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*APPLICATION NUMBER:*

**206256Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type	NDA
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Division / Office	DHP/OHOP
Reviewer Name	Hyon-Zu Lee, Pharm.D.
Review Completion Date	May 16, 2014
Established Name	Belinostat
Trade Name	Beleodaq
Therapeutic Class	Histone deacetylase inhibitor
Applicant	Spectrum Pharmaceuticals, Inc.
Formulation	500 mg single-use vial for reconstitution (50 mg/mL)
Dosing Regimen	1000 mg/m <sup>2</sup> intravenously on Days 1-5 of a 21-day cycle
Indication	Patients with relapsed or refractory peripheral T-cell lymphoma (PTCL)
Intended Population	≥ 18 years of age

Template Version: March 6, 2009

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## Table of Abbreviations

AE	adverse event
AITL	angioimmunoblastic T-cell lymphoma
ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATLL	adult T-cell lymphoma/leukemia
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisone
CI	confidence interval
C <sub>max</sub>	maximum concentration
CMC	Chemistry, Manufacturing and Controls
CNS	central nervous system
CPRG	Central Pathology Review Group
CR	complete response
Cru	Complete Response unconfirmed
CTCL	Cutaneous T-cell lymphoma
CYP	cytochrome P450
DLT	dose-limiting toxicity
DOR	duration of response
EAS	Efficacy Analysis Set
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	electronic Common Technical Document
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte macrophage colony-stimulating factor
HDAC	Histone deacetylase inhibitor
IRC	Independent Review Committee
ITT	intention to treat
IWG	International Working Group
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDA	New Drug Application
NK	natural killer

NOS	not otherwise specified
ODAC	Oncologic Drugs Advisory Committee
OPD	Orphan Product designation
ORR	overall response rate
OS	overall survival
OSI	Office of Scientific Investigations
PD	progressive disease
PFS	progression free survival
PMR	post-marketing requirement
PTCL	Peripheral T-cell lymphoma
PR	partial response
PREA	Pediatric Research Equity Act
QTc	corrected QT interval
QTcF	corrected QT interval using the Fridericia formula
REMS	Risk Evaluation and Mitigation Strategy
SD	stable disease
SAP	Statistical analysis plan
SPA	Special Protocol Assessment
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
ULN	upper limit normal
WHO	World Health Organization

## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

This reviewer recommends that belinostat be granted accelerated approval for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma.

### 1.2 Risk Benefit Assessment

#### Analysis of Condition

##### Summary of evidence

Peripheral T-cell lymphomas (PTCL) are a rare and heterogeneous group of disorders representing for approximately 10% to 15% of all non-Hodgkin lymphomas in North America and are associated with a poor prognosis (1, 2). Patients with PTCL commonly relapse after available therapies and there are few effective options for salvage therapy (3). Stem cell transplantation remains a potentially curative option for a subset of patients. According to the International T-Cell Lymphoma Project data (1314 cases from 22 countries worldwide), the most common subtypes were the following: PTCL not otherwise specified (PTCL-NOS, 25.9%), angioimmunoblastic T-cell lymphoma (AITL, 18.5%), natural killer (NK)/T-cell lymphoma (10.4%), adult T-cell lymphoma/leukemia (ATLL, 9.6%), and anaplastic large cell lymphoma [ALCL: anaplastic lymphoma kinase (ALK)-positive, 6.6% and ALK-negative, 5.5%]. The revised 2008 World Health Organization (WHO) classified the mature T-cell lymphomas into 4 groups: nodal, extranodal, cutaneous, and leukemic or disseminated disease and 13 different types (4).

**Table 1 WHO 2008 PTCL Classification**

T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Aggressive NK-cell leukemia
Indolent large granular NK-cell lymphoproliferative disorder (provisional)
ATL/adult T-cell leukemia
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma ( $\alpha\beta$ only)
Primary cutaneous $\gamma\delta$ T-cell lymphoma
Mycosis fungoides/Sezary syndrome
ALCL, ALK+
ALCL, ALK- (provisional)

PTCL, NOS
AITL

The International Prognostic Index (IPI) has shown to be predictive of outcome in some subtypes (PTCL-NOS, ALCL ALK-positive) of PTCL (4).

Risk factors (IPI):

- Age > 60 years
- Serum LDH > normal
- Performance status 2-4
- Stage III or IV
- Extranodal involvement > 1 site

**Table 2 Risk Category and Prognosis for PTCL-NOS by IPI**

<b>Risk category</b>	<b>Risk factors (n)</b>	<b>PTCL-NOS, 5 year OS<sup>5</sup></b>
Low	0 or 1	50%
Low intermediate	2	33%
High intermediate	3	16%
High	4 or 5	11%

## **Conclusions**

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) (6).

## **Unmet Medical Need**

### **Summary of evidence**

Two drugs have received accelerated approval in the second line PTCL setting: pralatrexate and romidepsin. 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%).

## **Conclusions**

NCCN guidelines recommend enrollment in a clinical trial as the preferred treatment for first-line and second-line treatment. Given the aggressive nature of PTCL, which has a poor prognosis, this patient population represents an unmet medical need. There is no available therapy for patients with relapsed/refractory PTCL as pralatrexate and romidepsin are approved under the accelerated approval regulations.

## **Clinical Benefit**

### **Summary of evidence**

The review of efficacy and safety for belinostat was primarily based on the CLN-19 trial, 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. This trial enrolled a total of 129 patients from 62 sites in 16 countries. All efficacy analyses were based upon the 'Efficacy Analysis Set' which was comprised of 120 patients that had confirmed diagnoses of PTCL by the Central Pathology Review Group (CPRG) and received at least one dose of belinostat.

The primary efficacy endpoint was overall response rate (ORR) based on central radiology and clinical review by the Independent Review Committee (IRC). At the clinical cutoff date of August 31, 2012, seven patients remained on treatment. The IRC-assessed ORR was 25.8% (31/120 patients, 95% CI: 18.3-34.6). The complete response rate was 10.8% (13/120 patients, 95% CI: 5.9-17.8) and the partial response rate was 15.0% (18/120 patients, 95% CI: 9.1-22.7).

The key secondary efficacy endpoint, median duration of response was 8.4 months (95% CI: 4.5-29.4) based on the 31 responding patients by the SAP-defined criteria. However, there were no multiplicity adjustments for the secondary efficacy endpoints.

### **Conclusions**

The key efficacy results of the CLN-19 trial (ORR and duration of response) for belinostat are similar to those of Folutyn (pralatrexate) and Istodax (romidepsin) that led to accelerated approval. Therefore, accelerated approval is recommended for belinostat. A confirmatory randomized trial is required to further characterize and verify the clinical benefit of belinostat for the treatment of patients with relapsed or refractory PTCL.

## **Risk**

### **Summary of evidence**

The safety review of belinostat was primarily based on the 129 patients enrolled in the CLN-19 trial who were dosed intravenously at 1000 mg/m<sup>2</sup> over 30 minutes on Days 1-5 of a 21-day cycle. The pooled data of intravenous belinostat monotherapy trials, CLN-6 and CLN-20 (n=80) and other IV belinostat monotherapy trials (TT-20, TT-30, 301-G) (n=87) provided supportive safety data.

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.

Nine patients (7.0%) died during the CLN-19 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 and 13 patients (10.1%) experienced cardiac AEs [grade 3 and grade 5 AEs occurred in two patients each (1.6%)]. Tumor lysis syndrome occurred in 4 patients (3.1%) with no cases of grade 5. One patient had a treatment-related death with hepatic failure and there was another patient who experienced increased AST and ALT assessed as related to belinostat.

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 [grade 3 AEs occurred in 3 patients (1.8%) and there was one grade 5 event (0.6%)].

## **Conclusions**

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.

## **Risk Management**

The main toxicities of belinostat include myelosuppression, infection, hepatotoxicity, tumor lysis syndrome, and gastrointestinal toxicities. In general, belinostat therapy should be delayed or dose-reduced to recover from toxicities or discontinued. For gastrointestinal toxicities, appropriate prophylactic or symptomatic treatment should be instituted. For tumor lysis syndrome, patients at high risk (such as advanced disease stage, high tumor burden, and renal insufficiency) should be monitored closely and appropriate prophylaxis and treatment should be provided.

## **Benefit-Risk Summary and Assessment**

The efficacy results of the CLN-19 trial were similar to those of pralatrexate and romidepsin which are approved under the accelerated approval regulations. The safety profile of belinostat

is acceptable for a serious and life-threatening disease such as PTCL with limited treatment options. However, the safety and efficacy should be confirmed in a post-approval randomized trial.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

Risk Evaluation and Mitigation Strategy (REMS) is not required for belinostat for the treatment of patients with relapsed or refractory PTCL.

### **1.4 Recommendations for Postmarket Requirements and Commitments**

#### **1.4.1 Regulatory Background**

Spectrum Pharmaceuticals is the applicant of Beleodaq (belinostat) and Folutyn (pralatrexate). Folutyn was approved under the accelerated approval regulations in 2009 for the same indication as Beleodaq, for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) with two PMRs. Both of the PMRs for pralatrexate are pending at this time and little progress had been made on accrual to the confirmatory trials. Since PTCL is a rare disease, the likelihood of completing multiple randomized trials in this small population is negligible. In order to expedite the fulfillment of the post-marketing requirements (PMRs) for both drugs it was determined that a single confirmatory trial would be the optimal path forward.

On April 11, 2014, FDA had a meeting with Spectrum to discuss the alternative confirmatory clinical phase 3 trial for belinostat and pralatrexate. It was agreed that Spectrum would conduct the following trial: “A Phase 3, Randomized, Open-Label, Study Comparing Efficacy and Safety of Beleodaq-CHOP or Folutyn-CHOP versus CHOP Regimen Alone in Newly Diagnosed Patients with Previously Untreated Peripheral T-Cell Lymphoma” to fulfill the PMRs for belinostat and pralatrexate. In this trial, patients with previously untreated PTCL will be randomized 1:1:1 into one of three treatment arms: two combination experimental arms; Beleodaq + CHOP or Folutyn + CHOP or the active comparator arm (CHOP). The primary efficacy endpoint is progression free survival and secondary efficacy endpoints include overall response rate, duration of response and overall survival.

#### **1.4.2 Recommendations for PMR**

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 belinostat when used in combination with a treatment regimen such as CHOP, versus 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.

## 2 Introduction and Regulatory Background

### 2.1 Product Information

Established Name:	Belinostat (also known as PXD101)
Trade Name:	Beleodaq
Applicant:	Spectrum Pharmaceuticals, Inc. 157 Technology Drive Irvine, CA 92618
Drug Class:	Histone deacetylase (HDAC) inhibitor
Proposed Indication:	For the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL).
Proposed Dosage and Administration:	The recommended dose of belinostat is 1000 mg/m <sup>2</sup> by intravenous infusion administered over 30 minutes on Days 1-5 of a 21-day cycle.
Drug Product:	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.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

The proposed indication is for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL).

Although not specifically approved as regimens, commonly used first-line therapies for PTCL include CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) and HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with high-dose methotrexate and cytarabine) (7). Cure rates for PTCL are low with the exception of localized extranodal NK/T-cell lymphoma which is usually treated with localized radiotherapy plus anthracycline based chemotherapy and anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL).

Consolidation therapy is considered for patients who enter remission following chemotherapy with the exception of patients determined at low risk for a relapse/recurrence and patients with ALK positive ALCL who, in general, have a good prognosis and do not need bone marrow transplant if in remission. Typical first-line consolidation treatments include high-dose chemotherapy followed by stem cell transplant. However, only a select few PTCL patients are eligible for stem cell transplant.

For relapsed or refractory PTCL, Folutyn (pralatrexate) and Istodax (romidepsin) are the only two approved drugs, however they are not considered as available therapy because they are approved under accelerated approval. The table below shows the results of the pivotal trials that led to the accelerated approval of these drugs.

**Table 3 Approved Drugs for Relapsed or Refractory PTCL**

Drug and year/type of approval	Patient population	Efficacy Results
Folutyn (pralatrexate): 2009/accelerated	N=109 Median age: 59 Median number of prior therapies: 3	Overall response rate: 27% (CR+CRu: 8%, PR: 18%) Duration of response: 9.4 months
Istodax (romidepsin): 2011/accelerated	N=130 Median age: 61 Median number of prior therapies: 2	Overall response rate: 25.4% (CR+ CRu: 14.6%, PR: 10.8%) Duration of Response: 9.2+ months <sup>a</sup>

<sup>a</sup> The responses in 11 of the 19 patients achieving CR and CRu were known to exceed 9.2 months; the follow-up on the remaining 8 patients was discontinued prior to 9.2 months at the data lock date of October 31, 2010.

Other recommended second-line therapies by the National Comprehensive Cancer Network (NCCN) guidelines include combination chemotherapies such as DHAP (dexamethasone, cisplatin, cytarabine), ICE (ifosfamide, carboplatin, etoposide) or single agent chemotherapy

such as brentuximab vedotin (for nodal ALCL only excluding cutaneous ALCL), bortezomib, gemcitabine or radiation therapy.

### 2.3 Availability of Proposed Active Ingredient in the United States

Belinostat is not currently marketed in the United States.

### 2.4 Important Safety Issues With Consideration to Related Drugs

Pralatrexate and romidepsin are the only available drugs with the same indication as belinostat. Pralatrexate is a folate analog metabolic inhibitor that competitively inhibits dihydrofolate reductase. Romidepsin is an HDAC inhibitor. The toxicity profile of romidepsin is most relevant to the safety review of belinostat.

The most frequently reported adverse reactions ( $\geq 30\%$ ) with pralatrexate were mucositis (70%), thrombocytopenia (41%), nausea (40%), fatigue (36%), anemia (34%), constipation (33%), pyrexia (32%), and edema (30%). The most common grade 3 or 4 AEs with pralatrexate included thrombocytopenia (33%), mucositis (21%), neutropenia (20%), and anemia (17%).

The most frequently reported adverse reactions with romidepsin ( $\geq 30\%$ ) were nausea (59%), asthenia/fatigue (55%), thrombocytopenia (41%), vomiting (39%), diarrhea (36%) pyrexia (35%), neutropenia (30%) and constipation (30%). The most common grade 3 or 4 AEs with romidepsin included thrombocytopenia (24%), neutropenia (20%), and anemia (11%).

Belinostat is a histone deacetylase (HDAC) inhibitor. Commercially available HDAC inhibitors include Zolinza (vorinostat) and Istodex (romidepsin). The table below summarizes the toxicities listed in the Warnings and Precautions section in the US package inserts for these drugs. Note: pralatrexate is also included in the table as it has the same indication as belinostat.

**Table 4 USPI Warnings and Precautions**

	<b>Vorinostat (HDACi)</b>	<b>Romidepsin (HDACi)</b>	<b>Pralatrexate</b>
Thromboembolism	X		
Hematologic	X	X	X
Gastrointestinal disturbances	X		
Hyperglycemia	X		
Monitoring of chemistry tests	X		
Thrombocytopenia and gastrointestinal bleeding	X		
Fetal harm	X	X	X
Infection		X	
Electrocardiographic changes		X	

Tumor lysis syndrome		X	X
Mucositis			X
Dermatologic reactions			X
Hepatic toxicity			X
Risk of increased toxicity with renal impairment			X

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

The IND for belinostat was originally filed by CuraGen Corporation on November 15, 2004 and was then transferred to Topotarget in April 2008. 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.

The table below shows the regulatory history pertaining to the clinical review of the NDA.

**Table 5 Regulatory History**

Date	Event
November 29, 2007	<p>Type B End of Phase 1/2 meeting with CuraGen.</p> <ul style="list-style-type: none"> <li>FDA stated that objective response rate is acceptable as a primary endpoint. The significance of ORR is assessed by its magnitude and duration, the percentage of complete responses, and an acceptable risk/benefit ratio. The results of time to event endpoints, such as PFS and OS in a single arm study are not interpretable and should be considered as exploratory. Refer to the FDA guidance “Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products” <a href="http://www.fda.gov/cder/guidance/1397fnl.pdf">www.fda.gov/cder/guidance/1397fnl.pdf</a>.</li> <li>FDA commented that the proposed enrollment of (b) (4) patients is not likely to adequately assess the efficacy of the investigational agent and encouraged to enroll a larger number of patients.</li> </ul> <p><i>The sponsor requested clarification on the sample size requirement. The FDA clarified that in general, 100 patients would be required for this indication.</i> (b) (4)</p> <p>(b) (4)</p> <ul style="list-style-type: none"> <li>FDA stated that local institution pathology confirmation for eligibility is</li> </ul>

	<p>acceptable, but to include adequate minimum pathology evaluation parameters in the protocol required for the diagnosis of each patient. Also, plan to capture these pathology evaluation parameters in Case Report Forms.</p> <ul style="list-style-type: none"> <li>• FDA stated that the adequacy of the safety population will be a review issue at the time of NDA submission.</li> <li>• FDA stated a single, small, one-arm trial in PTCL is not likely to be considered adequate to support an NDA in this indication. In addition, for a single trial to support an NDA, the trial should be well designed, well conducted, internally consistent, and provide statistically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform.</li> <li>• FDA stated that a drug that has an Orphan Product designation (OPD) is exempt from PREA. If belinostat does not receive OPD for the proposed indication, a waiver or deferral of pediatric study requirements may be requested by submitting adequate justification.</li> </ul>
<p>July 25, 2008</p>	<p>Type A meeting communications with Topotarget to discuss trial CLN-19 submitted under Special Protocol Assessment (SPA).</p> <p>This meeting was cancelled as the FDA preliminary responses sent to the Sponsor were clear.</p>
<p>September 4, 2008</p>	<p>FDA issued the SPA agreement letter for trial CLN-19.</p>
<p>July 20, 2011</p>	<p>Type C guidance meeting for reporting and handling of cardiac, hepatic impairment, mass balance and baseline bone marrow evaluation data.</p> <ul style="list-style-type: none"> <li>• The Sponsor indicated that 25 patients were enrolled in the trial under version 3.0. Of the 25 patients, there are 12 patients that did not have a baseline bone marrow assessment based on the investigators' discretion. The Sponsor proposed to include these 12 patients in the safety population only. The efficacy population of at least 100 evaluable patients will include patients with centrally-confirmed PTCL pathology and a bone marrow biopsy at baseline as mandated by Cheson 2007 and at the follow-up visit, if indicated.</li> </ul> <p>FDA reiterated that this would be a review issue based on the totality of the data at the time of submission. The precedent for treating missing assessments, regardless of response, is that they are removed from the numerator, but included in the denominator. The Division recommended providing a case-by-case justification for handling the initial 12 patients. It</p>

	<p>may be reasonable to add 12 additional patients to the population.</p> <ul style="list-style-type: none"> <li>• FDA stated that initial registration based on single arm clinical trials is 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.</li> <li>• FDA stated that post-approval confirmatory clinical trials are required in order to be considered for accelerated approval and to discuss the development plan for Belinostat that may be used to satisfy the confirmatory requirements for accelerated approval.</li> <li>• FDA stated that post-marketing trial(s) should be discussed at the time of pre-NDA meeting (not necessarily part of the Pre-NDA meeting) and should be ongoing at the time of NDA submission.</li> </ul>
February 7, 2013	Type C meeting to discuss the proposed post-marketing phase 1 and phase 3 clinical development plans.
May 29, 2013	<p>Type B pre-NDA meeting to discuss the proposed structure and contents of the NDA.</p> <ul style="list-style-type: none"> <li>• FDA stated that both the response rate and duration of response will be taken into consideration for determination of efficacy and recommended a minimum of 6 months of follow-up for the last responding patient to ensure that the duration of response data is mature.</li> </ul> <p>The Sponsor indicated that by the proposed data cut-off date of August 31, 2012, all patients who responded per the Independent Review Committee had either progressive disease (PD) or were in response for &gt;10 months, except for one patient. This patient had a documented partial response (PR) by Central Review, starting on June 14, 2012 with documented PD on September 6, 2012; one week after the proposed data cut-off date. Extending the data cut-off date by one week to include the disease progression of this patient would have no effect on the objective response rate or the median duration of response. Therefore, the Sponsor proposed to keep the planned data cut-off date of August 31, 2012 for the analyses of data from the CLN-19 pivotal study. Standardized response criteria, including IWG (Cheson et al, JCO, 25:5, page 579-586, 2007) will be applied to the belinostat data to provide uniform end points to allow for appropriate comparisons among PTCL clinical trials with other agents.</p>

	<ul style="list-style-type: none"> <li>• FDA asked that the Sponsor include the forms generated during the independent Central Pathology Review Group (CPRG) review process in the NDA submission.</li> <li>• FDA stated time to event endpoints such as PFS and OS are not interpretable in a single arm trial and no labeling claims can be made based on these endpoints.</li> </ul>
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## 2.6 Other Relevant Background Information

On May 28, 2008, belinostat was granted Fast Track designation for the treatment of relapsed or refractory PTCL after at least one prior systemic therapy and orphan drug designation for the treatment of PTCL on September 3, 2009 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.

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

This NDA was submitted as an electronic Common Technical Document (eCTD) and follows the FDA Guidance for Industry: Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications. The overall quality and integrity of this NDA were adequate to allow review.

### 3.2 Compliance with Good Clinical Practices

The trials included in this NDA were conducted in compliance with the principles of Good Clinical Practice (GCP) guidelines as stated in the US Federal regulations as well as “Guidance for Good Clinical Practice” and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. The protocols including amendments and patient consent forms were reviewed and approved by relevant Institutional Review Boards and Independent Ethics Committees.

Since CLN-19 is the primary trial to support efficacy and safety of belinostat, two clinical sites of the CLN-19 trial were chosen for Office of Scientific Investigations (OSI) inspections. The site selections were based on enrollment of large number of patients (table 4).

**Table 6 Requested OSI Clinical Site Audits for CLN-19**

Site ID	Number of enrolled patients	Name of the PI	Location
907	7	Andrei R. Shustov	Seattle Cancer Care Alliance

			825 Eastlake Avenue East Seattle, WA 98109
914	6	Steven Horwitz	Memorial Sloan-Kettering Cancer Center 1275 York Avenue New York, NY 10021

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.

