/refractory peripheral T-cell lymphoma.

- Benefit/Risk Assessment

PTCL is a serious and life-threatening disease. PTCL has an aggressive clinical course with inferior outcomes to those of aggressive B-cell lymphomas and the overall 5-year disease-free survival is less than 30% (except for anaplastic large cell lymphoma, ALK-positive). The benefit/risk assessment is positive for belinostat in the treatment of patients with relapsed/refractory PTCL.

In the treatment of 129 patients with relapsed or refractory PTCL who had received at least one prior systemic therapy, a 26% Overall Response Rate was reported. This included an 11% Complete Response rate and a 15% Partial Response rate. The median duration of response was 8.4 months based upon the 31 responding patients by the SAP-defined criteria. These results are very similar to those seen in the other two products that have accelerated approval for this indication (pralatrexate and romidepsin).

In the CLN-19 trial, the most common treatment-emergent adverse events (TEAEs) of belinostat (>25%) included nausea, fatigue, pyrexia, anemia and vomiting. Grade 3/4 TEAEs (>5.0%) were anemia (10.9%), thrombocytopenia (7.0%), dyspnea (6.2%), neutropenia (6.2%), fatigue (5.4%), pneumonia (5.4%) and hypokalemia (5.4%). Though inter-trial comparisons are not reliable, the incidences of grade 3/4 treatment-emergent hematologic toxicities occurred less often in the CLN-19 trial than in the pivotal trials of romidepsin and pralatrexate.

Belinostat is an HDAC inhibitor. The safety profile of belinostat appears to be similar to that of romidepsin, another HDAC inhibitor approved for the same indication. Since trial CLN-19 was a single-arm trial, the safety profile of belinostat could not be adequately evaluated. The safety profile of belinostat will be further evaluated in the post-marketing confirmatory randomized trial.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

Post-marketing pharmacovigilance is recommended. No REMS is recommended at this time.

- Recommendation for other Postmarketing Requirements and Commitments

Clinical PMRs: Spectrum should conduct the following clinical trials for Beleodaq (a phase 1 dose finding trial of belinostat for the combination regimen and the phase 3 trial):

- Establish the optimal safe dose of belinostat in combination with the cyclophosphamide/vincristine/doxorubicin/prednisone (CHOP) regimen. Perform a phase 1 dose finding trial of belinostat plus CHOP for the treatment of patients with peripheral T-cell lymphoma (PTCL). Enroll a sufficient number of patients to characterize the safety of the combination of belinostat in combination with the CHOP regimen. Submit a complete study report with all supporting datasets.

- Characterize the comparative efficacy and safety of Beleodaq when used in combination with a treatment regimen such as CHOP versus CHOP alone or pralatrexate plus CHOP versus CHOP alone for the initial therapy of patients with PTCL. Perform a confirmatory, prospective randomized (1:1:1) trial of previously untreated patients with PTCL, with progression free survival (PFS) as the primary efficacy endpoint. Enroll a sufficient number of patients to characterize the efficacy and safety of each drug added to CHOP, versus CHOP alone. The PFS endpoint should be determined by a blinded independent review committee. PFS analysis should be performed when the trial has experienced the planned number of events necessary for trial completion. Using the same data cutoff date as the PFS analysis, perform an interim analysis of overall survival. Submit a complete study report with all supporting datasets.

  The clinical PMRs are required under Subpart H, to verify and describe the clinical benefit of belinostat in the treatment of patients with relapsed/refractory PTCL after 1 prior therapy. The clinical PMRs remain under negotiation but are nearly final at this time.

Clinical Pharmacology PMRs:

There are six proposed Post-Marketing Requirements pertinent to Clinical Pharmacology. These are under negotiation with the Applicant at this time.

1. Submit the final clinical trial report for the ongoing human mass balance trial (protocol NCT01583777) designed to evaluate the excretion route of belinostat in humans.
2. Submit the final clinical trial report for the ongoing hepatic impairment trial that is designed to evaluate the influence of hepatic impairment on the PK and safety of belinostat.

3. Conduct a clinical trial evaluating the influence of strong UGT1A1 inhibitors on the pharmacokinetics of belinostat in patients with cancer.
4. Evaluate the safety and pharmacokinetics of belinostat in patients with wild-type, heterozygous, and homozygous UGT1A1*28 genotypes. The evaluations should be conducted for sufficient duration in order to evaluate safety following multiple dose administration.
5. Conduct a clinical trial in patients with varying degrees of renal impairment to evaluate the pharmacokinetic and safety of belinostat patients with impaired renal function. The trial should be conducted for sufficient duration in order to evaluate safety following multiple dose administration.
6. Conduct an in vitro study to determine the exact contributions of UGT1A1, CYP3A4, CYP2C9, and CYP2A6 in the biotransformation of belinostat.

The clinical pharmacology trials are required under FDAAA to provide safe and actionable labeling for patients in the subgroups described in each PMR.

- Recommended Comments to Applicant

There are no comments to be communicated to the Applicant at this time.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VIRGINIA E KWITKOWSKI
06/06/2014