OSI’s overall assessment of findings and general recommendations for these sites were as follows:

“For this open label, single arm, randomized study, two domestic sites were selected for inspection supporting this NDA: Andrei R. Shustov, M.D., and Steven M. Horwitz, M.D. The sponsor (Spectrum Pharmaceuticals, Inc.) was also inspected. The final regulatory classification for Dr. Horwitz is NAI (No Action Indicated). The preliminary regulatory classification for Dr. Shustov is VAI (Voluntary Action Indicated). The preliminary classification for Spectrum Pharmaceuticals, Inc. is NAI (No Action Indicated). The study data collected from these clinical sites and the sponsor appear generally reliable in support of the requested indication.”

This reviewer concludes that the overall compliance with GCP is acceptable.

### 3.3 Financial Disclosures

The applicant provided FDA financial certification form 3454 signed by the Executive Vice President and Chief Financial Officer, Kurt Gustafson dated November 14, 2013.

Based on the “Guidance for Clinical Investigators, Industry, and FDA Staff Financial Disclosure by Clinical Investigators” and in compliance with 21 CFR §54, the applicant only provided financial certification and disclosure by clinical investigators for the CLN-19 trial as CLN-19 is the pivotal trial for efficacy and safety in the proposed indication. The NDA includes a list of 118 clinical investigators who participated in the CLN-19 trial and a certification letter confirming that none of the clinical investigators who participated in the CLN-19 trial have

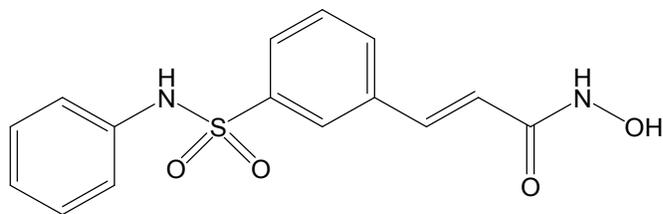
financial interests or agreements that require disclosure. None of the investigators that participated in the CLN-19 trial were full-time or part-time sponsor employees.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

Belinostat is a pan-histone deacetylase (HDAC) inhibitor with a sulfonamide-hydroxamide structure. The chemical name of belinostat is (2E)-N-hydroxy-3-[3-(phenylsulfamoyl)phenyl]prop-2-enamide. The molecular weight is 318.35 g/mol. The molecular formula is C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>S and the molecular weight is 318.35 g/mol. The structural formula is shown in Figure 1.

**Figure 1 Structure of Belinostat**



Belinostat is a white to off-white powder. It is slightly soluble in distilled water (0.14 mg/mL) and polyethylene glycol 400 (about 1.5 mg/mL), and is freely soluble in ethanol (> 200 mg/mL). The pK<sub>a</sub> values are 7.87 and 8.71 by potentiometry and 7.86 and 8.59 by UV.

Refer to Chemistry, Manufacturing and Controls (CMC) review for details.

### 4.2 Clinical Microbiology

Not applicable.

### 4.3 Preclinical Pharmacology/Toxicology

Refer to Pharmacology/Toxicology review for details.

No carcinogenicity studies have been performed with belinostat. *In vitro* studies in bacterial cells and murine lymphoma cells indicated that belinostat was genotoxic. The *in vivo* genotoxicity study rat bone marrow micronucleus assay indicated that belinostat was not clastogenic.

No reproductive toxicology studies have been performed with belinostat. HDAC inhibitors including belinostat are known to cause developmental toxicity. Belinostat is a genotoxic agent that targets rapidly dividing cells.

#### 4.4 Clinical Pharmacology

Refer to Clinical Pharmacology review for details.

##### 4.4.1 Mechanism of Action

Belinostat is a low molecular weight pan-HDAC inhibitor. Belinostat inhibits the enzymatic activity of (b) (4) (Class I) (b) (4) (Class II) (b) (4) (Class IV) (b) (4). *In vitro*, belinostat induces an increase in acetylated histones and other proteins resulting in cell cycle arrest, apoptosis, and a decrease in tumor cell proliferation. Belinostat shows preferential cytotoxicity towards tumor cells compared to normal cells.

##### 4.4.2 Pharmacodynamics

The effect of belinostat on acetylation of histone H4 was evaluated in a phase 1 dose escalation study. The extent and duration of histone acetylation increased with increasing doses of belinostat up to 1000 mg/m<sup>2</sup>. Mean acetylation activity appeared to reach a maximum at belinostat plasma concentrations above 1 μM.

##### 4.4.3 Pharmacokinetics

###### Absorption:

The pharmacokinetics of belinostat were evaluated from the pooled data from phase 1/2 studies that used belinostat doses of 150-1200 mg/m<sup>2</sup>. The total mean plasma clearance and elimination half-life were 1240.3 mL/min and 1.1 hours, respectively. The total clearance approximates average hepatic blood flow (1500 mL/min), suggesting high hepatic extraction.

###### Distribution:

The plasma protein binding assessment for belinostat showed that it was highly bound to human plasma protein (>92%) and was independent of belinostat plasma concentrations from 500 to 25,000 ng/mL. The mean volume of distribution approaches total body water, indicating limited body tissue distribution.

###### Metabolism:

In humans, belinostat was shown to be rapidly metabolized to five major metabolites: belinostat glucuronide, methyl belinostat, belinostat amide, belinostat acid and 3-(anilinosulfonyl) benzene carboxylic acid (3-ASBA). These metabolites were shown to be inactive at clinically relevant

concentrations. Phase 2 glucuronidation is the major route of elimination in humans. Belinostat was also shown to undergo hepatic metabolism by CYP2A6, CYP2C9, and CYP3A4.

Excretion:

Belinostat is predominantly eliminated via hepatic metabolism. Renal excretion was not shown to be a major route of elimination of belinostat, with less than 2% of the dose recovered unchanged in urine.

Special population:

Belinostat has not been studied in patients with hepatic or moderate to severe renal impairment.

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

A total of 14 clinical oncology trials were included in this NDA which are summarized in the table below.

**Table 7 Clinical Trial Reports Included in NDA 206256**

<b>Trial ID</b>	<b>Design</b>	<b>Dosing regimen and combination</b>	<b>Patient population</b>	<b>No. of subjects</b>
Pivotal, uncontrolled trial of IV belinostat in patients with PTCL				
CLN-19*	Phase 2, open-label, single-arm, non-randomized	1000 mg/m <sup>2</sup> 30 min IV, days 1-5 (every 21days)	Relapsed or refractory PTCL	129
Supportive, uncontrolled trial of IV belinostat monotherapy (150-1200 mg/m <sup>2</sup> , days 1-5, every 21 days) in patients with various advanced malignancies				
CLN-20*	Phase 1, open-label, PK/PD	1000 mg/m <sup>2</sup> 30 min IV, days 1-5 (drug-drug interaction with warfarin)	Solid tumors or hematologic malignancies	27
TT-20*	Phase 1, open-label, dose-escalation	various	Advanced solid tumors	46
TT-30	Phase 1, open-label, dose-escalation	various	Advanced hematologic neoplasia	16
CLN-6	Phase 2, open-label, non-randomized	1000 mg/m <sup>2</sup> 30 min IV, days 1-5 (every 21days)	Recurrent or refractory CTCL or PTCL	29 CTCL, 24 PTCL
301-G*	Phase 2, open-label, non-randomized	various	Advanced multiple myeloma	25
Supportive, controlled trial of IV/oral belinostat combination therapy in patients with untreated cancer of unknown primary				
CLN-17	Phase 2, open-label,	1000 mg/m <sup>2</sup> IV, days 1-5	Untreated	86

	randomized	(every 21days), in combination with carboplatin and paclitaxel	carcinoma of unknown primary	(42/44)
Supportive, uncontrolled trial of IV belinostat (300-1000 mg/m <sup>2</sup> , days 1-5, every 21 days) combination therapy with various advanced malignancies				
CLN-4*	Phase 1, open-label, dose escalation	Various, in combination with 5-FU	Advanced solid tumors	35
CLN-5	Phase 1b/2, open-label, dose escalation	Various, in combination with bortezomib	Refractory/ relapsed multiple myeloma	3
CLN-8*	Phase 1/2, open-label, dose escalation	Various, in combination with carboplatin and paclitaxel	Advanced solid tumors/ ovarian and bladder cancer	80
CLN-14	Phase 1/2, open-label, dose escalation	Various, in combination with doxorubicin	Advanced solid tumors/ soft tissue sarcoma	41
CLN-15*	Phase 1/2, open-label, dose escalation	Various, in combination with idarubicin	AML not suitable for standard intensive therapy	41
CLN-16	Phase 2, open-label, non-randomized	Various, in combination with bortezomib	Refractory/ relapsed multiple myeloma	4
Supportive, uncontrolled trial of oral belinostat monotherapy in patients with various advanced malignancies				
CLN-9	Phase 1, open-label, dose escalation	Various	Solid tumors or hematologic malignancies	120

\*Trials used for pharmacokinetic analyses

## 5.2 Review Strategy

As CLN-19 was the pivotal trial for efficacy and safety, the clinical review was primarily based on the CLN-19 trial data to support the proposed indication and also included the following:

- Trial CLN-6 was reviewed to support efficacy and safety of belinostat;
- Trials TT-20, TT-30, 301-G, and CLN-20 were reviewed to support safety of belinostat;
- Electronic submission with clinical study reports and other relevant portions of the NDA;
- Efficacy and safety data analyses were audited or reproduced;
- Regulatory history of belinostat;
- Applicant's presentation on January 6, 2014;
- Applicant's responses to FDA information requests;
- Relevant published literature in PTCL; and
- The 120-day safety update report submitted on April 3, 2014.

## 5.3 Discussion of Individual Studies/Clinical Trials

### 5.3.1 Clinical Trial

#### **CLN-19**

##### Trial ID and Title:

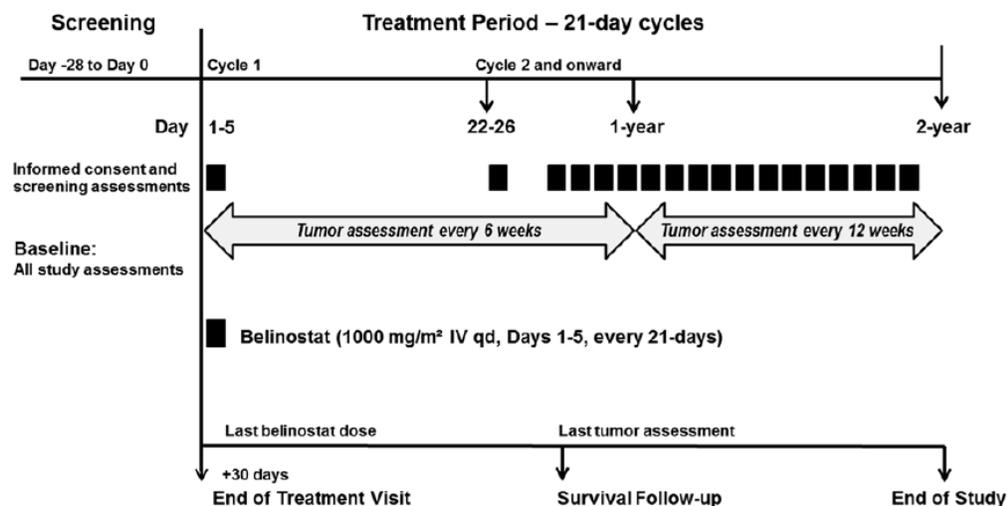
PXD101-CLN-19 (referred to as CLN-19 throughout this review): A Multicenter, Open Label Trial of Belinostat in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma.

##### 5.3.1.1 Trial Design

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.

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.

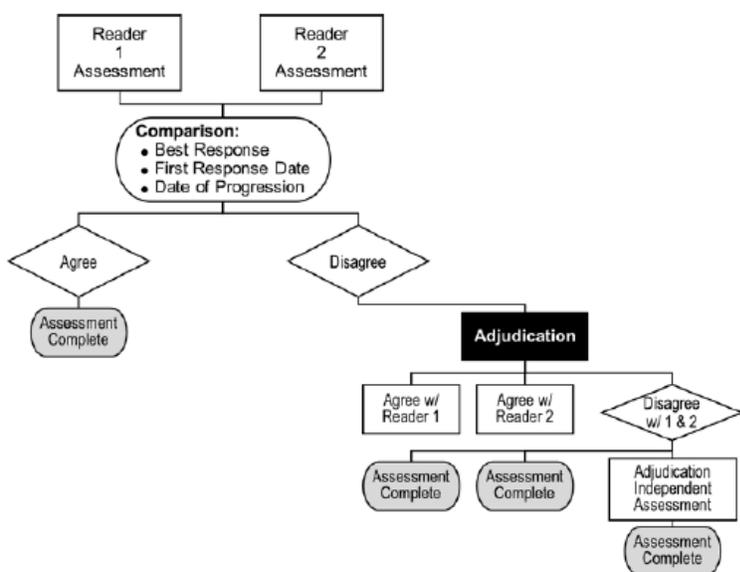
**Figure 2 CLN-19: Trial Design and Assessments**



Source: ISE page 18.

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.

**Figure 3 CLN-9: Independent Assessment Process**



Source: Sponsor's response to information request on February 19, 2014.

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.

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:  $\beta$ F1, 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  $\geq$  18 years.
6. Laboratory status:
  - a. Absolute neutrophil count  $\geq$   $1.0 \times 10^9/L$ , platelets  $\geq$   $50 \times 10^9/L$ .

- b. Total bilirubin  $\leq 1.5$  x upper limit normal (ULN), or  $\leq 3$  x ULN if documented hepatic involvement with lymphoma, or  $\leq 5$  x ULN if history of Gilbert's Disease.
  - c. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)  $\leq 2.5$  x ULN ( $\leq 5$  x ULN if documented hepatic involvement with lymphoma).
  - d. Serum potassium within normal range.
  - e. Calculated creatinine clearance  $\geq 45$  mL/min /1.73 m<sup>2</sup> based on Cockcroft and Gault's method.
  - f. PT or INR, and APTT  $\leq 1.5$  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<sup>2</sup> 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  $\leq 2$  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)  $\geq 1.0 \times 10^9/L$  and platelet count  $\geq 50 \times 10^9/L$ . Treatment was to be resumed according the table below.

**Table 8 CLN-19: Dose Adjustments Based on Nadir Hematologic Values**

Platelets ( $\times 10^9/L$ ) nadir	ANC ( $\times 10^9/L$ ) nadir	Daily dose
$\geq 25$	and $\geq 0.5$	No change
Any	and $< 0.5$	Decrease dose by 25%
$< 25$	and Any	Decrease dose by 25%

Source: Protocol CLN-19, page 23.

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

Dose modifications for non-hematologic toxicities were conducted according to Table 9 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  $\leq 2$  prior to re-treatment.

**Table 9 CLN-19: Dose Adjustments Based on Non-Hematologic Toxicities**

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

<sup>a</sup> For nausea, vomiting, and diarrhea, only if duration  $> 7$  days with supportive management.

<sup>b</sup> 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.

Oral anticoagulants that are substrates of P450 CYP2C8 and CYP2C9 enzymes were to be avoided, unless deemed medically necessary. If there was a medical necessity it was recommended that INR be monitored at least once per week for the first month, then monthly if the INR was stable in the desired therapeutic range. Subcutaneous heparin was permitted.

Low doses of steroids (equivalent to prednisone  $\leq$  20 mg/day) including doses appropriate for prophylaxis of nausea and vomiting as per ASCO guidelines were permitted. Patients in need of higher doses of steroids than equivalent to prednisone 20 mg/day to prevent, or treat, allergic conditions (for instance IV contrast allergies) could be administered such doses when medically indicated.

Loperamide was the recommended standard therapy for diarrhea. Hematopoietic growth factors (i.e., G-CSF or GM-CSF) could be used according to institutional or other specific guideline to treat febrile neutropenia, but not as primary or secondary prophylaxis. Growth factors were to be discontinued at least 48 hours prior to initiation of the next cycle of therapy. Concomitant medication that may cause *Torsades de Pointes* were not to be taken.

Schedule of Events:

**Table 10 CLN-19: Schedule of Events**

	Baseline Day -28 to 0	Baseline Day -14 to 0	Cycle 1					Cycle 2 and onward					End of Treatment <sup>14</sup>	Follow Up	
			Day 1	Day 2	Day 3	Day 4	Day 5	Day 11-15	Day 1	Day 2	Day 3	Day 4			Day 5
<b>BELINOSTAT TREATMENT</b>			X	X	X	X	X		X	X	X	X	X		
Informed Consent	X														
Pathology material for central review <sup>16</sup>	X														
Electrocardiogram (ECG) <sup>1</sup>	X		X	X	X	X	X						X	X	
Pregnancy test (serum or urine)		X													
Medical history <sup>2</sup>		X													
Performance status (ECOG)		X	X						X					X	
Physical examination <sup>3</sup>		X	X						X					X	
Vital signs <sup>4</sup>		X	X	X	X	X	X		X	X	X	X	X	X	
Hematology <sup>5</sup>		X	X				X	X	X				X	X	
Blood chemistry <sup>6</sup>		X	X				X	X	X				X	X	
Coagulation <sup>7</sup>		X	[X]						[X]					X	
Urinalysis/dipstick <sup>8</sup>		X												X	
Creatinine clearance <sup>9</sup>		X													
PK blood sampling <sup>10</sup>			X			X									
Concomitant medications review		X	X	X	X	X	X	X	X	X	X	X	X	X	X <sup>11</sup>
Adverse event assessment			X	X	X	X	X	X	X	X	X	X	X	X	
Tumor assessment <sup>12</sup>	X								Tumor assessments (see below) <sup>12</sup>					X <sup>14</sup>	X <sup>12</sup>
Survival information <sup>13</sup>															X

12. Tumor assessments were according to IHP/IWG by appropriate radiologic imaging or other techniques. For radiographic assessment, CT of neck, chest, abdomen and pelvis was to be done at every assessment. Examination and documentation of the clinically measurable size and location of all palpable and skin tumor lesions were to be done, i.e., index and non-index lesions. Index and non-index lesions that were not followed by radiological methods were to be documented appropriately (e.g., by photographs that include a ruler).

Tumor assessments were to be made at baseline and by the same techniques every 6 weeks for the first 12 months, then every 12 weeks until 2 years from the start of study treatment. Tumor assessments were to be stopped at the time of disease progression as evaluated by the investigator, or upon initiation of new anticancer treatment. Tumor assessments were to be performed at the end of study treatment visit if they had not been performed within the previous tumor assessment interval (i.e., previous 6 weeks for the first 12 months).

Bone Marrow assessment was to be performed at baseline within 28 days of protocol treatment start. If the 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).

13. Survival follow-up was to start after tumor assessments had been terminated, to be carried out every 3 months until 2 years from the start of study treatment, or until study closure.

14. End of treatment activities were to occur for all patients. Tumor assessments were to be performed if not done within last scheduled time frame (i.e., last 6 weeks if patient discontinued during first 12 months of treatment). If patient discontinued treatment for reasons other than PD, tumor assessments were to continue as above.

Source: Protocol CLN-19, page 65

### 5.3.1.2 Clinical Trial Landmarks and Protocol Amendments

The clinical trial landmarks and protocol amendments of the CLN-19 trial are summarized below.

**Table 11 CLN-19: Landmarks and Protocol Amendments**

Date	Trial CLN-19 Landmark
April 25, 2008	SPA by CuraGen (version 1.0)
July 23, 2008	SPA by Topotarget (version 2.0)
September 4, 2008	FDA issued SPA agreement letter
September 9, 2008	Protocol amendment (version 3.0): Added clarification on blood chemistry test schedule.
May 4, 2009	First patient enrolled (under version 3.0)
November 13, 2009	Protocol amendment (version 4.0): Added baseline bone marrow in “Treatment Period” and in Appendix C.
January 4, 2010	Protocol amendment (version 5.0): Added baseline bone marrow biopsy in “Baseline Period”.
August 2, 2011	Last patient enrolled
August 31, 2012	Data cutoff (7 patients remained on treatment at the database time cutoff)
March 1, 2013	Database lock date

### 5.3.1.3 Statistics

Endpoints:

The primary efficacy endpoint was ORR defined as complete response (CR) or partial response (PR) based on central radiology and clinical review by the independent radiology review (IRC). The best overall response according to the IHP/IWG criteria was the best response recorded from the start of the treatment until disease progression/recurrence or withdrawal from the trial, whichever comes first.

Secondary efficacy endpoints were time to response, duration of response, time to progression (TTP), progression-free survival (PFS), one-year PFS, one-year survival rate, and OS.

Analysis:

The Efficacy Analysis Set consisted of all patients who receive at least one dose of belinostat and have a confirmed PTCL diagnosis by the central pathology review. The Efficacy Analysis Set was used for all efficacy analyses.

The Full Analysis Set included all patients who received at least one dose of belinostat and was used for safety analyses.

All efficacy analyses were to be repeated for the Full Analysis Set and All Enrolled Analysis Set (which included all patients who have signed an informed consent for the trial, whether or not they have received any treatment with belinostat).

For efficacy analyses specific for regulatory submissions outside of the USA, “primary refractory” and “secondary refractory” were defined as follows:

- A patient who never responded, before progression occurred, to a given therapy was defined as “primary refractory” to that therapy.
- A patient who initially responded, and then progressed, on a given therapy was defined as “secondary refractory” to that therapy.

Dropouts were not to be replaced. For the primary efficacy analysis, all patients with missing response status were to be classified as treatment failures. For the primary efficacy analysis of ORR, the significance level (alpha) was set at 0.05 for the two hypothesis tests (interim and final). These inferential analyses were planned based on the two stage optimal design which included adjustment for multiplicity. No further consideration of multiplicity adjustments was planned.

Objective response rate was defined as the percentage of patients in the Efficacy Analysis Set for whom the best overall response is either CR or PR based on the tumor assessments provided by independent radiology review.

Time-to-event efficacy endpoints were to be calculated from the time of first administration of belinostat (Day 1) until the stated event or the end of trial. Time to response and duration of response were calculated only for patients who had a response.

Time to response was to be measured as the time from start of treatment to the first time when the measurement criteria for CR or PR (whichever status is recorded first) are met (for patients with overall best response being CR or PR). Patients who did not have a confirmed response were to be censored at the date of the last tumor assessment.

Time to progression was defined as the number of days from the start of treatment to the date of disease progression based on tumor assessments made according to the IHP/IWG criteria as assessed by an independent radiology committee. Clinical progression in the absence of radiologic progression was not to be considered disease progression. Patients without disease progression were to be censored at the date of the last tumor assessment. Patients who commenced new anticancer therapy in the absence of radiologic progression were to be censored at the date of last tumor assessment prior to the initiation of new anti-cancer treatment. Patients with no tumor assessments after baseline were to be censored at the first day of treatment (Day 1). If several response evaluations for a patient were progressive disease (PD), the first of these measurements were to be used in the analysis of time to progression.

Overall survival was to be measured as the time from the date of start of treatment to the date of death. Patients who were not reported as having died at the time of the analysis were to be censored using the date they were last known to be alive. The first analysis of overall survival was to be conducted at the time of the primary analysis of ORR (end of study). At least one further follow-up survival analysis is planned.

Progression free survival was defined as the number of days from the treatment start date to the date of documented disease progression or death due to any cause based on tumor assessments according to the IHP/IWG criteria as assessed by an independent radiology committee. Clinical progression in the absence of radiologic progression was not to be considered disease progression. Patients who neither progressed nor died were to be censored at the date of the last tumor assessment. Patients who commenced new anticancer therapy in the absence of radiologic progression were to be censored at the date of last tumor assessment prior to the initiation of new anti-cancer treatment. Patients with no tumor assessments after baseline were to be censored at the first day of treatment (Day 1). If several response evaluations for a patient were PD, the first of these measurements were to be used in the analysis of time to progression.

Duration of overall response was to be measured from the time that measurement criteria were first met for CR or PR (whichever status is recorded first) until the first date that progressive disease or death was documented. This analysis was to include patients with overall best response being CR or PR only. Patients who neither progressed nor died were to be censored at the date of the last tumor assessment. For complete responders, the duration of overall complete response was measured from the time measurement criteria were first met for complete response until the date that progressive disease (or death) was documented.

The one year progression free rate was defined as the percent of patients who did not have documented progression or death one year after their start of treatment (Day 1).

The one year survival rate was defined as the percent of patients who were alive one year after their start of treatment (Day 1).

**Sample size:**

The sample size was determined based on a two stage optimal design with a hypothesized ORR of  $p_1=20\%$  for belinostat and a minimal or uninteresting ORR of  $p_0=9\%$ . Based on assumed attrition rate of 15% (+/- 5%), 120 patients were to be enrolled to allow analysis of at least 10 patients. At least 14 objective responses in 100 patients were required for the 20% target response rate (with an alpha of 0.05 and 90% power).

One interim assessment was planned and was to be conducted by a Data Monitoring Committee (DMC) on the first 41 evaluable patients for safety and efficacy. If there were less than 5 ORR in the first 41 evaluable patients, then the trial could be recommended to be discontinued for futility. In this trial, the DMC met two times to review the clinical data (after the first 41 patients who received at least 1 dose of belinostat and at the end of study enrollment). No efficacy or safety issues were identified.

**CLN-6**

**Trial ID and Title:**

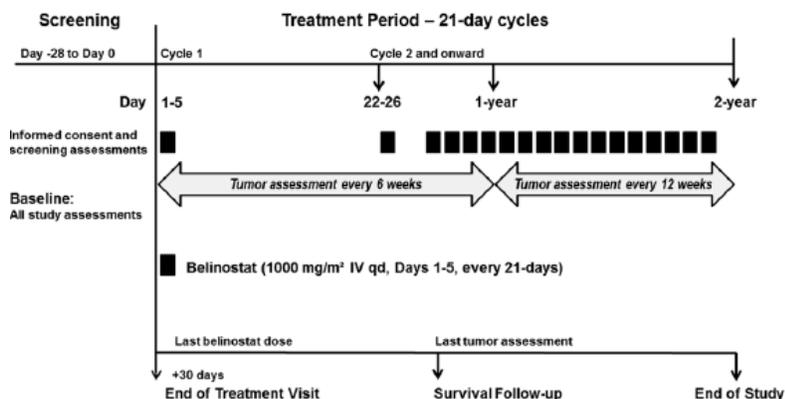
PXD101-CLN-6 (CLN-6): A Phase 2 Clinical Trial of PXD101 in Patients with Recurrent or Refractory Cutaneous and Peripheral T-Cell Lymphomas

**Trial Design:**

CLN-6 was an open-label, multicenter, two-arm, phase 2 trial of patients (n=53) with relapsed or refractory PTCL (n=24) or CTCL (n=29) who had failed prior systemic therapy (with no limitation to the number of prior therapies).

The phase 2 trial included two parallel arms: Arm A was comprised of patients with recurrent CTCL, and arm B was of comprised patients with PTCL or other T-cell subtypes that were relapsed or refractory from prior treatment, and that had verified diagnosis of T-cell NHL. Patients were to have received at least one prior systemic therapy.

**Figure 4 CLN-6: Trial Design and Assessments**



Source: ISE, page 23.

Treatment:

Patients were to receive belinostat for up to eight 21-day cycles. In the first cycle, belinostat was to be administered at 1000 mg/m<sup>2</sup> as a 30 minute IV infusion. The treatment was to be given every 24 hours for five consecutive days, followed by two weeks of observation. Cycle two was to begin on Day 22 and to last for three weeks at which point patients were to be evaluated for determination of response. The dose to be delivered in cycle 2 and subsequent cycles was determined by the individual patient tolerability. Prior to cycle 3 dosing, patients experiencing PD after the first 2 cycles were to have treatment terminated. Patients with PR or SD after the first 2 cycles were to continue to receive belinostat for up to 8 cycles or until a diagnosis of PD. Patients with CR could be re-treated upon recurrence (RD). CTCL patients were to be evaluated every cycle while on therapy and PTCL patients were to be evaluated every two cycles while on treatment. After completion of therapy, patients were to be evaluated every 3 months until progression.

Patients with unacceptable toxicity, who had documented clinical benefit (CR, PR or SD) could continue to be treated with belinostat at a reduced dose level. Any patient in whom this occurred during any cycle were to have the treatment withheld until toxicity resolved to baseline or grade 1 or less. Therapy could be restarted at a 25% lower dose upon toxicity resolution. If toxicity was seen, patients could receive reduced doses of belinostat and based on tolerability the belinostat dose could be escalated.

Objectives:

The primary objective was to determine the efficacy as measured by ORR for patients with relapsed or refractory PTCL or CTCL. Objective response (OR) was the best overall response of CR or PR. PTCL response was to be assessed using the 2007 revised Cheson IWG criteria. The secondary objectives included additional efficacy parameters [time to progression (TTP), time to response, and duration of response] and the safety of belinostat administered as a single agent.

Trial Population:

The key inclusion and exclusion criteria were as follows:

Inclusion criteria:

1. A histologically confirmed diagnosis of CTCL or PTCL or other T-cell NHL (World Health Organization/Revised European-American Lymphoma classification) by local pathology review.
2. Relapsed or refractory disease after at least 1 line of prior systemic therapy.
3. Presence of measurable disease.
4. Adequate bone marrow (ANC  $\geq 1.0 \times 10^9/L$ , platelets  $\geq 40 \times 10^9/L$ ) and hepatic function.
5. Karnofsky performance status  $\geq 70\%$ .

Exclusion criteria:

1. Any use of anticancer therapies or investigational drugs within 4 weeks.
2. Prior allogeneic bone marrow transplant.

3. Patients with a diagnosis of Adult T-cell Leukemia/Lymphoma (ATLL) or precursor T-cell lymphoblastic lymphoma
4. Baseline prolongation of QT/QTc interval, i.e., repeated demonstration of a QTc interval >450 msec; long QT Syndrome; the required use of a concomitant medication that may cause *Torsades de Pointes*.

Schedule of Events:

For PTCL patients, assessment of tumor was performed at the end of cycle 2 and then at the end of every other cycle. If there was a response, a follow-up radiographic evaluation was to be done at 4 weeks to confirm response.

**Table 12 CLN-6: Schedule of Events**

	Baseline <sup>1</sup>	CYCLE 1						CYCLE 2					Study Day 42		
		Study Day 1	Study Day 2	Study Day 3	Study Day 4	Study Day 5	Study Day 8-11	Study Day 15-21	Study Day 1	Study Day 2	Study Day 3	Study Day 4	Study Day 5	Study Day 8-11	Study Day 15-21
Study week		1					2	3	4					5	6
PXD101 TREATMENT Once daily on cycle Days 1 - 5		X	X	X	X	X			X	X	X	X	X		
Medical history <sup>2</sup>	X														
AE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination <sup>3</sup>	X	X					X	X	X					X	X
Performance status (Karnofsky)	X	X					X	X	X					X	X
Concomitant medications review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs <sup>4</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG) <sup>5</sup>	X	X	X	X	X	X			X	[X]	[X]	[X]	[X]		
Pregnancy test (serum) <sup>6</sup>	X														
Haematology <sup>7</sup>	X	X				X	X	X	X				X	X	X
Coagulation <sup>8</sup>	X	X							X						
Blood chemistry <sup>9</sup>	X	X				X	X	X	X				X	X	X
Urinalysis/dipstick <sup>10</sup>	X														
Chest x-ray	X														
Echo/MUGA <sup>11</sup>	X														
IPI	X														
Radiographic assessment <sup>12</sup>	X														X
Tissue & Bone marrow aspiration/biopsy <sup>13</sup>															
SWAT/Pruritus Assessment <sup>14</sup>	X	X						X							X
Flow cytometry <sup>15</sup>		X							X						
Photography (CTCL arm only) <sup>16</sup>	[X]							[X]							[X]
Correlative study: Blood sampling <sup>17</sup>		[X]							[X]						
Correlative study: Tumor biopsy <sup>18</sup>		[X] <sup>18</sup>					[X] <sup>18</sup>								

	Study Day 43	Cycle 3		Study day 64	Cycle 4		Study day 85	Cycle 5		Study day 106	Cycle 6		Study day 127	Cycle 7		Study day 148	Cycle 8		Study day 169
	Cycle Day 1	Cycle Day 8-11	Cycle Day 15-21	Cycle Day 1	Cycle Day 8-11	Cycle Day 15-21	Cycle Day 1	Cycle Day 8-11	Cycle Day 15-21	Cycle Day 1	Cycle Day 8-11	Cycle Day 15-21	Cycle Day 1	Cycle Day 8-11	Cycle Day 15-21	Cycle Day 1	Cycle Day 8-11	Cycle Day 15-21	Trial Conclu. <sup>17</sup>
Study week:	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
PXD101 TREATMENT Once daily on cycle days 1 - 5	X Day 1-5			X Day 1-5			X Day 1-5			X Day 1-5			X Day 1-5			X Day 1-5			
Medical history																			
AE Assessment <sup>2</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination <sup>3</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Performance status (Karnofsky)	X			X			X			X			X			X			X
Concomitant medications review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs <sup>4</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG <sup>5</sup>	X			X			X			X			X			X			X
Pregnancy test <sup>6</sup>																			
Haematology <sup>7</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation <sup>8</sup>	X			X			X			X			X			X			X
Blood chemistry <sup>9</sup>	X			X			X			X			X			X			X
Urinalysis/dipstick <sup>10</sup>																			X
Chest x-ray																			X
ECHO/MUGA <sup>11</sup>																			
IPI																			X
Radiographic Assessment <sup>12</sup>						X						X						X	X
Tissue & bone marrow aspiration /biopsy <sup>13</sup>																			
SWAT/Pruritus Assessment <sup>14</sup>			X			X			X			X			X			X	X
Flow cytometry <sup>15</sup>			X			X			X			X			X			X	X
Photography (CTCL arm) <sup>16</sup>			[X]			[X]			[X]			[X]			[X]			[X]	[X]
Correlative study: Blood Sampling <sup>17</sup>	[X]			[X]			[X]			[X]			[X]			[X]			
Correlative study: Tumor biopsy <sup>17</sup>																			[X] <sup>17</sup>

Source: CLN-6 protocol, page 36-39.

### Statistics:

In the CLN-6 trial, a 2-stage Simon design was used. It allowed for early termination of the trial if the predetermined level of anti-tumor activity (>10%) was not reached in the first stage of the trial. In the first 13 patients, 2 or more responses were needed to expand each cohort to the next stage; and 5 or more responses were required out of 34 evaluable patients in the second stage to meet the pre-defined efficacy level (which was 25%). Enrollment was stopped early prior to reaching the originally planned number of patients. For the PTCL arm, more than the number of expected responses (n=6) was observed in the first 24 patients. Since the targeted number of responses had already been reached in PTCL patients, it was considered sufficient to begin the pivotal registration trial for PTCL (i.e., CLN-19).

### Efficacy Endpoints:

The primary efficacy endpoint was ORR defined as CR or PR based on local review and a 25% ORR was pre-defined as clinically meaningful. The secondary efficacy endpoints included TTP, time to response and duration of response.

The following patient subset were used in this trial:

- Full Analysis Set (FAS): included all patients enrolled in the trial.

- Per Protocol Analysis Set (PP): consisted of all patients in the FAS who received at least 1 dose of belinostat and had post-baseline response data.
- Intention-to-Treat Analysis Set (ITT): consisted of all patients in the FAS who received at least 1 dose of belinostat and was used for all efficacy endpoint analyses. The ITT Analysis Set was the same as the Safety Analysis Set.
- Safety Analysis Set consisted of all patients in the FAS who received at least 1 dose of belinostat and were analyzed according to actual treatment received. It was used for all safety analyses.

The primary and the secondary efficacy endpoints were analyzed using the Intent to treat (ITT) and per protocol (PP) datasets. The ITT analysis set is acceptable for efficacy analysis because it includes all patients enrolled who received at least one dose of belinostat. This population is appropriate for the evaluation of efficacy in a single-arm trial.

There was no central assessment of tumor responses in CLN-6. Patients without progression and patients who dropped out were censored at the day of their termination from the trial. Time to progression was defined as the interval between the first date of treatment and the first notation of disease progression. Time to response was defined as the interval between the first date of treatment and the first notation of a response. Duration of response was defined as the time from first notation of response until the time of first notation of disease progression.

## 6 Review of Efficacy

### Efficacy Summary

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 comparable to those of pralatrexate and romidepsin (see section 2.2):

- 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 13 CLN-19: Summary Efficacy Results**

	<b>Efficacy Analysis Set (n=120)</b>
<b>Primary endpoint</b>	
ORR by IRC	31 (25.8%)
95% CI	18.3-34.6
Complete response	13 (10.8%)
Partial response	18 (15.0%)
<b>Secondary endpoints</b>	
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

## 6.1 Indication

The applicant's proposed indication is for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL).

### 6.1.1 Methods

The efficacy review was concentrated on the CLN-19 trial and supportive CLN-6 trial. The review included following items:

- Clinical study reports
- Protocol and statistical analysis plans
- Raw and derived datasets
- Case report forms

- Response to information requests
- Proposed labeling

## 6.1.2 Demographics

### CLN-19

Trial CLN-19 enrolled a total of 129 patients from 62 sites in 16 countries mostly from US (29%) and Europe (61%).

The Full Analysis Set (FAS) included all patients (n=129) who received at least one dose of belinostat and all safety analysis was performed on the FAS. The Efficacy Analysis Set (EAS) was comprised of 120 patients that had confirmed diagnoses of PTCL by CPRG and received at least one dose of belinostat and was used for all efficacy analyses. The table below shows patient enrollment by country.

**Table 14 CLN-19: Patient Enrollment by Country (Full Analysis Set)**

Country	Full Analysis Set (n=129)	Efficacy Analysis Set (n=120)
US	37 (29%)	34 (28%)
Germany	16 (12%)	12 (10%)
Belgium	11 (9%)	11 (9%)
Hungary	11 (9%)	11 (9%)
Netherlands	10 (8%)	9 (8%)
Poland	8 (6%)	8 (7%)
Canada	7 (5%)	7 (6%)
Others (<5 patients each)	29 (22%)	28 (23%)

Patient baseline demographics and disease characteristics are summarized in Tables 15 and 16.

In general, baseline demographics and disease characteristics were similar between the FAS and EAS: the median age was 63 years (range 29-81) in FAS and 64 years (range 29-81) in EAS, there were more males (FAS: 54%, EAS: 52%) than females (FAS: 47%, EAS: 48%), most of the patients were white (FAS: 86%, EAS: 88%), and 78% of patients had an ECOG performance score of 0 or 1 (both in FAS and EAS).

**Table 15 CLN-19: Patient Demographics**

	Full Analysis Set (n=129)	Efficacy Analysis Set (n=120)
Gender		
Male	69 (53.5%)	62 (51.7%)
Female	60 (46.5%)	58 (48.3%)

Age (years)		
Median	63.0	64.0
Range	29-81	29-81
< 65	67 (51.9%)	61 (50.8%)
≥ 65	62 (48.1%)	59 (49.2%)
Race		
White	111 (86.0%)	105 (87.5%)
Black	9 (7.0%)	7 (5.8%)
Asian	3 (2.3%)	3 (2.5%)
Latin	3 (2.3%)	3 (2.5%)
Other	3 (2.3%)	2 (1.7%)
Weight (kg)		
Median	73	72.5
Range	40.0.0-149.0	40.0.0-149.0
Height (cm)		
Median	167.5	166.3
Range	145.0-193.0	145.0-193.0
Baseline ECOG score		
0	44 (34.1%)	41 (34.2%)
1	57 (44.2%)	52 (43.3%)
2	27 (20.9%)	26 (21.7%)
3	1 (0.8%)	1 (0.8%)

In the EAS, the median time from initial PTCL diagnosis and the median time from the most recently confirmed disease progression to study entry were 12.0 months and 1 month, respectively.

Central Pathology Review Group (CPRG) reviewers were provided with tissues and/or slides to confirm histopathology. In the EAS, the majority of the patients had PTCL-NOS (64%) followed by angioimmunoblastic T-cell lymphoma (18%) and ALCL (ALK-negative: 11%, ALK-positive: 2%). There were 9 patients in the FAS that were determined to be unevaluable for efficacy due to either inadequate specimens for assessment by CPRG (7 patients: patients 140-001, 144-001, 147-001, 147-002, 221-001, 914-002, and 914-009) or non-eligible PTCL histopathology (no PTCL present in the tissue sample analyzed) (2 patients: patients 162-002 and 901-001). These 9 patients were excluded from the EAS. In general, there was concordance between the histopathology assessed by the investigator and the CPRG in the EAS. The primary differences were that the CPRG classified more patients in PTCL-NOS category compared with the investigator assessments (64.2% vs. 59.2%) and fewer patients were characterized by CPRG as having angioimmunoblastic T-cell lymphoma (18.3% vs. 22.5%).

The median number of prior systemic therapy for PTCL was 2 (range 1-8) and 37% of patients had received three or more prior PTCL systemic therapy before enrolling in this trial in the EAS.

Most of the patients (97%) had received prior CHOP chemotherapy, 21% of patients had received prior stem cell transplant and 8% of patients had previously been treated with pralatrexate in the EAS. The majority of patients (85%) in the EAS had Stage III or IV disease at baseline. Nineteen percent and 17% of patients in the FAS and EAS, respectively, had baseline platelet counts less than 100,000/mcL.

**Table 16 CLN-19: Patient Baseline Disease Information**

	<b>Full Analysis Set (n=129)</b>	<b>Efficacy Analysis Set (n=120)</b>
Median months from initial PTCL diagnosis (range)	12.2 (2.6-266.4)	12.0 (2.6-266.4)
Median months from the last progression to study entry (range)	1.0 (0.1-54.5)	0.95 (0.1-54.5)
Lymphoma diagnosis by CPRG		
PTCL, NOS	77 (59.7%)	77 (64.2%)
Angioimmunoblastic T-cell Lymphoma	22 (17.1%)	22 (18.3%)
ALCL, ALK-negative	13 (10.1%)	13 (10.8%)
ALCL, ALK-positive	2 (1.6%)	2 (1.7%)
Enteropathy-associated T-cell Lymphoma	2 (1.6%)	2 (1.7%)
Extranodal NK/T-cell Lymphoma, nasal type	2 (1.6%)	2 (1.7%)
Hepatosplenic T-cell Lymphoma	2 (1.6%)	2 (1.7%)
No Peripheral T-cell Lymphoma present	2 (1.6%)	-
Inadequate Sample for Assessment	7 (5.4%)	-
Lymphoma diagnosis by investigator		
PTCL, NOS	75 (58.1%)	71 (59.2%)
Angioimmunoblastic T-cell Lymphoma	31 (24.0%)	27 (22.5%)
ALCL, ALK-negative	15 (11.6%)	15 (12.5%)
Hepatosplenic T-cell Lymphoma	3 (2.3%)	2 (1.7%)
ALCL, ALK-positive	2 (1.6%)	2 (1.7%)
Enteropathy-associated T-cell Lymphoma	2 (1.6%)	2 (1.7%)
Extranodal NK/T-cell Lymphoma, nasal type	1 (0.8%)	1 (0.8%)
Prior systemic therapies		
Median (range)	2.0 (1.0-8.0)	2.0 (1.0-8.0)
≥ 3 prior therapies	48 (37.2%)	44 (36.7%)
Prior CHOP or CHOP-like regimen	125 (96.9%)	116 (96.7%)
Platinum containing regimens	42 (32.6%)	38 (31.7%)
Other multi-agent regimens	48 (37.2%)	44 (36.7%)
Prior pralatrexate	11 (8.5%)	10 (8.3%)
Corticosteroids	6 (4.7%)	4 (3.3%)
Other single-agent regimens	21 (16.3%)	20 (16.7%)
Prior stem cell transplant	29 (22.5%)	25 (20.8%)
Stage		
I	11 (8.5%)	5 (4.2)
II	11 (8.5%)	11 (9.2%)
III	51 (39.5%)	42 (35.0%)
IV	53 (41.1%)	60 (50.0%)

Unknown	3 (2.3%)	2 (1.7%)
Platelet counts		
< 100,000/mcL	24 (18.6%)	20 (16.7%)
≥ 100,000/mcL	105 (81.4%)	100 (83.3%)

CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone

A total of 12 patients in the EAS did not have a baseline bone marrow assessment. One patient (patient 516-006) was enrolled into the trial after amendment of protocol version 5.0 after which the protocol required baseline bone marrow assessment. This patient (516-006) received 1 cycle of belinostat, did not have follow-up CT scans and was not considered evaluable. Among the patients that did not have a baseline bone marrow assessment, there was another patient (patient 161-001) who was enrolled under protocol version 3.0 and had a PR by IRC. However, according to the 2007 IWG criteria bone marrow assessment is irrelevant for determination of a PR.

In the EAS, 35 patients (29.2%) had bone marrow involvement, 65 patients (54.2%) did not have involvement and 8 patients (6.7%) had bone marrow that was indeterminate. The table below shows the 12 patients that were enrolled with no baseline bone marrow biopsy.

**Table 17 CLN-19: Patients Enrolled with No Baseline Bone Marrow Biopsy**

Patient number	PTCL diagnosis by GPRG	Best response by IRC
161-001	PTCL, NOS	PR
180-001	PTCL, NOS	PD
180-002	ALCL, Alk-Negative	PD
180-003	Angioimmunoblastic T-Cell Lymphoma	SD
206-001	PTCL, NOS	NE
224-001	PTCL, NOS	NE
240-001	Extranodal NK/T-Cell Lymphoma, nasal type	SD
240-002	PTCL, NOS	PD
244-001	PTCL, NOS	PD
516-006*	Angioimmunoblastic T-Cell Lymphoma	NE
752-001	ALCL, Alk-Negative	NE
900-001	PTCL, NOS	SD

\*All patients were enrolled under protocol version 3, except patient 516-006 (enrolled under version 5.0).

### **CLN-6:**

In the CLN-6 trial, 24 patients with PTCL and 29 patients with CTCL were enrolled across 15 sites in 5 countries (US, Thailand, Israel, France and Germany). Since the proposed indication is for PTCL, only data pertaining to the 24 patients with PTCL is summarized in the efficacy review. There were more males (70.8%) than females (29.2%), the median age was 64 years (range 22-76), and two-thirds of the patients were white (66.7%). Thirteen patients (54.2%) had unspecified PTCL, 3 patients (12.5%) each had ALCL and angioimmunoblastic T-cell lymphoma, and one patient each had extranodal NK/T-cell lymphoma nasal type, NK/T-cell

lymphoma nasal type, NK/T-cell intravascular, skin limited PTCL, and subcutaneous panniculitis-like T-cell lymphoma.

**Table 18 CLN-6: Baseline Patient Demographics (ITT, FAS Population)**

	<b>PTCL patients (n=24)</b>
Gender	
Male	17 (70.8%)
Female	7 (29.2%)
Age (years)	
Median	64
Range	22-76
< 65	12 (50.0%)
≥ 65	12 (50.0%)
Race	
White	16 (66.7%)
Black	1 (4.2%)
Asian	7 (29.2%)
PTCL subtype	
ALCL	3 (12.5%)
Angioimmunoblastic T-cell lymphoma	3 (12.5%)
Extranodal NK/T-cell lymphoma, nasal type	1 (4.2%)
NK/T-cell lymphoma, nasal type	1 (4.2%)
NK/T-cell intravascular	1 (4.2%)
PTCL, unspecified	13 (54.2%)
Skin limited PTCL	1 (4.2%)
Subcutaneous panniculitis-like T-cell lymphoma	1 (4.2%)
Karnofsky Performance Status	
Median	90
Range	30-100

PTCL subtype source: CNL-6, CSR, page 119

### 6.1.3 Subject Disposition

#### **CLN-19:**

In the CLN-19 trial, a total of 161 patients were screened and 129 patients were enrolled. Nine patients did not have confirmed diagnoses of PTCL by CPRG and was eliminated from the Efficacy Analysis Dataset (n=120). As of the database time cutoff of August 31, 2012, 7 patients remained on belinostat treatment while majority of patients (63%) in the EAS discontinued due to progressive disease. The table below shows patient disposition of the CLN-19 trial.

**Table 19 CLN-19: Patient Disposition (database cutoff of August 31, 2012)**

Patient Status	Full Analysis Set (n=129)	Efficacy Analysis Set (n=120)
Still on study therapy	7 (5.4%)	7 (5.8%)
Discontinued study therapy	122 (94.6%)	113 (94.2%)
Progressive disease	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%)
Withdrawal by patient	11 (8.5%)	10 (8.3%)
Physician decision	1 (0.8%)	1 (0.8%)
Lost to follow-up	1 (0.8%)	1 (0.8%)

As of August 31, 2012, 29% of patients were still alive and 9% of patients were lost to follow-up in the EAS.

**Table 20 CLN-19: Survival Status (as of August 31, 2012)**

Survival status	Full Analysis Set (n=129)	Efficacy Analysis Set (n=120)
Dead	79 (61.2%)	74 (61.7%)
Alive	39 (30.2%)	35 (29.2%)
No follow-up $\geq$ 12 months	11 (8.5%)	11 (9.2%)

**CLN-6:**

In the CLN-6 trial, since there were more than expected numbers of responses (6 patients) observed in the PTCL arm in the first 24 patients, enrollment was halted prior to reaching the planned number of patients. Among the 24 patients enrolled in the PTCL arm, 4 patients completed the trial and 20 patients discontinued from the trial. The table below shows patient disposition in the PTCL arm.

**Table 21 CLN-6: Patient Disposition in the PTCL arm**

	PTCL
Full analysis set, safety and intension to treat	24 (100%)
Per protocol	17 (71%)
Completed the trial	4 (17%)
Discontinued from the trial	20 (83%)
Reason for Discontinuation	
Adverse Event	3 (13%)
Lack of Efficacy	6 (25%)
Patient Died	3 (13%)
Voluntary Withdrew	1 (4%)
Physician Decision	7 (29%)

#### 6.1.4 Analysis of Primary Endpoint(s)

Based on the IRC data, the ORR for the CLN-19 trial 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). Of the 13 patients that had achieved a CR, 4 patients (patients 244-003, 534-001, 901-006, 911-001) experienced subsequent disease progression and 1 patient died (patient 934-003) at the time of the data cut-off. Of the 18 patients that had achieved a PR, 9 patients had disease progression (patients 100-002, 161-001, 245-001, 532-003, 534-003, 600-003, 752-002, 915-001, 938-001). Of the 7 patients that remained on therapy at the time of data cut-off (August 31, 2012), 5 patients (patients 146-001, 220-002, 534-002, 534-006, 541-001) had a CR and 2 patient (patient 516-004, 543-001) had a PR. Patient 543-001 was reported by the applicant as having a SD, but from the dataset and IRC document, the patient had a PR.

Twenty-four patients (20.0%) were not evaluable by the IRC and they were considered non-responders.

**Table 22 CLN-19: Primary Endpoint Analysis Based on IRC (EAS)**

	<b>Efficacy Analysis Set (n=120)</b>
ORR (CR+PR)	31 (25.8%)
95% CI	18.3-34.6
Complete response	13 (10.8%)
Partial response	18 (15.0%)
Stable disease	18 (15.0%)
Progressive disease	47 (39.2%)
Not evaluable	24 (20.0%)
Reasons for not-evaluable assessments	
Clinical progression prior to 1 <sup>st</sup> on-study assessment	9 (7.5%)
Death prior to 1 <sup>st</sup> on-study assessment	7 (5.8%)
Withdrawal by patient prior to 1 <sup>st</sup> on-study assessment	5 (4.2%)
Lost to follow-up prior to 1 <sup>st</sup> on-study assessment	1 (0.8%)
No index lesion identified by IRC radiologists	1 (0.8%)
Other	1 (0.8%)

Nineteen patients (61.3% of the responders) responded at the first scheduled tumor assessment within 30-45 days of first dose.

Among the 31 patients that had an ORR, the readers did not agree on the assessment on 12 patients (38.7%) and went through an adjudication analysis process (4 of the 13 CRs and 8 of the 18 PRs).

Based on the investigator, the 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).

The table below summarizes the concordance between the IRC and investigator assessments for best tumor response. The applicant reported that of the 31 patients that were assessed as responders by IRC, 27 patients (87.1%) were also considered as responders by investigator. However, using the datasets, out of 31 IRC-assessed responders 25 patients (80.6%) were also assessed by the investigator as responders. In addition, there were 2 patients that were assessed by the IRC as SD that were assessed by the investigators as PR.

**Table 23 CLN-19: Concordance between IRC and Investigator Assessment for Best Tumor Response (EAS)**

	<b>Efficacy Analysis Set (n=120)</b>
CR by IRC	13
Agreement of CR by investigator	9 (69%)
PR by investigator	4 (31%)
PR by IRC	18
Agreement of PR by investigator	10 (56%)
CR by investigator	2 (11%)
SD by investigator	5 (28%)
PD by investigator	1 (6%)
SD by IRC	18
Agreement of SD by investigator	13 (72%)
PR by investigator	2 (11%)
PD by investigator	3 (17%)
PD by IRC	47
Agreement of PD by investigator	36 (77%)
SD by investigator	10 (21%)
Not evaluable by investigator	1 (1%)
Not evaluable by IRC	24
Agreement by investigator	10 (42%)
SD by investigator	1 (4%)
PD by investigator	13 (54%)

When assessing the ORR in the Full Analysis Set as sensitivity analysis, the ORR was 24.0% (31/129 patients, 95% CI: 16.9-32.3) thus supporting the primary efficacy analysis.

**CLN-6:**

In the CLN-6 trial, the primary efficacy endpoint was ORR defined as CR or PR based on local review and a 25% ORR was pre-defined as clinically meaningful.

Among the first 24 enrolled patients, a total of 6 patients had objective responses (2 CRs, 4 PRs) with an ORR of 25.0% (95CI: 9.8-46.7) in the ITT population.

**Table 24 CLN-6: Primary Endpoint Analysis in PTCL**

	ITT (n=24)
Objective response rate	
ORR (CR+PR)	6 (25.0%)
95% CI	9.8-46.7
Best tumor response	
Complete response	2 (8.3%)
Partial response	4 (16.7%)

### 6.1.5 Analysis of Secondary Endpoints(s)

For the CLN-19 trial, key secondary efficacy endpoints included time to response (TTR), duration of response (DOR), time to progression (TTP), progression-free survival (PFS), one-year PFS, one-year survival rate, and OS. However, in single-arm trials, time-to-event endpoints are not interpretable. In addition, there were no multiplicity adjustments for secondary efficacy endpoints.

#### Time to response (TTR):

For the 31 patients who had a response based on IRC, the median TTR was 5.6 weeks (range 4.3-50.4 weeks) and for the 27 patients that had a response based on investigator review, the median TTR was 6.3 weeks (range 4.1-44.1).

When analyzing by baseline platelet counts among the IRC-assessed responders, the median TTR was 5.6 weeks (range 5.3-50.4) for the 28 responders who had baseline platelet counts of  $\geq 100,000/\text{mcL}$  and 6.4 weeks (range 4.3-12.7) for the 3 responders who had baseline platelet counts of  $< 100,000/\text{mcL}$ . Because of the small number of responders in this analysis, the results should be interpreted with caution.

**Table 25 CLN-19: Time to Response (EAS)**

	Efficacy Analysis Set (n=120)
By IRC	
Total number of responders	31 (25.8%)
Median time to response (weeks)	5.6
Range	4.3-50.4
Baseline platelets $\geq 100,000/\text{mcL}$	
Patients included in analysis	100
Responders	28 (28.0%)
Median time to response (weeks)	5.6

Range	4.3-50.4
Baseline platelets < 100,000/mcL	
Patients included in analysis	20
Responders	3 (15.0%)
Median time to response (weeks)	6.4
Range	4.3-12.7
By local investigator	
Total number of responders	27 (22.5%)
Median time to response (weeks)	6.3
Range	4.1-44.1

Duration of response (DOR):

The applicant performed the analyses of DOR in two different methods:

- a) One was defined by IWG criteria, 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 and otherwise censored at the last disease assessment; and
- b) the second by SAP-defined criteria that expanded on the standard IWG criteria by also including death in addition to relapse or progression, 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 and otherwise censored at the last disease assessment prior to a new therapy.

The median duration of response based on the 31 responding patients by IRC and estimated by Kaplan-Meier method a) using the IWG criteria was 13.6 months (95% CI: 4.5-29.4) while the median duration of response assessed by b) SAP-defined criteria, which expanded the IWG criteria by adding the subsequent date of death (IWG + death) was 8.4 months (95% CI: 4.5-29.4). The difference of these two analyses was that there were 2 patients (142-005, 154-001) that died and in a) these 2 patients were censored while in b) these patients were not censored. According to the Case Report Forms, patient 142-005 died due to progression of PTCL and patient 154-001 died due to hepatic failure. In total, by a) 54.8% of patients were censored and by b) 48.4% of patients were censored.

Seven patients remained on belinostat treatment at the database time cutoff of August 31, 2012. All 7 patients had a response (5 patients with a CR and 2 patients with a PR). Thus the final median duration of response will be longer than the results shown below.

**Table 26 CLN-19: Duration of Response (EAS)**

	<b>Efficacy Analysis Set (n=120)</b>
<b>Duration of response (per IWG)</b>	
Patients included in analysis	31
Patients with event	14 (45.2%)
Patients without event	17 (54.8%)
Median (months)	13.6
95% CI	4.5-29.4
<b>Baseline platelets <math>\geq</math> 100,000/mcl</b>	
Patients included in analysis	28
Patients with event	12 (42.9%)
Patients without event	16 (57.1%)
Median (months)	13.6
95% CI	5.6-29.4
<b>Baseline platelets &lt; 100,000/mcL</b>	
Patients included in analysis	3
Patients with event	2 (66.7%)
Patients without event	1 (33.3%)
Median (months)	4.1
95% CI	2.2-9.8
<b>Duration of response (per SAP)</b>	
Patients included in analysis	31
Patients with event	16 (51.6%)
Patients without event	15 (48.4%)
Median (months)	8.4
95% CI	4.5-29.4
<b>Baseline platelets <math>\geq</math> 100,000/mcl</b>	
Patients included in analysis	28
Patients with event	14 (50.0%)
Patients without event	14 (50.0%)
Median (months)	13.6
95% CI	4.5-29.4
<b>Baseline platelets &lt; 100,000/mcL</b>	
Patients included in analysis	3
Patients with event	2 (66.7%)
Patients without event	1 (33.3%)
Median (months)	4.1
95% CI	2.2-9.8

**Figure 5 CLN-9: Kaplan-Meier Estimates of Duration of Response (per SAP)**

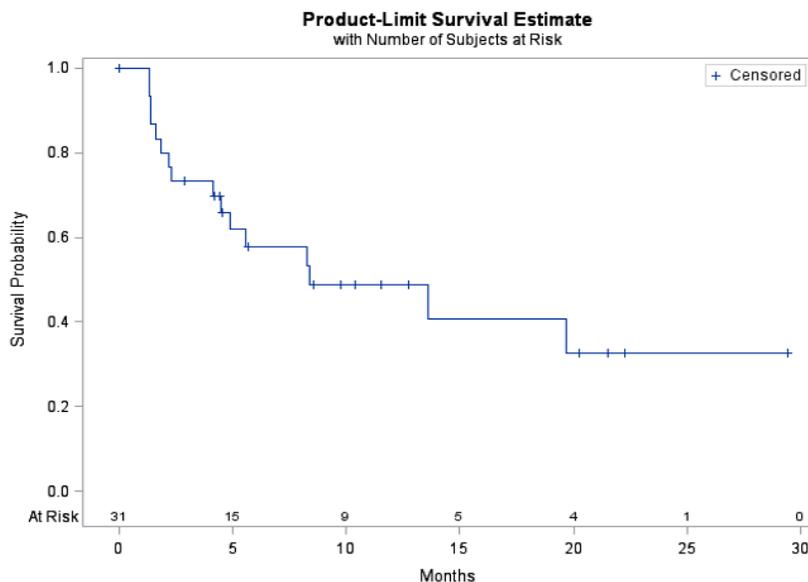


Figure 5 was provided by the Statistical Reviewer, Dr. Erik Bloomquist.

**Time to progression (TTP):**

The median TTP as assessed by IRC and estimated by Kaplan-Meier method was 2.0 months (95% CI: 1.5-2.8). Seventy-two patients (60.0%) in the EAS had an event.

**Progression-free survival (PFS):**

The median PFS as assessed by IRC and estimated by Kaplan-Meier method was 1.6 months (95% CI: 1.4-2.7). Eighty-eight patients (73.3%) in the EAS had an event. One-year (IRC-assessed) PFS defined as the percent of patients who did not have documented progression or death one year after their start of treatment was 19.3%.

The median PFS for the subgroup of 100 patients with baseline platelet counts of  $\geq 100,000/\text{mcL}$  was 1.8 months (95% CI: 1.5-2.8) while for the 20 patients with baseline platelet counts of  $<100,000/\text{mcL}$ , it was 1.3 months (95% CI: 1.1-1.5).

**Overall survival (OS):**

The median OS as assessed by IRC and estimated by Kaplan-Meier method was 7.9 months (95% CI: 6.1-13.9). Seventy-four patients (61.7%) had died. One-year OS (probability of being alive at one year) by IRC was 40.9%.

The median OS for the subgroup of 100 patients with baseline platelet counts of  $\geq 100,000/\text{mcL}$ , was 9.2 months (95% CI: 6.4-17.7) while for the 20 patients with baseline platelet counts of  $<100,000/\text{mcL}$ , it was 4.3 months (95% CI: 2.4-7.9).

**Table 27 CLN-19: IRC-Assessed Other Secondary Endpoints Analyses (EAS)**

	<b>Efficacy Analysis Set (n=120)</b>
<b>Time to progression</b>	
Patients included in analysis	120
Patients with event	72 (60.0%)
Patients without event	48 (40.0%)
Median (months)	2
95% CI	1.5-2.8
<b>Progression-free survival</b>	
Patients included in analysis	120
Patients with event	88 (73.3%)
Patients without event	32 (26.7%)
Median (months)	1.6
95% CI	1.4-2.7
<b>Baseline platelets <math>\geq</math> 100,000/mcl</b>	
Patients included in analysis	100
Patients with event	71 (71.0%)
Patients without event	29 (29.0%)
Median (months)	1.8
95% CI	1.5-2.8
<b>Baseline platelets &lt; 100,000/mcl</b>	
Patients included in analysis	20
Patients with event	17 (85.0%)
Patients without event	3 (15.0%)
Median (months)	1.3
95% CI	1.1-1.5
<b>Overall survival</b>	
Patients included in analysis	120
Patients with event	74 (61.7%)
Patients without event	46 (38.3%)
Median (months)	7.9
95% CI	6.1-13.9
<b>Baseline platelets <math>\geq</math> 100,000/mcl</b>	
Patients included in analysis	100
Patients with event	57 (57.0%)
Patients without event	43 (43.0%)
Median (months)	9.2
95% CI	6.4-17.7
<b>Baseline platelets &lt; 100,000/mcl</b>	

Patients included in analysis	20
Patients with event	17 (85.0%)
Patients without event	3 (15.0%)
Median (months)	4.3
95% CI	2.4-7.9

**CLN-6:**

In the CLN-6 trial, the secondary efficacy endpoints included TTP, time to response and duration of response. The results of the secondary efficacy endpoints in the ITT population are summarized in the table below. Because of the small number of patients included in these analyses, the results should be interpreted with caution.

**Table 28 CLN-6: Secondary Endpoints Analysis in PTCL (ITT Population)**

	ITT (n=24)
Time to progression	
Patients with disease progression	14 (58.3%)
Censored	10 (41.7%)
Median (days)	82
Time to response	
Patients with response	6 (25.0%)
Median time to response (days)	100
Duration of response	
Patients with response	6 (25.0%)
Censored	2 (8.3%)
Median duration of response (days)	109

Source: CLN-6 CSR, pages 144-155 and Listings in 16.2.6.2

6.1.6 Other Endpoints

No analyses of other endpoints were included in the NDA submission.

6.1.7 Subpopulations

The applicant also provided efficacy data for subgroup analysis. In the CLN-19 trial, the ORR were higher in the  $\geq 65$  years of age population (35.6%) than  $< 65$  years of age (16.4%), in females (31.0%) than in males (21.0%), and in patients with ECOG performance status of 2 (42.3%) than in ECOG PS of 0, 1 or 3. Among PTCL subtype, patients with AITL had the highest ORR (45.5%).

Of the 100 patients who had a baseline bone marrow assessment, 35 patients (29.2%) had bone marrow involvement and 65 patients (54.2%) did not have involvement at baseline. Among the

patients with bone marrow involvement, the response rate was 22.9% and 30.8% in patients who did not have bone marrow involvement.

In the EAS, 70 patients (58.3%) did not have a response (SD, PD, not evaluable, unknown) to their last systemic therapy. Among the 70 patients, 11 patients (15.7%) responded to belinostat therapy.

The ORR results by baseline characteristics are shown in the table below. In some categories, the numbers of the denominators are small (i.e., ALCL ALK-negative and extranodal NK/T-cell lymphoma, nasal type). These should be interpreted with caution.

**Table 29 CLN-19: Overall Response Rate by Baseline Characteristics Assessed by IRC (EAS)**

	<b>Group Size N (%)</b>	<b>Response N (%)</b>	<b>95% CI</b>
All patients (EAS)	120 (100.0)	31 (25.8)	18.3-34.6
Gender			
Male	62 (51.7)	13 (21.0)	11.7-33.2
Female	58 (48.3)	18 (31.0)	19.5-44.5
Race			
White	105 (87.5)	26 (24.8)	16.9-34.1
Non-white	15 (12.5)	5 (33.3)	11.8-61.6
Age			
< 65 years	61 (50.8)	10 (16.4)	8.2-28.1
≥ 65 years	59 (49.2)	21 (35.6)	23.6-49.1
ECOG Performance status			
0	41 (34.2)	12 (29.3)	16.1-45.5
1	52 (43.3)	8 (15.4)	6.9-28.1
2	26 (21.7)	11 (42.3)	23.4-63.1
3	1 (0.8)	0 (0)	0.0-97.5
CPRG lymphoma diagnosis			
PTCL, NOS	77 (64.2)	18 (23.4)	14.5-34.4
AITL	22 (18.3)	10 (45.5)	24.4-67.8
ALCL, ALK-negative	13 (10.8)	2 (15.4)	1.9-45.5
ALCL, ALK-positive	2 (1.7)	0 (0)	0.0-84.2
Extranodal NK/T-cell lymphoma, nasal type	2 (1.7)	1 (50.0)	1.3-98.7
Enteropathy-associated T-cell lymphoma	2 (1.7)	0 (0)	0.0-84.2
Hepatosplenic T-cell Lymphoma	2 (1.7)	0 (0)	0.0-84.2
Bone marrow involvement			
Yes	35 (29.2)	8 (22.9)	10.4-40.1

No	65 (54.2)	20 (30.8)	19.9-43.4
Indeterminate	8 (6.7)	2 (25.0)	3.2-65.1
Not assessed	12 (10.0)	1 (8.3)	0.2-38.5
<b>Prior pralatrexate therapy</b>			
Yes	10 (8.3)	1 (10.0)	0.3-44.5
No	110 (91.7)	30 (27.3)	19.2-36.6
<b>Response to last systemic therapy</b>			
Complete response	29 (24.2)	14 (48.3)	29.4-67.5
Partial response	21 (17.5)	6 (28.6)	11.3-52.2
Stable disease	20 (16.7)	5 (25.0)	8.7-49.1
Progressive disease	37 (30.8)	3 (8.1)	1.7- 21.9
Not evaluable	11 (9.2)	3 (27.3)	6.0- 61.0
Unknown	2 (1.7)	0 (0.0)	0.0- 84.2
<b>Baseline platelet count</b>			
≥ 100,000/mcL	100 (83.3)	28 (28.0)	19.5-37.9
< 100,000/mcL	20 (16.7)	3 (15.0)	3.2-37.9

The table below summarizes CR and PR results by CPRG lymphoma diagnosis in the CLN-19 trial.

**Table 30 CLN-9: CR and PR by CPRG Lymphoma Diagnosis as Assessed by IRC (EAS)**

<b>CPRG lymphoma diagnosis</b>	<b>EAS N (%)</b>	<b>OR N (%)</b>	<b>CR N (%)</b>	<b>PR N (%)</b>
All patients	120 (100.0)	31 (25.8)	13 (10.8)	18 (15.0)
PTCL, NOS	77 (64.2)	18 (23.4)	7 (9.1)	11 (14.3)
AITL	22 (18.3)	10 (45.5)	4 (18.2)	6 (27.3)
ALCL, ALK-negative	13 (10.8)	2 (15.4)	1 (7.7)	1 (7.7)
ALCL, ALK-positive	2 (1.7)	0 (0)	0	0
Extranodal NK/T-cell lymphoma, nasal type	2 (1.7)	1 (50.0)	1 (50.0)	0
Enteropathy-associated T-cell lymphoma	2 (1.7)	0 (0)	0	0
Hepatosplenic T-cell lymphoma	2 (1.7)	0 (0)	0	0

Among the 31 patients that had a response, there were 3 patients [CR: 1 patient (534-006), PR: 2 patients] that had baseline platelet counts < 100,000/mcL. The efficacy endpoints for patients with baseline platelet counts of ≥ 100,000/mcL and <100,000/mcL are summarized in the table below. Again, because of the small number of patients included in the analysis, the results should be interpreted with caution.

**Table 31 CLN: Efficacy Endpoints by Baseline Platelet Count by IRC (EAS)**

Parameter	EAS (n=120)	Platelets $\geq$ 100,000/mcl (n=100)	Platelets < 100,000/mcl (n=20)
Responders (%)	31 (25.8%)	28 (28.0%)	3 (15.0%)
Median DOR, months, 95% CI (SAP)	8.4 (4.5-29.4)	13.6 (4.5-29.4)	4.1 (2.2-9.8)
Median DOR, months, 95% CI (IWG)	13.6 (4.5-29.4)	13.6 (5.6-29.4)	4.1 (2.2-9.8)
Median PFS, months, 95% CI	1.6 (1.4-2.7)	1.8 (1.5-2.8)	1.3 (1.1-1.5)
Median OS, months, 95% CI	7.9 (6.1-13.9)	9.2 (6.4-17.7)	4.3 (2.4-7.9)
Median TTR, weeks, 95% CI	5.6 (4.3-50.4)	5.6 (4.3-50.4)	6.4 (4.3-12.7)

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The recommended belinostat dosing regimen was identified in the TT20 and TT30 trials as 1000 mg/m<sup>2</sup> IV infusion over 30 minutes on days 1-5 every 21 days. In the TT30 dose-escalation trial in patients with advanced hematological neoplasia, a total of 16 patients received at least one treatment with belinostat with doses of 600 mg/m<sup>2</sup>/day (3 patients), 900 mg/m<sup>2</sup>/day (3 patients), and 1000 mg/m<sup>2</sup>/day (10 patients). Disease stabilization was seen in 6 patients (38%): at the 600 mg/m<sup>2</sup>/day dose level (1 patient with CLL), at the 900 mg/m<sup>2</sup>/day (1 patient each with CLL and NHL), and at the 1000 mg/m<sup>2</sup>/day [1 patient with non-Hodgkin's lymphoma centroblastic lymphoma (transformed CLL) and 2 patients with multiple myeloma]. There were no complete or partial responses.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of efficacy can be defined in PTCL as “duration of response”. Duration of response was a secondary endpoint for the CLN-6 and CLN-19 trials. The reader is referred to Section 6.1.5 for results of duration of response.

### 6.1.10 Additional Efficacy Issues/Analyses

#### **CLN-19:**

##### Protocol violations:

In the CLN-19 trial, there were a total of 24 patients that had at least one major protocol violations:

- Fifteen patients had inclusion criteria violations. Thirteen of the 15 patients were included in the Efficacy Analysis Set [13/120 (11%)].
- Two patients had exclusion criteria violations. Both patients were included in the Efficacy Analysis Set [2/120 (2%)].

- Sixteen patients had on-study violations. All 16 patients were included in the Efficacy Analysis Set [(16/120 (13%)].

All 24 patients were included in the Full Analysis Set. Twenty-two of the 24 patients received a waiver and were included in the Efficacy Analysis Set [22/120 (18%)].

**Table 32 CLN-19: Protocol Violations**

<b>Protocol violations<sup>a</sup></b>	<b>Total (n=24)</b>	<b>No. of Patients included in the Full Analysis Set (24/129)</b>	<b>No. of Patients included in the Efficacy Analysis Set (22/120)</b>
Patients with inclusion criteria violations	15/24	15/129	13/120
Patient did not have histologically confirmed diagnosis of PTCL (due to absence of T-cell and/or B-cell markers) <sup>b</sup>	13	13	12
Patients did not have the required laboratory test values <sup>c</sup>	2	2	1
Patients with exclusion criteria violations	2/24	2/129	2/120
Anticancer therapy within 2 weeks prior to first study treatment, with recovery from prior treatment-related toxicities <sup>d</sup>	1	1	1
Relapse within 100 days of autologous or allogeneic bone marrow transplant	1	1	1
Patients with on-study violations	16/24	16/129	16/120
Patient continued treatment although had developed withdrawal criteria <sup>e</sup>	1	1	1
Patients that were treated after disease progression	7	7	7
Patients received incorrect dose <sup>f</sup>	5	5	5
Received prohibited medications during the trial <sup>g</sup>	3	3	3

<sup>a</sup> Based on the number of patients, not the number of violations. Although a patient may have had 2 or more violations, the patient is counted only once. The same patient may appear in different categories.

<sup>b</sup> Based on CPRG, 12 of the 13 patients were found to meet the eligibility requirements for PTCL and had all of the required markers. One patient (140-001) did not have the assessment for MIB and Ki-67 and was not included in the Efficacy Analysis Set.

<sup>c</sup> Among the two patients, patient (513-001) was enrolled with low serum potassium (3.3 mmol/L on Day -18 and 3.2 mmol/L on Day 1 prior belinostat) administration and was included in the Efficacy Analysis Set.

<sup>d</sup> One patient (patient 244-002) stopped CHOP on July 22, 2010 and started Chlorambucil on July 22, 2010 to September 24, 2010, stopped due to PD. Belinostat was started (on October 4, 2010) prior to completion of a 2 week recovery period.

<sup>e</sup> One patient (600-003), who was reported as having a PR was continued in the trial although the patient had developed withdrawal criteria during the trial (2 new lesions; longest diameters <15mm).

<sup>f</sup> Five (240-001, 534-006, 600-003, 752-002, and 900-001) patients received incorrect dose. Patient 900-001 received 2050 mg of belinostat at Cycle 5 instead of 1,970 mg based on the Cycle 1 dose, although there was not a 10% change in the patient's weight from Cycle 1 (82.6 kg) to Cycle 5 (86 kg). Among the 5 patients who received an incorrect dose, 3 patients experienced Grade 3/4 AEs (1 case each of nasopharyngeal infection, worsening autoimmune hemolytic anemia, and pharyngitis), but the dose was not reduced by 25% as specified in the protocol. For the other 2 patients, 1 patient (752-002) received a 50-mg lower dose at Cycle 4 and 1 patient (Patient 900-001) received an 80-mg higher dose at Cycle 5.

<sup>g</sup> Three patients (Patients 126-002, 223-002, and 600-003) received prohibited concomitant. Patient 126-002 received a short course of hydrocortisone as allowed per protocol to treat an infusion reaction. Patient 223-002 received 70 mg of prednisolone (equivalent to 70 mg prednisone) once a day for 2 short courses followed by 50 mg prednisolone (equivalent to 50 mg prednisone) daily for 1 course to treat anemia. Patient 600-003 received 4 mg of dexamethasone (equivalent to prednisone 25mg) twice a day for 3 days for Grade 3 mucosal pharyngitis.

In addition, there was one patient that was not enrolled in the trial and had not signed an informed consent who received four vials of belinostat in error. This patient was not included in either the Full Analysis or the Efficacy Analysis Set.

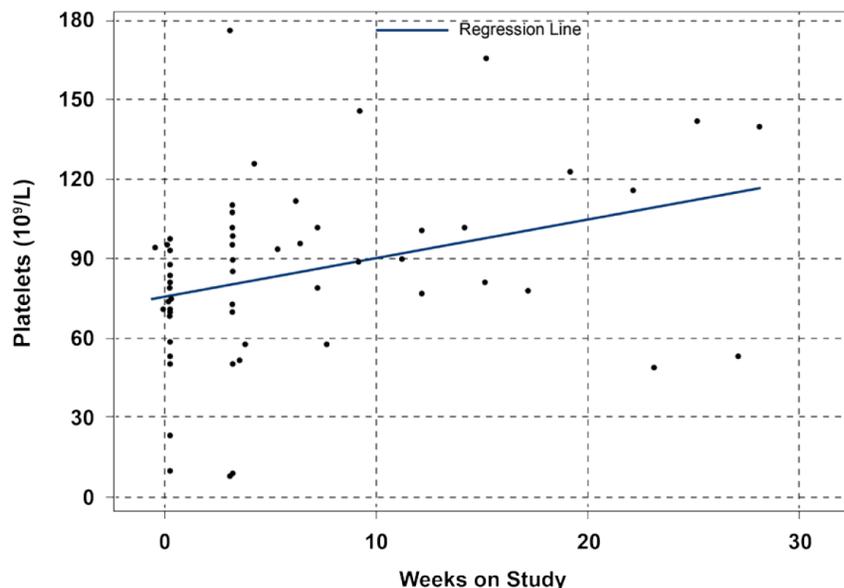
Although 18% of the patients in Efficacy Analysis Set had one or more major protocol violations, it is not likely that these protocol violations affected the overall analysis of the primary endpoint. See Table 32 and footnotes describing these cases.

#### Patients with baseline platelet counts of <100,000/mcL:

In the CLN-19 trial, there were 20 patients (16.7%) among the Efficacy Analysis Set that had baseline platelet < 100,000/mcL. To be eligible for the trial, the requirement for baseline platelet count was  $\geq 50,000/\text{mcL}$ . However, there were two patients, 144-001 and 532-002, that had platelet counts of 10,000/mcL and 23,000/mcL at pre-treatment on Cycle 1, Day1, respectively. These patients had platelet counts of 52,000/mcL and 51,000/mcL at screening and were eligible for enrollment. Patient 144-001 completed Cycle 1 without any hematologic AEs. Prior to Cycle 2, the patient received several platelet transfusions and started Cycle 2 with a platelet count of 9,000/mcL. On Cycle 2, Day 5, this patient's platelet count was 2,000/mcL and belinostat treatment was discontinued due to progressive disease after Cycle 2. Patient 532-002 started Cycle 1 at a 25% reduced dose. Between the Cycle 1 and 2, the patient received 3 platelet transfusions, which increased the platelet count to 94,000/mcL before the Cycle 2. On Cycle 2, Day 5, the patient's platelet count decreased to 6,000/mcL. Before Cycle 3, the patient was taken off study for progressive disease and died 20 days after the last dose.

The applicant performed an analysis of change in platelet counts over the course of the trial in patients with baseline platelet counts of <100,000/mcL. In general, there was a trend toward platelet counts increase in this subgroup over time (R-Square=0.1110, p-value for slope of time on X-axis=0.0087).

**Figure 6 CLN-19: Platelet Count Values during the Trial in the Subgroup of Patients with Baseline Platelets of <100,000/mcL**



Source: CLN-19 Clinical Study Report, page 82.

Thrombocytopenia:

During the CLN-19 trial, a total of 13 patients experienced grade 3 or 4 treatment emergent thrombocytopenia (see section 7.3.2). Out of these 13 patients, 5 patients (154-001, 161-001, 600-003, 801-001, and 938-001) achieved a PR.

Subsequent therapy:

In the FAS, after discontinuing treatment with belinostat a total of 82 patients (63.6%) received subsequent therapy. Seventy-seven patients (59.7%) received subsequent drug treatment, 13 patients (10.1%) received radiation therapy and 12 patients (9.3%) received a stem cell transplant. The applicant reported that 102 patients (79.1%) went on with a subsequent therapy after discontinuing belinostat treatment, however, there were patients that received both systemic and radiation therapy or systemic therapy and a stem cell transplant or all three.

Of the 12 patients who subsequently received stem cell transplant, 9 patients were in the EAS and 10 patients were alive at the data cutoff. The table below shows the survival status of patients who received subsequent stem cell transplant.

**Table 33 CLN-19: Survival Status of Belinostat-treated Patients Who Subsequently Received a Stem Cell Transplant (Full Analysis Set)**

Patient	IRC best response	Survival status	Overall survival (months)
140-002	PD	Alive	17.6
147-001	NE	Alive	10.2

147-002	NE	Alive	9.4
221-003	CR	Alive	20.4
245-001	PR	Dead	19.9
907-001	PD	Alive	22.9
907-005	PD	Alive	13.6
907-006	SD	Alive	13.9
907-007	SD	Alive	12.1
914-002	PD	Dead	7.8
914-006	NE	Alive	13.7
931-003	CR	Alive	11.6

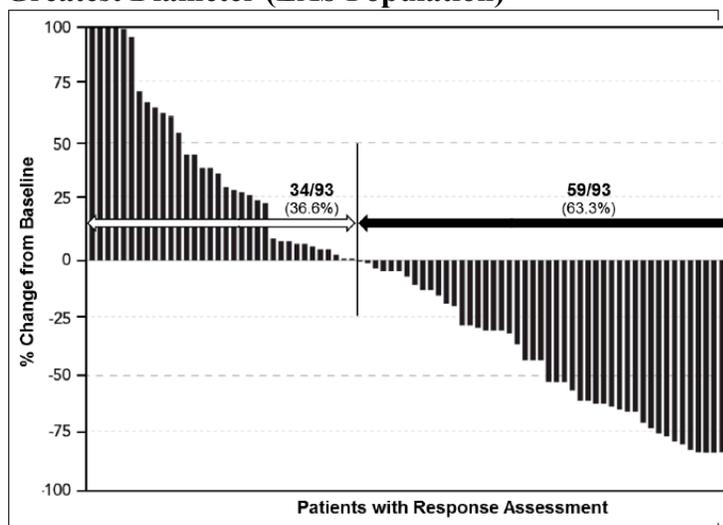
NE: Not evaluable

The most common subsequent drug therapy was chemotherapy with gemcitabine (n=24, 18.6%). Fourteen patients (10.9%) received pralatrexate and 5 patients (3.9%) received romidepsin.

Individual tumor response:

The applicant provided a waterfall plot that displays the maximum difference in the sum of the products of the greatest diameters (SPD) values as the percentage change from baseline for 93 patients (77.5%) who had measurable disease at baseline and post-treatment assessment. The remaining 27 patients (22.5%) did not have a baseline or post-treatment assessment: 24 patients were not evaluable for assessment (Table 22) and there were 3 patients (141-001, 240-002 and 243-001) that did not have the first radiology assessment. Of the 93 patients, 59 patients (63.3%) had a decrease in tumor volume (as measured by the difference in the SPD between baseline value and maximum decrease on study) and 34 patients (36.6%) had an increase in the SPD compared to baseline values.

**Figure 7 CLN-19: Maximum Change from Baseline in Sum of the Products of the Greatest Diameter (EAS Population)**



Source: ISE, page 53.

## **CLN-6:**

In the CLN-6 trial, 24 patients with PTCL were enrolled. Out of the 24 patients, 10 patients had inclusion/exclusion criteria violations.

Waivers were not granted for 6 of the 10 patients:

- Measurable disease was not present (2 patients: 041-003, 042-004)
- Baseline X-ray/CT scan was not performed (1 patient: 007-001)
- Patient had clinically significant cardiovascular disease (1 patient: 006-005)
- Patient had other malignant diseases within 5 years (1 patient: 003-005)
- Karnofsky performance status not > 70% (1 patient: 042-003)

However, none of the above 6 patients had a response. Therefore, these major protocol violations did not affect the analysis of the primary endpoint.

## **7 Review of Safety**

### **Safety Summary**

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.

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.

## 7.1 Methods

See section 5.2 of this review.

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The evaluation of safety was focused on the CLN-19 trial. In the CLN-19 trial, safety analyses was conducted on the Full Analysis Set (n=129) who received at least 1 dose if belinostat.

Safety evaluation was also conducted using the data from the pooled supportive IV belinostat monotherapy trials, CLN-6 and CLN-20. The belinostat dose in these trials was the same as the pivotal trial (CLN-19), 1,000 mg/m<sup>2</sup>, administered by a 30-minute IV infusion and on Days 1 through 5 of every 21-day cycle (except in Cycle 1 of Arm B in the CLN-20 trial where patients received only one dose of belinostat 1,000 mg/m<sup>2</sup> on Cycle 1 Day 1). The safety population of these two IV belinostat monotherapy trials was comprised of 80 patients (CLN-6: 53 patients, CLN-20: 27 patients).

In addition, other trials of IV belinostat monotherapy (TT-20, TT-30, 301-G) were also reviewed. The table below describes the safety population of supportive IV belinostat monotherapy trials.

**Table 34 Safety Population of Supportive IV Belinostat Monotherapy Trials**

<b>Trial ID</b>	<b>Patient population</b>	<b>Dose regimen</b>	<b>No. of patients</b>
TT-20	Advanced solid tumors (dose-escalation trial)	150, 300, 600, 900, 1,000, 1,200 mg/m <sup>2</sup> 30-min IV, Days 1-5 (every 21 days)*	46
TT-30	Advanced hematologic neoplasia (dose-escalation trial)	600, 900, 1,000 mg/m <sup>2</sup> 30-min IV, Day 1-5 (every 21 days)	16
301-G	Advanced multiple myeloma (dexamethasone was added after the first cycle)	900, 1,000 mg/m <sup>2</sup> 30-min IV, Days 1-5 (q21 days)	25
CLN-6	Recurrent or refractory CTCL or PTCL	1000 mg/m <sup>2</sup> 30 min IV, Days 1-5 (every 21days)	53
CLN-20	Solid tumors or hematologic malignancies (drug-drug interaction trial with warfarin)	1000 mg/m <sup>2</sup> 30 min IV, Days 1-5 (every 21 days)	27
<b>Total</b>			<b>167</b>

\*Oral belinostat was also explored in TT20. A total of 15 patients received oral belinostat as a replacement for 1 or more scheduled IV belinostat doses.

### 7.1.2 Categorization of Adverse Events

In the CLN-19 trial, MedDRA terminology version 14 was used to categorize adverse events. For the pooled safety analyses from various trials, AEs were mapped using the MedDRA version 15.0. AEs were graded according to the National Cancer Institute Common Technology Criteria for Adverse Events (NCI-CTCAE) version 3.0 coding system. Mapping of the verbatim AE terms to MedDRA Preferred Term and System Organ Class (SOC) was acceptable.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Refer to section 7.1.1 of this review.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

#### **CLN-19:**

For demographics of the FAS population, see section 6.1.2.

In the FAS, 46 patients (36%) were treated for  $\geq 3$  months, 22 patients (18%) for  $\geq 6$  months, and 13 patients (10%) were treated for  $\geq 1$  year. The median total duration of treatment with belinostat was 7 weeks (range 3-135). Seven patients remained on treatment at the time of data cut-off. 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 long-term safety of belinostat is not evaluable from this trial data because of the relatively limited duration of exposure.

In patients with baseline platelet counts  $<100,000/\text{mcL}$ , 3 patients (13%) were treated for  $\geq 3$  months, 2 patients (8%) for  $\geq 6$  months, and 1 patient (4%) was treated for  $\geq 1$  year. Among subgroups of patients with PTCL NOS, angioimmunoblastic T-cell lymphoma (AITL), ALCL ALK-negative, the median number of cycles/number of doses/cumulative dose as well as the percentage of patients treated with belinostat for  $\geq 3$  months, 6 months and 1 year was the highest in patients with AITL.

The table below provides a summary of the extent of belinostat exposure for the FAS and subgroups.

**Table 35 CLN-19: Extent of Exposure to Study Medication (Full Analysis Set)**

	FAS (n=129)	PTCL, NOS (n=77)	AITL (n=22)	ALCL, ALK- negative (n=13)	Patients with baseline platelets $<100\text{K}/\text{mcL}$ (n=24)
Total duration of treatment (weeks)					
Median	7	8.3	11.3	7	6
Range	3-135	3-112	3-135	3-63	3-55
Patients treated with belinostat					
$\geq 3$ months	46 (35.7%)	29 (37.7%)	11 (50.0%)	3 (23.1%)	3 (12.5%)
$\geq 6$ months	22 (17.8%)	13 (16.9%)	7 (31.8%)	1 (7.7%)	2 (8.3%)
$\geq 12$ months	13 (10.1%)	6 (7.8%)	5 (22.7%)	1 (7.7%)	1 (4.2%)
Number of cycles received					
Median	2	2	3.5	2	2
Range	1-33	1-33	1-29	1-18	1-18
Number of doses received					

Median	10	10	17	10	10
Range	1-165	4-165	5-144	1-90	3-90
Total cumulative dose per patient (mg/m <sup>2</sup> )					
Median	10,520	10,520	17,263	10,000	9,310
Range	994-164,021	3,960-164,021	4,880-124,515	994-91,010	3,084-90,850
Relative dose intensity (%)					
Median	98.30	98.8	94.3	98.6	98.50
Range	19.9 - 105.2	54.9- 105.2	49.1- 100.6	19.9-101.5	54.9 - 102.6
Dose delay ≥ 7 days	37 (28.7%)	20 (26.0%)	11 (50.0%)	3 (23.1%)	6 (25.0%)
Infusion interruption	22 (17.1%)	17 (13.2%)	4 (3.1%)	1 (<1%)	3 (2.3%)

In the FAS, the median total cumulative belinostat dose was 10,500 mg/m<sup>2</sup> and the relative dose intensity was 98.3% (i.e., the majority of patients were able to tolerate and receive all intended treatment at the target dose). Sixteen patients (12.4%) required belinostat dose reductions and 37 patients (28.7%) had a cycle delay of ≥ 7 days. The most frequent reason for dose delay was due to holidays (5 patients, 3.9%) and fever, rash, and upper respiratory infection (2 patients each, 1.6%). Causes for dose reduction that occurred in 2 patients were QTc prolongation and transaminases increased. There was only 1 patient (534-002) that had two dose reductions in Cycle 2 and Cycle 3 due to grade 3 and grade 2 ECG prolonged QT, respectively.

Twenty-two patients (17.1%) had infusion interruptions mostly due to extravasation (3 patients), poor venous access (3 patients), vomiting (3 patients), nausea (2 patients), hypersensitivity (2 patients), injection site pain (2 patients), and injection site phlebitis (2 patients).

The reasons for dose reductions are shown in the table below.

**Table 36 CLN-19: Dose Reductions**

	FAS (n=129)
Total number of patients that required dose reduction(s)	16 (12.4%)
Number of dose reduction	
1	15 (11.6%)
2	1 (<1%)
Reason for dose reduction	
Bronchospasm	1 (<1%)
Dyspnea	1 (<1%)
Hyperbilirubinemia	1 (<1%)
Hypoglycemia	1 (<1%)
Hypokalemia	1 (<1%)
Immune hemolytic anemia	1 (<1%)

Nausea	1 (<1%)
Neutropenia	1 (<1%)
Pancytopenia	1 (<1%)
Prolonged QTc	2 (2%)
Pulmonary embolus	1 (<1%)
Rash	1 (<1%)
Thrombocytopenia	1 (<1%)
Transaminases increased	2 (2%)

The belinostat dose in the CLN-19 trial was 1,000 mg/m<sup>2</sup> for 5 days repeated every 21 days. Overall, belinostat was well tolerated with 113 patients (87.6%) receiving the drug without dose reductions.

**Pooled data from the supportive IV belinostat monotherapy trials (CLN-20 and CLN-6):**

In general, the pooled baseline patient demographics of CLN-6 and CLN-20 were similar to the pivotal trial, CLN-19. The median age was 64 years (range 22-84), there were more males (59%) than females (41%), most of the patients were white (78%), and 89% of patients had a ECOG performance score of 0 or 1. Patient baseline demographics are summarized in table 37.

**Table 37 Pooled Data of CLN-20 and CLN-6: Patient Demographics**

	No. of patients (n=80)
Gender	
Male	47 (58.8%)
Female	33 (41.3%)
Age (years)	
Median	64
Range	22-84
< 65	40 (50.0%)
≥ 65	40 (50.0%)
Race	
White	62 (77.5%)
Black	6 (7.5%)
Asian	9 (11.3%)
Latin	3 (3.8%)
Baseline ECOG score	
0	26 (32.5%)
1	45 (56.3%)
2	8 (10.0%)
3	0
4	1 (1.3%)

## 7.2.2 Explorations for Dose Response

In the CLN-19 trial, all patients were started at the 1000 mg/m<sup>2</sup> (days 1-5, every 3 weeks) dose level. Thus, exploration for dose response is not possible.

In the TT20 dose-escalation trial in patients with advanced cancer, 1000 mg/m<sup>2</sup> (days 1-5, every 3 weeks) dose level was defined as the MTD. The 1200 mg/m<sup>2</sup> (days 1-5, every 3 weeks) dose was not tolerable as 3 of the 5 patients experienced a DLT (supraventricular tachycardia subsequently developing into atrial fibrillation, fatigue, diarrhea with fatigue). In the TT30 dose-escalation trial in patients with advanced hematological neoplasia, there were no DLTs observed at the 600 to 1000 mg/m<sup>2</sup>/day dose levels. Therefore, the 1000 mg/m<sup>2</sup>/day dose level was determined as the recommended phase 2 dose.

## 7.2.3 Special Animal and/or In Vitro Testing

Refer to the Pharmacology/Toxicology review.

## 7.2.4 Routine Clinical Testing

Refer to sections 7.4.2, 7.4.3, and 7.4.4.

Routine clinical assessments in the CLN-19 trial included performance status (ECOG), physical examinations, vital signs, ECG, and laboratory tests. Refer to Table 10 for detailed schedule of safety assessments. The schedule of assessment was acceptable.

## 7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to the Clinical Pharmacology review.

## 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

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.

Other approved HDAC inhibitors include vorinostat and valproic acid. The table below summarizes major toxicities of approved HDAC inhibitors.

**Table 38 HDAC Inhibitors: Major Toxicities**

	<b>Vorinostat</b>	<b>Romidepsin</b>	<b>Valproic acid</b>
Thromboembolism	X		
Hematologic	X	X	X <sup>a</sup>
Gastrointestinal disturbances	X		
Hyperglycemia	X		
Monitoring of chemistry tests	X		
Thrombocytopenia and gastrointestinal bleeding	X		
Fetal harm	X	X	X
Infection		X	
Electrocardiographic changes		X	
Tumor lysis syndrome		X	
Hepatotoxicity			X
Pancreatitis			X
Suicidal behavior and ideation			X
Hyperammonemia			X
Hypothermia			X
Multi-organ hypersensitivity reactions			X
Effect on HIV and CMV viruses replication			X

<sup>a</sup>Thrombocytopenia

### 7.3 Major Safety Results

#### **CLN-19:**

In the CLN-19 trial, a total of 125 patients (97%) experienced at least one treatment-emergent AE (TEAE). Seventy-nine patients (61%) reported grade 3/4 TEAEs and 9 patients (7%) had a fatal outcome.

**Table 39 CLN-19: Safety Summary**

<b>Event</b>	<b>FAS (n=129)</b>
Any TEAE	125 (97%)
Any grade 3 or 4 TEAE	79 (61%)
Serious TEAE	61 (47%)
Discontinuation due to TEAE	25 (19%)
Reported deaths within 30 days of last dose of belinostat	22 (17%)
Progressive disease	13 (10%)
Adverse event	9 (7%)

**Pooled data from the supportive IV belinostat monotherapy trials (CLN-6 and CLN- 20):**

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.

**Table 40 Pooled Analysis of CLN-6 and CLN-20: Safety Summary**

<b>Event</b>	<b>No. of patients (n=80)</b>
Any TEAE	79 (99%)
Any grade 3 or 4 TEAE	30 (38%)
Serious TEAE	23 (29%)
Discontinuation due to TEAE	19 (24%)
Reported deaths within 30 days of last dose of belinostat	7 (9%)
Progressive disease	4 (5%)
Adverse event	3 (4%)

7.3.1 Deaths

**CLN-19:**

Twenty-two patients (17.1%) were reported to have died during the trial or within 30 days of the last dose of belinostat: 13 patients (10.1%) due to disease progression and 9 patients (7.0%) due to an adverse event. According to the applicant only one death was assessed as related to the study drug; patient 154-001 who died due to hepatic failure.

The most common causes of death were multi-organ failure (2 cases) and cardiac failure (2 cases). Additional causes of death were hepatic failure, lung infection, gastrointestinal hemorrhage, euthanasia and shock (1 case, respectively).

The applicant also included a case of death due to multi-organ failure among the deaths due to an AE. However, this case is not counted in this review as death due to an AE. In this case, the patient was diagnosed with progressive disease and was withdrawn from the trial. Then the patient was started on a new treatment (CHOP chemotherapy) and subsequently developed cardiac arrest and multi-organ failure secondary to disease progression and died 22 days after the last dose of belinostat.

**Table 41 CLN-19: Reported Deaths on Study and Within 30 days of the Last Dose of Belinostat due to Adverse Event (Full Analysis Set)**

MedDRA Preferred Term	Patient ID	Age/Sex	Days on Study	Day of death relative to last dose
Lung infection	221-004	81/Male	132	2
Shock	922-001	72/Female	86	2
Gastrointestinal hemorrhage	244-002	76/Male	30	5
Multi-organ failure	146-002	76/Female	14	10
Multi-organ failure	513-001	56/Female	34	10
Euthanasia	244-004	76/Male	18	14
Hepatic failure	154-001	73/Male	219	25
Cardiac failure	142-001	72/Female	30	26
Cardiac failure	513-003	58/Male	138	29

In addition, there was one patient (patient 752-002) who had grade 5 pneumonia and died 39 days after the last dose of belinostat.

Below are the narratives for the patients that died within 30 days of the last dose of belinostat due to an adverse event:

Two patients died due to multi-organ failure within 10 days after the last belinostat dose:

Patient 146-002 was a 76-year-old female with PTCL, NOS with a history of arterial hypertension, ovarian cyst, MRSA (nose), osteochondrosis, chronic bronchitis, and pleural effusion treated with multiple concomitant medications, started Cycle 1 of belinostat at a dose of 1,640 mg/day. She was hospitalized with respiratory insufficiency, fever of unknown origin and was diagnosed with Grade 4 tumor lysis syndrome 9 days after her last dose. The patient subsequently developed heart and renal failure and died 10 days after the last dose of belinostat.

Patient 513-001 was a 56-year-old female with ALCL ALK (-) and a history of angioliopoma (kidney and hepatic) treated with multiple concomitant medications, was administered 2 cycles of belinostat (1,560 mg/day). The Cycle 2, Day 5 dose was not administered due to a Grade 4 decreased platelet count. The patient received multiple platelet transfusions, but became unconscious 9 days after her last belinostat dose. The patient expired due to multiple organ system failure 10 days after the last dose of belinostat.

One patient died due to multifactorial shock two days after the last belinostat dose:

Patient 922-001 was a 73-year-old female with PTCL, NOS, with a history of atherosclerotic vascular disease, cardiomegaly, hypertension, chronic kidney disease, chemotherapy-induced anemia, and hyperlipidemia treated with multiple concomitant medications, received 5 cycles of belinostat (2,260 mg/day) with 2 dose delays due to multiple AEs (Cycle 3, Day1 and Cycle 4,

Day1). The patient had a very complicated course with multiple hospitalizations for dehydration, acute renal failure, MRSA endocarditis, urosepsis, CHF, and hypotension requiring fluids, antibiotics, vasopressors, and an ICU stay. She was again admitted to the ICU 2 days after her last belinostat dose with hypotension and hypovolemia, received IV fluids, antibiotics and vasopressors, developed atrial fibrillation with a rapid ventricular response and cardiopulmonary arrest; she expired due to multifactorial shock 2 days after the last dose of belinostat.

Two patients died due to cardiac failure between 26-29 days after the last belinostat dose:

Patient 142-001 was a 72-year-old female with AITL and a previous history of hypotension, peripheral edema (ankle), hyperuricemia, tumor-related anemia, and tumor-related cough treated with multiple concomitant medications, was administered 1 cycle of belinostat (1,990 mg/day). The patient was hospitalized 9 days after her last dose with worsening ankle edema, dyspnea and diarrhea, and was diagnosed with Grade 4 cardiac decompensation. She expired due to cardiac decompensation and renal failure 26 days after the last dose of belinostat.

Patient 513-003 was a 58-year-old male with PTCL-NOS, history of *Klebsiella pneumoniae* (extended-spectrum  $\beta$ -lactamase carrier), and pulmonary embolism treated with multiple concomitant medications, was administered 6 cycles of belinostat (Cycle 1-3: 2,150 mg/day; Cycle 4-7: 2,250 mg/day). The patient was withdrawn from the study due to disease progression 10 days after Cycle 6, Day 5. He was subsequently hospitalized with weakness, fever, skin changes, thrombocytopenia, kidney and liver failure 27 days after his last belinostat dose, and expired due to Grade 5 acute heart failure 29 days after the last dose of belinostat.

Three patients died due to lung infection, gastrointestinal hemorrhage, and euthanasia between 2-14 days after the last belinostat dose:

Patient 244-002 was a 77-year-old male with Enteropathy-associated T-cell lymphoma and a previous history of abdominal pain, antral ulceration, and prostate carcinoma treated with multiple concomitant medications, was administered 2 cycles of belinostat (Cycle 1: 1,600 mg/day; Cycle 2: 1,570 mg/day). The patient was hospitalized 2 days after his last belinostat dose with hematemesis and melena, and was diagnosed with a Grade 5 GI bleed. He died due to severe GI bleeding 5 days after his last dose of belinostat.

Patient 244-004 was a 76-year-old male diagnosed with AITL with bone marrow involvement and ascites, previously treated with 7 cycles of CHOP, was administered 1 cycle of belinostat. The patient's ascites worsened during Cycle 1 and he withdrew consent 6 days after his last belinostat dose. He refused further treatments and opted for euthanasia, and died 14 days after the last dose of belinostat.

Patient 221-004 was an 80-year-old male with ALCL ALK (-) with a history of hypertension, treated with multiple concomitant medications, started Cycle 1 of belinostat at a dose of 2,000 mg/day, which was reduced to 1,500 mg/day at the start of Cycle 3, due to a rash. Cycle 6 of

belinostat was initiated as scheduled, despite worsening general condition and a swollen, painful lower limb. Lab assessments indicated that hemoglobin was 6.3 mmol/L and an ECHO was negative for thrombosis. The patient initiated celecoxib treatment. On Cycle 6, Day 3, the patient experienced tachycardia, with a heart rate greater than 110 beats per minute (BPM). Chest X-ray was normal and hemoglobin was 6.3 mmol/L. The patient received a blood transfusion. During Cycle 6, the patient complained of periodic episodes of nausea, vomiting, diarrhea, and abdominal complaints. On Cycle 6, Day 5, the patient completed Cycle 6 and the lower limb pain resolved. The patient was admitted to the hospital due to worsened general condition. A chest X-ray suggested infiltration in the bilateral basal lung fields. The patient was treated with prednisolone, antibiotics, and intravenous fluids for Grade 3 intercurrent pulmonary infection with secondary dehydration. The patient expired on Cycle 6, Day 6; 2 days after the last dose of belinostat.

One patient died due to hepatic failure 25 days after the last dose of belinostat which was considered related to the belinostat therapy by the investigator:

Patient 154-001 was a 73-year-old male with PTCL, NOS and a history of hepatitis A, monoclonal gammopathy, peripheral neuropathy and nicotine abuse treated with multiple concomitant medications including allopurinol and Voltaren, was administered 10 cycles of belinostat (2,040 mg/day). The patient completed 9 cycles of treatment without complication, and then he developed hyperuricemia, which was treated with allopurinol, and otitis media and was treated with diclofenac. Liver enzymes were noted to be elevated on Cycle 10, Day 1 at the time of dosing, and the patient completed Cycle 10 of belinostat with stable/decreased liver function tests (LFTs). He was subsequently hospitalized 17 days after his last belinostat dose with fever and generalized worsening at that time his LFTs were noted to be markedly elevated. The patient left the hospital against medical advice, but was readmitted 21 days after his last belinostat dose at which time his LFTs had further elevated. The patient expired 25 days after the last dose of belinostat with an autopsy showing subtotal liver necrosis as the cause of death. The patient's underlying disease, complicated medical history and the use of Voltaren were confounding factors.

**Pooled data from the supportive IV belinostat monotherapy trials (CLN-20 and CLN-6):**

In the pooled analysis of CLN-6 and CLN-20, a total of 7 patients (8.8%) were reported to have died during the trial or within 30 days of the last dose of belinostat: 4 patients (5.0%) due to disease progression and 3 patients (3.8%) due to an AE (patient CLN6-005-001: ventricular fibrillation, CLN6-006-005: pneumonia, CLN6-006-001: sepsis). The applicant reported that only one death was considered related to the study drug treatment (patient CLN6-005-001 due to ventricular fibrillation).

**Table 42 Pooled Analysis of CLN-6 and CLN-20: Reported Deaths on Study and Within 30 days of the Last Dose of Belinostat due to Adverse Event**

MedDRA Preferred Term	Patient ID	Age/Sex	Days on Study	Day of death relative to last dose
Ventricular fibrillation	CLN6-005-001	62/Male	39	6
Pneumonia	CLN6-006-005	74/Male	20	15
Sepsis	CLN6-006-001	72/Female	40	17

The cases for the 3 patients that died within 30 days of the last dose of belinostat due to adverse event in the CLN-6 and CLN-20 trials are described below:

Patient CLN6-005-001 was a 62 year old male diagnosed with PTCL. Six days after the last study drug dose in Cycle 2, the patient presented to an emergency department with ventricular fibrillation and respiratory failure and expired later that day from cardiac arrest. The event was considered related to belinostat by the Investigator. On [REDACTED] (b)(6), serum potassium was noted to be 2.9mmol/L (normal range 3.5-5.0 mmol/L) and the patient received KCl at 40meq/15mL BID. Later on [REDACTED] (b)(6), the patient was found lethargic and unresponsive at home at 19:05 and emergency services (EMS) were notified. Upon EMS arrival, the patient was tachycardic and in ventricular fibrillation. The patient had a “do not resuscitate / do not intubate” status reflective of the advanced state of his disease and poor prognosis but proper documentation could not be produced. The patient was therefore intubated via assisted ventilation (bag) and defibrillated 3 times. Medications administered en route to the hospital included: Epinephrine (x6), Atropine (x3), Sodium bicarbonate, Sodium chloride-IV, and Lidocaine. Upon arrival to the hospital, the patient was noted to be pale, dusky, cyanotic and mottled, and his skin was cold, paper thin, and dry. The patient was unresponsive to all stimuli and CPR was initiated. The patient was extubated at 20:45 and time of death was reported as 21:23. ECGs collected for this patient pre- and post-study drug infusion were submitted to a central ECG laboratory [REDACTED] (b)(4) for a blinded digital manual analysis. The data and results of that analysis did not indicate QTc prolongation or cardiac toxicity as defined by NCI CTC standards. In a follow-up report received October 18, 2007 from [REDACTED] (b)(4) Dr. [REDACTED] (b)(4) reviewed all of this patient’s ECG’s, from [REDACTED] (b)(6) (baseline) through [REDACTED] (b)(6) (beginning of Cycle 2) in addition to the patient’s final ECG performed [REDACTED] (b)(6) taken after he was resuscitated. Dr. [REDACTED] (b)(4) reported that “A review of all of the ECGs submitted for the patient shows consistency with relatively stable HR, QRS, QT and QTc measurements from [REDACTED] (b)(6) through [REDACTED] (b)(6) Morphology interpretations were also very consistent showing left anterior hemiblock (LAHB) on all tracings and with 2 tracings also showing VPCs. The patient’s final ECG taken after he was resuscitated showed sinus tachycardia new ST depression in the lateral leads. There was no evidence of prolonged QTc”. Dr. [REDACTED] (b)(4) also provided his Summary and Conclusion and reported “This patient’s QTc measurements are consistent for all measurements. Therefore, it is unlikely that the rhythm that was diagnosed as ventricular fibrillation was *torsade de pointes* as a prolonged QTc would be expected, at a minimum, in the ECG that was taken after the patient was resuscitated and yet it was not present.

Although the lateral ST depression could be indicative of a new myocardial injury, it could also have been reflective of underlying coronary artery disease that was exposed with the increased heart rate or might have been secondary to the efforts to defibrillate the patient. Overall, I find no evidence that this patient's condition was a result of the investigational drug being studied, but the findings of this patient will need to be placed in the context of the overall safety findings for this drug."

Patient CLN6-006-005 was a 74 year old male diagnosed with PTCL. The patient was hospitalized on [REDACTED]<sup>(b) (6)</sup>, 7 days after the last study drug dose due to increasing shortness of breath, productive cough of yellowish sputum, chills, and fever. The patient medical history included coronary artery disease, myocardial infarction, chronic obstructive pulmonary disease (COPD) with history of lung cancer including left upper lobectomy. The patient was presumed to have sepsis with possible skin etiology based on the open blisters on his left leg. The patient was treated with IV vancomycin as well as board-spectrum antibiotics. Clinical course became progressively worse. The patient was diuresed initially with transient improvement in respiratory status before progression of symptoms on the third day of hospitalization associated with increasing dyspnea, increasing cough, and increasing bronchospasm. A CT scan of the chest revealed a dense right upper lobe pneumonia plus focal infiltrates elsewhere consistent with multifocal pneumonia. Despite broad-spectrum antibiotics, symptoms progressed with acute renal failure and the patient expired on [REDACTED]<sup>(b) (6)</sup>, 8 days after onset. The cause of death was reported as pneumonia.

Patient CLN6-006-001 was a 72 year old female who was diagnosed with Sezary Syndrome and CTCL Stage IV A. The patient presented to the emergency room with a fever of 105.9°F, HR of 134 bpm, and BP of 77/49 mmHg. A chest x-ray noted right apical fibrosis, but no pneumothorax. Urine sample collected for culture was reported as positive for Klebsiella pneumoniae. Laboratory blood test results showed abnormal coagulation tests indicating coagulopathy and severe vitamin K deficiency in addition to abnormal electrolytes and kidney function tests which reportedly indicated metabolic acidosis secondary to the sepsis. CT-scans of the head, abdomen and pelvis reported no evidence of acute intracranial hemorrhage or intra/extra axial collections, no evidence of acute transcortical infarct or mass effect and no evidence of hydro-ureteronephrosis or urinary calculus, respectively. The patient was treated with IV-antibiotics and also received RBC and platelet transfusions and IV fluids. The event outcome was fatal and the patient died on [REDACTED]<sup>(b) (6)</sup>, 5 days after onset. The principal investigator attributed the event of sepsis to be caused by the urinary tract infection.

### 7.3.2 Nonfatal Serious Adverse Events

#### **CLN-19:**

In the CLN-19 trial, 79 patients (61.2%) had a grade 3 or 4 AEs. 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%).

While there were 9 patients that had a grade 3/4 event with the Preferred Term for “thrombocytopenia”, there were 4 more additional patients that had a grade 3/4 Preferred Term “platelet count decreased”. Thus, a total of 13 patients (10.1%) had experienced grade 3/4 thrombocytopenia.

**Table 43 CLN-19: Grade 3 or 4 TEAEs Occurring > 3 Patients (Full Analysis Set)**

<b>MedDRA Preferred Term</b>	<b>Grades 3-4 N (%)</b>
Grade 3-4 TEAEs	79 (61.2)
Anemia	14 (10.9%)
Thrombocytopenia	9 (7.0%)
Dyspnea	8 (6.2%)
Neutropenia	8 (6.2%)
Fatigue	7 (5.4%)
Pneumonia	7 (5.4%)
Hypokalemia	7 (5.4%)
Lymphopenia	6 (4.7%)
Febrile neutropenia	6 (4.7%)
QT prolongation	5 (3.9%)
Pruritus	4 (3.1%)
Hypotension	4 (3.1%)
Asthenia	4 (3.1%)
AST increased	4 (3.1%)
ALT increased	4 (3.1%)
Platelet count decreased	4 (3.1%)
Deep vein thrombosis	4 (3.1%)
Infection	4 (3.1%)

#### **Pooled data from the supportive IV belinostat monotherapy trials (CLN-6 and CLN-20):**

In the pooled analysis of CLN-6 and CLN-20, 30 patients (37.5%) experienced a grade 3 or 4 TEAEs. The most frequently reported grade 3/4 TEAEs (>3.0%) were hypokalemia (5.0%) and fatigue (3.8%).

**Table 44 Pooled Analysis of CLN-6 and CLN-20: Grade 3 or 4 TEAEs Occurring > 1 Patients**

MedDRA Preferred Term	No. of patients (N=80)
	Grades 3-4 N (%)
Grade 3-4 TEAEs	30 (37.5)
Hypokalemia	4 (5.0)
Fatigue	3 (3.8)
Anemia	2 (2.5)
Back pain	2 (2.5)
Dehydration	2 (2.5)
Nausea	2 (2.5)
Thrombocytopenia	2 (2.5)

### 7.3.3 Dropouts and/or Discontinuations

#### **CLN-19:**

A total of 25 patients (19.4%) experienced an AE that lead to discontinuation of belinostat. Of the 25 patients, 14 patients (10.9%) discontinued due to SAEs. AEs that lead to treatment discontinuation that were reported in > 1 patient included anemia, fatigue, febrile neutropenia, multi-organ failure, each occurred in 2 patients (1.6%).

#### **Pooled data from the supportive IV belinostat monotherapy trials (CLN-6 and CLN-20):**

In the pooled analysis of CLN-6 and CLN-20, 19 patients (23.8%) discontinued treatment with belinostat due to an AE. Twelve patients (15.0%) discontinued due to SAEs. Other than the 7 patients that discontinued due to disease progression, the AEs that lead to treatment discontinuation were all different in the remaining 12 patients.

### 7.3.4 Significant Adverse Events

#### **CLN-19:**

In the CLN-19 trial, 61 patients (47.3%) had a treatment emergent SAE while on study or within 30 days after the last dose of belinostat. Overall, there were more non-hematologic treatment-emergent SAEs (TESAEs) reported than hematologic TESAEs. Hematologic TESAEs that were reported in >2 patients were anemia and thrombocytopenia, 3 patients each. Among the patients that had a TESAE, 6 patients had a fatal outcome (1 case due to pneumonia, 3 cases due to multi-organ failure, 2 cases due to cardiac failure). Among the 3 patients that experienced multi-organ failure, there was 1 patient that had multi-organ failure secondary to disease progression.

The table below summarizes TESAEs that were reported in more than 1 patient.

**Table 45 CLN-19: Treatment-Emergent Serious Adverse Events Reported in >1 Patient (Full Analysis Set)**

MedDRA Preferred Term	N (%)
All treatment-emergent SAEs	61 (47.3)
Pneumonia	9 (7.0)
Pyrexia	7 (5.4)
Infection	4 (3.1)
Anemia	3 (2.3)
Creatinine increased	3 (2.3)
Multi-organ failure	3 (2.3)
Thrombocytopenia	3 (2.3)
Bronchitis	2 (1.6)
Cardiac failure	2 (1.6)
Deep vein thrombosis	2 (1.6)
Fatigue	2 (1.6)
Febrile neutropenia	2 (1.6)
Hypotension	2 (1.6)
Pulmonary embolism	2 (1.6)
Sepsis	2 (1.6)
Tumor lysis syndrome	2 (1.6)

**Pooled data from the supportive IV belinostat monotherapy trials (CLN-6 and CLN-20):**

In the pooled analysis of CLN-6 and CLN-20, 23 patients (28.8%) had a TESAE. Of the patients that had a TESAE, 3 patients had a fatal outcome (patient CLN6-005-001: ventricular fibrillation, CLN6-006-005: pneumonia, CLN6-006-001: sepsis). The table below summarizes TESAEs that were reported in more than 1 patient.

**Table 46 Pooled Analysis of CLN-6 and CLN-20: Treatment-Emergent Serious Adverse Events Reported in >1 Patient**

MedDRA Preferred Term	No. of patients (N=80)
	N (%)
All treatment-emergent SAEs	23 (28.8)
Urinary tract infection	2 (2.5%)
Sepsis	2 (2.5%)
Pneumonia	2 (2.5%)
Abdominal pain	2 (2.5%)

### 7.3.5 Submission Specific Primary Safety Concerns

#### Myelosuppression:

##### CLN-19:

In the CLN-19 trial, 55 patients (42.6%) experienced AEs indicative of myelosuppression. The highest incidence was in the category of hemoglobin decreased and anemia (33.3%) and the category of platelet count decreased and thrombocytopenia had the highest grade 4 incidence (9.3%). There were no Grade 5 AEs. Adverse events that were indicative of myelosuppression are summarized in the table below.

**Table 47 CLN-19: Adverse Reactions Indicative of Myelosuppression**

MedDRA Preferred Term	Full Analysis Set (n=129)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
<b>Any AEs indicative of myelosuppression</b>	<b>55 (42.6%)</b>	<b>13 (10.1%)</b>	<b>19 (14.7%)</b>	<b>9 (7.0%)</b>	<b>14 (10.9%)</b>
Hemoglobin decreased and anemia	43 (33.3%)	8 (6.2%)	20 (15.5%)	9 (7.0%)	6 (4.7%)
Anemia	41 (31.8%)	7 (5.4%)	20 (15.5%)	8 (6.2%)	6 (4.7%)
Hemoglobin Decreased	2 (1.6%)	1 (0.8%)	0	1 (0.8%)	0
Neutrophil count decreased and neutropenia	14 (10.9%)	2 (1.6%)	3 (2.3%)	5 (3.9%)	4 (3.1%)
Neutropenia	12 (9.3%)	2 (1.6%)	2 (1.6%)	5 (3.9%)	3 (2.3%)
Neutrophil count decreased	2 (1.6%)	0	1 (0.8%)	0	1 (0.8%)
Platelet count decreased and thrombocytopenia	30 (23.3%)	10 (7.8%)	7 (5.4%)	1 (0.8%)	12 (9.3%)
Thrombocytopenia	21 (16.3%)	7 (5.4%)	5 (3.9%)	0	9 (7.0%)
Platelet count decreased	9 (7.0%)	3 (2.3%)	2 (1.6%)	1 (0.8%)	3 (2.3%)
WBC count decreased	14 (10.9%)	3 (2.3%)	7 (5.4%)	0	4 (3.1%)
Leukopenia	12 (9.3%)	3 (2.3%)	6 (4.7%)	0	3 (2.3%)
WBC count decreased	3 (2.3%)	0	1 (0.8%)	1 (0.8%)	1 (0.8%)

#### Cardiac safety:

##### CLN-19:

In the CLN-19 trial, a total of 13 patients (10.1%) experienced treatment emergent cardiac AEs. Grade 3 and grade 5 AEs occurred in two patients each (1.6%). There were no grade 4 events. Of the 13 patients that experienced treatment emergent cardiac events, AEs experienced by 3 patients (2.3%) were assessed as related to belinostat treatment by the investigator (one grade 1 atrial fibrillation, one grade 1 bundle branch block right, one grade 1 ventricular extrasystoles).

**Table 48 CLN-19: Treatment-Emergent AEs in Cardiac Disorders SOC (Full Analysis Set)\***

Preferred Term	Full Analysis Set (n=129)			
	All Grades	Grades 1/2	Grades 3/4	Grade 5
All patients	13 (10.1%)	9 (7.0%)	2 (1.6%)	2 (1.6%)
Atrial fibrillation	3 (2.3%)	3 (2.3%)	0	0
Bundle branch block right	1 (0.8%)	1 (0.8%)	0	0
Cardiac failure	2 (1.6%)	0	0	2 (1.6%)
Cardiac failure congestive	1 (0.8%)	0	1 (0.8%)	0
Cor pulmonale	1 (0.8%)	0	1 (0.8%)	0
Coronary artery disease	1 (0.8%)	1 (0.8%)	0	0
Sinus bradycardia	1 (0.8%)	1 (0.8%)	0	0
Sinus tachycardia	2 (1.6%)	1 (0.8%)	1 (0.8%)	0
Supraventricular tachycardia	1 (0.8%)	0	1 (0.8%)	0
Tachycardia	2 (1.6%)	2 (1.6%)	0	0
Ventricular extrasystoles	1 (0.8%)	1 (0.8%)	0	0

\* Based on number of patients. A patient can appear in more than one category.

A total of 15 patients (11.6%) had treatment-emergent ECG changes including 14 patients (10.9%) that experienced QT prolongation. Thirteen cases of QT prolongation were assessed as treatment related by the investigators. No cases of grade 4 or 5 study drug related QT prolongation were reported.

**Table 49 CLN-19: Treatment-Emergent ECG Changes (Full Analysis Set)\***

Preferred Term	Full Analysis Set (n=129)			
	All Grades	Grades 1/2	Grade 3	Grades 4/ 5
All patients	15 (11.6%)	10 (7.8%)	5 (3.9%)	0
QT prolongation	14 (10.9%)	9 (7.0%)	5 (3.9%)	0
ST segment depression	1 (0.8%)	1 (0.8%)	0	0

\* Based on number of patients. A patient can appear in more than one category.

**Table 50 CLN-19: QT Prolongations**

MedDRA Preferred Term	Full Analysis Set (n=129)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
<i>All AEs</i>					
Electrocardiogram QT prolongation	14 (10.9)	5 (3.9)	4 (3.1)	5 (3.9)	0

<i>Treatment-related AEs</i>					
Electrocardiogram QT prolongation	13 (10.1)	4 (3.1)	4 (3.1)	5 (3.9)	0

Five patients (3.9%) had grade 3 study drug related QTc prolongation as assessed by the investigator. Of the 5 cases of grade 3 study drug related QTc prolongation, 2 were confirmed by (b) (4) Inc ((b) (4) a separate central independent analysis of electrocardiogram to assess cardiac safety) and 3 cases were assessed as grade 1 AEs by the (b) (4) (Table 51).

**Table 51 CLN-19: Grade 3 QTc Prolongation by Investigator and (b) (4) Assessments**

Patient ID	No. of Cycle	Concomitant meds	Investigator assessment	(b) (4) assessment
144-001	2 cycles	No antiemetics	From C1D3-D5: Grade 3 QTc prolongation	Grade 1
147-002	3 days of Cycle 1	Kevatril 3 mg	C1D3: pre-dose ECG normal and post dose ECGs x5 were abnormal, clinically significant Grade 3 AE (related)	Confirmed grade 3
534-002	30 cycles	Dexamethasone	History of ischemic heart disease. Baseline ECG: abnormal. C1D5, post dose ECG: abnormal, grade 3 QTc prolongation reported as an AE	Grade 1
911-001	4 cycles	Zofran 24 mg and compazine 10 mg at each cycle from D1-D5	C2D5 Post dose ECG was reported as abnormal Grade 3 AE of QTcF	Grade 1
912-001	1 cycle	No antiemetics	C1D1 ECG post dose was "abnormal, clinically significant." Belinostat dose was reduced. C1D2 was delayed due to biliary stricture requiring biliary stent. The C1D2 was resumed 12 days later and C1 QTc prolongations were reported as Grade 3 and related.	Of all Grade 3 ECGs reported by investigators, 1 was confirmed as Grade 3 QTc prolongation by (b) (4)

Source: CSR, page 165-166.

Based on the central ECG analysis by (b) (4) for the 128 patients who met the ECG analysis criteria, no patients experienced new second or third degree heart block, new left bundle branch block, new right bundle branch block, new atrial flutter or atrial fibrillation, or new myocardial

infarction pattern. According to the (b) (4) assessment of CLN-19 ECGs, belinostat showed no effect on cardiac repolarization. There was no signal of clinically relevant changes in heart rate, PR or QRS duration or nonspecific ST-T changes. An average QTcF increase of 8.3 msec was noted after each infusion with some outliers. The PK-PD model revealed a positive intercept (the QTcF change from baseline at 0 ng/mL belinostat was 13.56 msec [y-axis intercept]) with a flat relationship (slope) between change in QTcF and concentration (0.00001772) suggesting that the effect on QTcF was not related to belinostat plasma concentration. No clinically relevant changes in other ECG parameters were noted).

A consult was sent to the QT Interdisciplinary Review Team (QT-IRT) team to review the effect of belinostat on cardiac repolarization. Their review comments of April 8, 2014 were as follows:

“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.

The sponsor’s exposure-response analysis showed that there is no direct relationship between plasma belinostat concentrations and dQTcF because the slope of the relationship was not statistically significant. However, the intercept (~10 ms) is significant. The sponsor is arguing that the significant intercept is due to background spontaneous variability in QTc changes over time which is not drug-related. However, there are various drug-related reasons may cause a significant intercept and a non-significant slope in the pooled analysis. For example:

1. QT prolongation stem from metabolites of belinostat. Belinostat plasma levels declined rapidly following administration to sub-pharmacological concentrations with an elimination half-life of ~1 h. However, belinostat metabolites could be detected up to one week in plasma and excreta after a single dose oral and IV administration. If the metabolites cause QT prolongation, it may explain the observed 10-ms change in QTcF from baseline at 0 belinostat concentration.
2. There may be a hysteresis between plasma belinostat concentrations and QTc prolongation (e.g., other off-target actions). One such mechanism might be block of hERG trafficking, but this would likely lead to progressive increases in QT over time.

Meanwhile, there are two other major limitations in the sponsor’s exposure-response analysis dataset:

1. The matched PK samples were not collected at the time of ECG recording. Because of the relative short half-life, a substantial difference in belinostat concentration level is expected (and was observed) even for a short time deviation.
2. The QT effect had not been monitored at the peak belinostat concentrations occur immediately after dosing. At the predicted  $C_{max}$  of mg/mL or higher, the observed information is very limited compared to the lower concentrations.

Events suggestive of proarrhythmia were not seen.

ECGs were reviewed in the ECG Warehouse. These ECGs are not of particularly high quality, but the sponsor’s analyses of QT appear to be reasonable and unbiased.”

**Pooled analysis of IV belinostat monotherapy (trials TT-20, TT-30, CLN-6, CLN20, 301-G):**

In the supportive IV belinostat monotherapy trials, a total of 35 patients (21.0%) reported treatment emergent cardiac AEs. Most patients (18.6%) had a grade 1 or 2 AE. Seven patients (4.2%) had serious AEs and cardiac events experienced by 17 patients (10.2%) were assessed as related to the study drug by the investigator. Three patients (1.8%) experienced grade 3 AEs and there were no grade 4 AEs. One patient (CLN6-005-001) died due to ventricular fibrillation.

The most frequently reported cardiac AE was tachycardia (12 patients, 7.2%) and the only other cardiac AEs reported in more than one patient were sinus tachycardia (3.6%), supraventricular tachycardia (2.4%), arrhythmia (1.8%), atrial fibrillation (1.2%), and bradycardia (1.2%).

**Table 52 Pooled Analysis of Supportive IV Belinostat Monotherapy Trials (TT-20, TT-30, CLN-6, CLN20, 301-G): Treatment-Emergent Cardiac Disorders**

Preferred Term	No. of patients (n=167)			
	All Grades	Grades 1/2	Grades 3/4	Grade 5
All patients	35 (21.0%)	31 (18.6%)	3 (1.8%)	1 (0.6%)
Angina pectoris	1 (0.6%)	1 (0.6%)	0	0
Arrhythmia	3 (1.8%)	3 (1.8%)	0	0
Arrhythmia supraventricular	1 (0.6%)	1 (0.6%)	0	0
Atrial fibrillation	2 (1.2%)	0	2 (1.2%)	0
Atrial flutter	1 (0.6%)	1 (0.6%)	0	0
Atrial tachycardia	1 (0.6%)	1 (0.6%)	0	0
Bradycardia	2 (1.2%)	2 (1.2%)	0	0
Bundle branch block left	1 (0.6%)	1 (0.2%)	0	0
Conduction disorder	1 (0.6%)	1 (0.6%)	0	0
Extrasystoles	1 (0.6%)	1 (0.6%)	0	0
Palpitations	1 (0.6%)	1 (0.6%)	0	0
Sinus arrhythmia	1 (0.6%)	1 (0.6%)	0	0
Sinus bradycardia	1 (0.6%)	1 (0.6%)	0	0
Sinus tachycardia	6 (3.6%)	6 (3.6%)	0	0
Supraventricular tachycardia	4 (2.4%)	3 (1.8%)	1 (0.6%)	0
Tachycardia	12 (7.2%)	12 (7.2%)	0	0

Ventricular dysfunction	1 (0.6%)	1 (0.6%)	0	0
Ventricular extrasystoles	1 (0.6%)	1 (0.6%)	0	0
Ventricular fibrillation	1 (0.6%)	0	0	1 (0.65)

\* Based on number of patients. A patient can appear in more than one category.

A total of 9 patients (5.4%) had treatment-emergent ECG changes including 2 patients (1.2%) each that experienced QT and QTc prolongation. One patient experienced grade 3 QTc prolongation. No cases of grade 4 or 5 treatment-emergent QT prolongation were reported.

The applicant included the ECG report by the (b) (4) (see Table 54). According to the (b) (4) review, the magnitude of belinostat on cardiac repolarization was <10 msec, and therefore not clinically problematic.

**Table 53 Pooled Analysis of Supportive IV Belinostat Monotherapy Trials (TT-20, TT-30, CLN-6, CLN20, 301-G): Treatment-Emergent ECG Changes**

Preferred Term	No. of patients (n=167)			
	All Grades	Grades 1/2	Grade 3	Grades 4/5
All patients	9 (5.4%)	8 (4.8%)	1 (0.6%)	0
QTc prolongation	2 (1.2%)	1 (0.6%)	1 (0.6%)	0
QT prolongation	2 (1.2%)	2 (1.2%)	0	0
ST segment depression	1 (0.6%)	1 (0.6%)	0	0
ST-T change	2 (1.2%)	2 (1.2%)	0	0
T wave abnormal	1 (0.6%)	1 (0.6%)	0	0
T-wave amplitude decreased	1 (0.6%)	1 (0.6%)	0	0

\* Based on number of patients. A patient can appear in more than one category.

**Table 54 Pooled Cardiac Central Electrocardiogram Reading of Supportive IV Belinostat Monotherapy Trials (TT-20, TT-30, CLN-6, 301-G):**

Trial	(b) (4) review
TT20	The ECG data revealed no signal of any changes in heart rate, AV conduction determined by the PR interval duration or cardiac depolarization as defined by the QRS interval duration. There was also no signal of any clear effect on cardiac repolarization as determined by the central tendency or specific outlier analyses, though the sample size precludes any definite determination in this regard. The PK-PD results in this trial were not interpretable due to too little ECG data collected around C <sub>max</sub> . It is likely that if there is an effect of belinostat on cardiac repolarization that the magnitude would be < 10 msec and hence not clinically problematic. In conclusion, this dose ranging study with 18 subjects treated at 1,000 mg/m <sup>2</sup> did not reveal any cardiac safety signal for belinostat on 12-lead ECG parameters except for a 5-10 msec change in QTcF duration, which could be a false positive or indicative of a small,

	not clinically important change. These data should be interpreted conservatively in light of the small sample sizes in this trial and the number of ECGs at $C_{max}$ .
TT30	The ECG data revealed no dose related signal of any changes in heart rate, AV conduction determined by the PR interval duration or cardiac depolarization as defined by the QRS interval duration. There was also no signal of any clear effect on cardiac repolarization as determined by the central tendency or specific outlier analyses though the sample size precludes any definite determination in this regard. It is likely that if there is an effect of belinostat on cardiac repolarization that the magnitude would be <10 msec and hence not clinically problematic. In conclusion, this dose range study with 12 patients treated at 600-1,000 mg/m <sup>2</sup> , who met ECG analysis population criteria, did not reveal any cardiac signal for belinostat on the 12-lead ECG parameters that was dose-related or likely of clinical importance; but caution should be exercised in light of the small sample sizes in this trial.
301G	The ECG data revealed for Part A [Part B had too few patients to provide interpretable data] no evidence of any changes in heart rate, AV conduction determined by the PR interval duration or cardiac depolarization as defined by the QRS interval duration. There was also no signal of any dose-related clear effect on cardiac repolarization as determined by the central tendency or specific outlier analyses though the sample size precludes any definite determination in this regard. It is likely that if there is an effect of belinostat on cardiac repolarization that the magnitude would be <10 msec and hence not clinically problematic.
CLN-6	The ECG data revealed no changes in AV conduction as observed on the PR interval duration or in depolarization as observed in the QRS duration. There was an apparent <5 bpm change in heart rate after each dose but on average about a 2 bpm increase in heart rate which is likely of no clinical importance. The effect of belinostat on cardiac repolarization as determined by the QTcF duration shows on average <5 msec change from Baseline in the 51 patients dosed at 1,000 mg/m <sup>2</sup> and in the time point analysis about a 10 msec change after each dose, which suggest belinostat may have some effect on cardiac repolarization that could be considered clinically relevant. There were minimal specific outlier changes that are in concert with a minimal effect of belinostat on QTcF duration. There were nonspecific ST-T changes (and 1 new RBBB) of no clear clinical consequence. In conclusion, belinostat appeared to have no clear clinically relevant effect on the ECG in this trial except for a minimal change in the QTcF duration in the 5-10 msec range which in this setting would have minimal clinical importance.

Source: ISS, page 191.

### Tumor lysis syndrome

In the CLN-19 trial, there were 4 patients (3.1%) who experienced treatment-emergent tumor lysis syndrome. Two patients (533-001, 902-001) had grade 2, and one patient each had grade 3 (224-001) and grade 4 (146-002).

## **7.4 Supportive Safety Results**

### 7.4.1 Common Adverse Events

#### **CLN-19:**

A total of 125 patients (96.9%) had treatment-emergent adverse events (TEAEs) in the CLN-19 trial. The most common AEs (> 25%) were nausea (41.9%), fatigue (37.2%), pyrexia (34.9%), anemia (31.8%), and vomiting (28.7%). TEAEs that were reported in  $\geq 10\%$  of patients are summarized in the table below.

**Table 55 CLN-19: Treatment-Emergent Adverse Events in  $\geq 10\%$  of Patients (Full Analysis Set)**

MedDRA Preferred Term	Full Analysis Set (n=129)		
	All Grades N (%)	Grades 1-2 N (%)	Grades 3-4 N (%)
All TEAEs	125 (96.9)	124 (96.1)	79 (61.2)
Nausea	54 (41.9)	53 (41.1)	1 (0.8)
Fatigue	48 (37.2)	41 (31.8)	7 (5.4)
Pyrexia	45 (34.9)	42 (32.6)	3 (2.3)
Anemia	41 (31.8)	27 (20.9)	14 (10.9)
Vomiting	37 (28.7)	36 (27.9)	1 (0.8)
Constipation	30 (23.3)	29 (22.5)	1 (0.8)
Diarrhea	29 (22.5)	27 (20.9)	2 (1.6)
Dyspnea	28 (21.7)	20 (15.5)	8 (6.2)
Peripheral edema	26 (20.2)	26 (20.2)	0 (0)
Rash	26 (20.2)	25 (19.4)	1 (0.8)
Cough	24 (18.6)	24 (18.6)	0 (0)
Chills	21 (16.3)	20 (15.5)	1 (0.8)
Pruritus	21 (16.3)	17 (13.2)	4 (3.1)
Thrombocytopenia	21 (16.3)	12 (9.3)	9 (7.0)
LDH increased	20 (15.5)	18 (14.0)	2 (1.6)
Decreased appetite	19 (14.7)	16 (12.4)	3 (2.3)
Headache	19 (14.7)	19 (14.7)	0 (0)
Infusion site pan	18 (14.0)	18 (14.0)	0 (0)
Hypokalemia	16 (12.4)	11 (8.5)	5 (3.9)
Abdominal pain	14 (10.9)	13 (10.1)	1 (0.8)
QT prolongation	14 (10.9)	9 (7.0)	5 (3.9)
Dizziness	13 (10.1)	13 (10.1)	0 (0)
Hypotension	13 (10.1)	9 (7.0)	4 (3.1)
Phlebitis	13 (10.1)	12 (9.3)	1 (0.8)

When analyzing TEAEs by System Organ Class (SOC), the highest incidence (> 45%) by all grades included General Disorders and Administration Site Conditions (79.8%), Gastrointestinal Disorders (72.1%), Infections and Infestations (49.6%), Investigations (48.8%), Blood and Lymphatic System Disorders (48.1%), Metabolism and Nutrition Disorders (47.3%), and Respiratory, Thoracic and Mediastinal Disorders (46.5%).

The highest incidence of grade 3-4 TEAEs (> 15%) included Blood and Lymphatic System Disorders (25.6%), Infections and Infestations (17.8%), and Investigations (17.1%).

**Table 56 CLN-19: Treatment-Emergent Adverse Events by MedDRA SOC (FAS)**

MedDRA SOC	Full Analysis Set (n=129)		
	All Grades N (%)	Grades 1-2 N (%)	Grades 3-4 N (%)
All TEAEs	125 (96.9)	124 (96.1)	79 (61.2)
General Disorders and Administration Site Conditions	103 (79.8)	83 (64.3)	16 (12.4)
Gastrointestinal Disorders	93 (72.1)	84 (65.1)	8 (6.2)
Infections and Infestations	64 (49.6)	39 (30.2)	23 (17.8)
Investigations	63 (48.8)	41 (31.8)	22 (17.1)
Blood and Lymphatic System Disorders	62 (48.1)	29 (22.5)	33 (25.6)
Metabolism and Nutrition Disorders	61 (47.3)	44 (34.1)	17 (13.2)
Respiratory, Thoracic and Mediastinal Disorders	60 (46.5)	44 (34.1)	16 (12.4)
Skin and Subcutaneous Tissue Disorders	56 (43.4)	47 (36.4)	9 (7.0)
Vascular Disorders	50 (38.8)	36 (27.9)	13 (10.1)
Musculoskeletal and Connective Tissue Disorders	45 (34.9)	36 (27.9)	9 (7.0)
Nervous System Disorders	45 (34.9)	42 (32.6)	3 (2.3)
Psychiatric Disorders	29 (22.5)	25 (19.4)	4 (3.1)
Injury, Poisoning and Procedural Complications	16 (12.4)	14 (10.9)	2 (1.6)
Eye Disorders	15 (11.6)	13 (10.1)	2 (1.6)
Cardiac Disorders	13 (10.1)	9 (7.0)	2 (1.6)
Renal and Urinary Disorders	13 (10.1)	11 (8.5)	2 (1.6)
Neoplasms Benign, Malignant and Unspecified (includes cysts and polyps)	11 (8.5)	8 (6.2)	3 (2.3)
Hepatobiliary Disorders	8 (6.2)	5 (3.9)	2 (1.6)
Ear and Labyrinth Disorders	6 (4.7)	6 (4.7)	0 (0)

Immune System Disorders	3 (2.3)	2 (1.6)	1 (0.8)
Reproductive System and Breast Disorders	3 (2.3)	3 (2.3)	0 (0)
Surgical and Medical Procedures	1 (0.8)	1 (0.8)	0 (0)

**Pooled data from the supportive IV belinostat monotherapy trials (CLN-6 and CLN-20):**

Almost all of the patients in the pooled analysis of CLN-6 and CLN-20 had a TEAE (79 patients, 98.8%). The most commonly reported TEAEs were nausea (70.0%), fatigue (48.8%), constipation (37.5%) and vomiting (32.5%). The pooled analysis did not identify any new AEs of concern over the CLN-19 trial.

**Table 57 Pooled Analysis of CLN-6 and CLN-20: Treatment-Emergent Adverse Events in ≥ 10% of Patients**

MedDRA Preferred Term	No. of patients (n=80)		
	All Grades N (%)	Grades 1-2 N (%)	Grades 3-4 N (%)
All TEAEs	79 (98.8)	43 (53.8)	36 (45.0)
Nausea	56 (70.0)	54 (67.5)	2 (2.5)
Fatigue	39 (48.8)	36 (45.0)	3 (3.8)
Constipation	30 (37.5)	29 (36.3)	1 (1.3)
Vomiting	26 (32.5)	25 (31.3)	1 (1.3)
Diarrhea	17 (21.3)	16 (20.0)	1 (1.3)
Dizziness	17 (21.3)	17 (21.3)	0
Pyrexia	15 (18.8)	15 (18.8)	0
Infusion site pain	14 (17.5)	14 (17.5)	0
Pruritus	13 (16.3)	11 (13.8)	2 (2.5)
Cough	12 (15.0)	12 (15.0)	0
Pain in extremity	12 (15.0)	12 (15.0)	0
Headache	11 (13.8)	11 (13.8)	0
Rash	11 (13.8)	10 (12.5)	1 (1.3)
Dyspepsia	10 (12.5)	10 (12.5)	0
Dyspnea	10 (12.5)	9 (11.3)	1 (1.3)
Anorexia	9 (11.3)	9 (11.3)	0
Insomnia	9 (11.3)	9 (11.3)	0
Hypokalemia	8 (10.0)	4 (5.0)	4 (5.0)
Hypotension	8 (10.0)	8 (10.0)	0
Muscle spasm	8 (10.0)	8 (10.0)	0
Urinary tract infection	8 (10.0)	7 (8.8)	1 (1.3)

## 7.4.2 Laboratory Findings

### **CLN-19:**

Treatment-emergent laboratory abnormalities that occurred in the CLN-19 trial are summarized in Table 58. Most of the abnormal laboratory values were grade 1 or 2. The most common grade 3/4 laboratory abnormalities were hematologic: lymphocytes decreased (47.7%), platelet counts decreased (14.7%), neutrophils decreased (12.5%) and leukocytes decreased (12.4%). No grade 5 laboratory abnormalities were reported. The table below summarizes treatment-emergent laboratory abnormalities occurring in  $\geq 10\%$  of patients using the laboratory datasets. In general, the values in the table below were higher than reported in the AE datasets.

**Table 58 CLN-19: Treatment-Emergent Laboratory Abnormalities Occurring in  $\geq 10\%$  of Patients**

	Patients with on-study test	Full Analysis Set (n=129)	
		All Grades N (%)	Grades 3 and 4 N (%)
<b>Hematology</b>			
Hgb decreased	129	118 (91.5)	15 (11.6)
Leukocytes decreased	129	60 (46.5)	16 (12.4)
Lymphocytes decreased	128	107 (83.6)	61 (47.7)
Neutrophils decreased	128	46 (35.9)	16 (12.5)
Platelets decreased	129	90 (69.8)	19 (14.7)
<b>Chemistry</b>			
ALT increased	129	55 (42.6)	5 (3.8)
AST increased	128	56 (43.8)	5 (3.9)
Alkaline Phosphatase increased	128	56 (43.8)	2 (1.6)
Albumin decreased	124	74 (59.7)	2 (1.6)
Bilirubin increased	129	38 (29.5)	7 (5.4)
BUN increased	129	65 (50.4)	0
Creatinine increased	129	41 (31.8)	1 (0.8)
Magnesium increased	125	18 (14.4)	1 (0.8)
Magnesium decreased	125	35 (28.0)	0
Potassium increased	129	20 (15.5)	3 (2.3)
Potassium decreased	129	56 (43.4)	8 (6.2)
Urate increased	129	29 (22.5)	4 (3.1)
Calcium increased	128	13 (10.2)	3 (2.3)
Calcium decreased	128	72 (56.3)	3 (2.3)
Glucose increased	128	111 (86.7)	10 (7.8)
Glucose decreased	128	12 (9.4)	1 (0.8)
Phosphate decreased	122	34 (27.9)	11 (9.0)

Source: Laboratory datasets

**Liver function:**

Among the reported SAEs in the CLN-19 trial, there was one patient (142-005) that experienced increased AST, ALT and GGT assessed as related to the study drug. The narrative of this case is presented below:

Patient 142-005 was a 63 year old female with an extensive medical history and on multiple concomitant medications started belinostat therapy on [REDACTED] (C1D1). The patient had elevated levels of ALT, AST and gamma-glutamyl transferase (GGT) before initiation of the treatment. Baseline levels on [REDACTED] were reported as ALT 37U/L, AST 79U/L and alkaline phosphatase 176U/L. Prior to C1D1 infusion on [REDACTED], the lab values were reported as ALT 45U/L, AST 104U/L and GGT 393U/L. The patient received 1,510mg of belinostat on treatment days 1 and 2. On [REDACTED] (C1D4), laboratory results revealed Grade 3 increased AST (358U/L) and Grade 2 increased ALT (182U/L), and belinostat was temporarily withheld. On [REDACTED] (C1D5), Grade 4 increased gamma GT (751U/L) was noted. On [REDACTED] (C1D7), the ALT levels decreased to Grade 2 (149U/L), and the AST levels decreased to Grade 2 (93U/L) on [REDACTED] (C1D8). A CT scan of the liver was performed on [REDACTED] (C1D9) and revealed no evidence of metastasis. A decision was made to continue treatment with belinostat and C1D3-5 doses were given on [REDACTED] (C1D11) to [REDACTED] (C1D13), at a reduced dose of 1,117mg (due to the event of GGT increased). The events of increased ALT and AST were considered resolved at Grade 1 levels. As the gamma-GT levels continued to be elevated at Grade 4, the event was considered as resolved with sequelae. The patient was discharged on [REDACTED] (C1D16) in stable condition. On [REDACTED] (C1D23), the gamma-GT levels returned to Grade 3 (baseline). On [REDACTED] (C1D30), the patient was discontinued from the study due to disease progression. The patient expired due to disease progression on [REDACTED] (C1D85). The events of increased GGT, increased ALT and increased AST were assessed as related to the study drug.

The table below summarizes shifts in liver function parameters to worst grade in the CLN-19 trial. Overall, there were 2 patients (154-001, 912-001) that experienced shift to grade 4 in liver function tests. Patient 154-001 died due to hepatic failure and had grade 4 increased ALT and AST. Patient 912-001 experienced grade 4 increased bilirubin (ALT and AST were grade 1). There were no true Hy's Law cases in the CLN-19 trial.

**Table 59 CLN-19: Shifts in Liver Function Parameters**

Baseline	Full Analysis Set (n=129)									
	Grade 0			Grade 1		Grade 2		Grade 3		Grade 4
Worst grade	2	3	4	3	4	3	4	3	4	4
ALT increased	9	3	0	1	1	0	0	0	0	0
AST increased	2	2	0	0	1	2	0	0	0	0
Alkaline Phosphatase increased	5	0	0	0	0	1	0	1	0	0
Albumin	9	0	0	1	0	1	0	0	0	0

decreased										
Bilirubin increased	4	4	1	0	0	1	0	1	0	0

Source: CLN-19 CSR, page 178.

#### Renal function:

In the CLN-19 trial, there were 9 patients that had grade 1 increased creatinine at baseline: during the trial, 1 patient improved to grade 0, 3 patients remained at grade 1, and 5 patients worsened to grade 2. In addition, there was 1 patient that had grade 2 increased creatinine at baseline that worsened to grade 3 during the trial.

#### 7.4.3 Vital Signs

In the CLN-19 trial, vital signs were within normal parameters following treatment with belinostat and the observed changes from baseline were not clinically relevant.

#### 7.4.4 Electrocardiograms (ECGs)

Refer to section 7.3.5.

#### 7.4.5 Special Safety Studies/Clinical Trials

This section is not applicable.

#### 7.4.6 Immunogenicity

The application did not contain evaluation regarding immunogenicity.

### **7.5 Other Safety Explorations**

#### 7.5.1 Dose Dependency for Adverse Events

Refer to section 7.2.2.

#### 7.5.2 Time Dependency for Adverse Events

In the CLN-19 trial, the median study day onset for AEs was 33 days: gastrointestinal disorders (26 days), blood and lymphatic system disorders (50 days), and infection and infestations (75 days).

### 7.5.3 Drug-Demographic Interactions

#### **CLN-19:**

The tables below summarize adverse reactions by sex, race, and age. In general, the incidences that occurred  $\geq 20\%$  were higher in females than in males and the incidences that occurred  $\geq 25\%$  were higher in non-whites than in whites. By age, the incidences of nausea, pyrexia, anemia, and vomiting occurred more in the  $< 65$  years of age than in the  $\geq 65$  years of age group.

When analyzing treatment-emergent SAEs by age, there were no clinically meaningful differences [ $< 65$  years of age: 45% (30 patients/67 patients),  $\geq 65$  years of age: 50% (31 patients/62 patients),  $< 75$  years of age: 47% (54 patients/116 patients),  $\geq 75$  years of age: 54% (7 patients/13 patients)].

The analysis by race should be interpreted with caution since there were only 18 patients (14.0%) in the non-white category (Table 61).

**Table 60 CLN-19: Adverse Reactions Occurring in  $\geq 20\%$  of Males or Females**

Preferred Term	Full Analysis Set (n=129)	
	Male (n=69)	Female (n=60)
Nausea	25 (36.2%)	29 (48.3%)
Fatigue	24 (34.8%)	24 (40.0%)
Anemia	18 (26.1%)	23 (38.3%)
Pyrexia	24 (34.8%)	21 (35.0%)
Vomiting	16 (23.2%)	21 (35.0%)
Constipation	14 (20.3%)	16 (26.7%)
Diarrhea	13 (18.8%)	16 (26.7%)
Headache	4 (5.8%)	15 (25.0%)
Rash	13 (18.8%)	13 (21.7%)
Cough	11 (15.9%)	13 (21.7%)
Dyspnea	16 (23.2%)	12 (20.0%)
Edema Peripheral	14 (20.3%)	12 (20.0%)
Pruritus	9 (13.0%)	12 (20.0%)

**Table 61 CLN-19: Adverse Reactions Occurring in  $\geq 25\%$  of White or Non-White**

Preferred Term	Full Analysis Set (n=129)	
	White (n=111)	Non-white (n=18)
Nausea	45 (40.5%)	9 (50.0%)
Fatigue	39 (35.1%)	9 (50.0%)
Pyrexia	38 (34.2%)	7 (38.9%)
Anemia	37 (33.3%)	4 (22.2%)

Vomiting	30 (27.0%)	7 (38.9%)
Diarrhea	23 (20.7%)	6 (33.3%)
Cough	19 (17.1%)	5 (27.8%)
Chills	16 (14.4%)	5 (27.8%)

**Table 62 CLN-19: Adverse Reactions Occurring in  $\geq 25\%$  of Patients Aged  $< 65$  Years or  $\geq 65$  Years**

Preferred Term	Full Analysis Set (n=129)	
	$< 65$ years (n=67)	$\geq 65$ years (n=62)
Fatigue	23 (34.3%)	25 (40.3%)
Nausea	31 (46.3%)	23 (37.1%)
Pyrexia	26 (38.8%)	19 (30.6%)
Anemia	22 (32.8%)	19 (30.6%)
Diarrhea	10 (14.9%)	19 (30.6%)
Constipation	12 (17.9%)	18 (29.0%)
Edema Peripheral	9 (13.4%)	17 (27.4%)
Rash	10 (14.9%)	16 (25.8%)
Cough	8 (11.9%)	16 (25.8%)
Vomiting	22 (32.8%)	15 (24.2%)

#### 7.5.4 Drug-Disease Interactions

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  $\leq$  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.

#### 7.5.5 Drug-Drug Interactions

Refer to Clinical Pharmacology review.

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<sup>2</sup> 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.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

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.

### 7.6.2 Human Reproduction and Pregnancy Data

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.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

In the belinostat trials, subjects under the age of 18 years of age were excluded from enrollment.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No cases of belinostat overdose were reported in the belinostat trials. The risk for abuse potential is minimal since the drug will be administered only in a hospital or clinic setting and does not appear to have effects of euphoria or sedation. Based on the pharmacological effects, belinostat is not expected to produce withdrawal effects.

## 7.7 Additional Submissions / Safety Issues

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.

### CLN-19:

At the time of the NDA data cutoff on August 31, 2012, 7 patients remained on treatment in the CLN-19 trial. In this safety report, the applicant included updated data for these 7 patients.

There were two new deaths reported within 30 days of last belinostat dose: patients 516-004 due to pulmonary hemorrhage and patient 534-002 due to disease progression. Both deaths were assessed by the investigator as not related to belinostat therapy. The narratives for these patients are presented below:

Patient 516-004 was a 40 year old male with no significant medical history or concomitant medications. The patient received Cycle 8 of belinostat treatment from [REDACTED] (b) (6). On [REDACTED] (b) (6), tumor assessment scans were performed per protocol and the patient was diagnosed with bilateral grade 2 lung masses. The patient was asymptomatic. Subsequent scans revealed an increase in the size and intensity of the lung masses, with suspicion of fungal disease, such as invasive bronchopulmonary aspergillosis. A biopsy performed on [REDACTED] (b) (6) was inconclusive. Scans performed on [REDACTED] (b) (6), revealed reduced intensity and density of the masses. A bronchoscopy and thoracoscopy were performed on [REDACTED] (b) (6) resulting in resection of segment VI of the left lung. The pathology report from the thoracoscopy samples revealed purulent lung inflammation, positive for methicillin-resistant *Staphylococcus aureus* (MRSA) and *Neisseria* species. The patient was also diagnosed with grade 2 purulent pneumonia and was discharged home on [REDACTED] (b) (6) in stable condition. The Investigator assessed the event of insertion of venous port as unrelated to belinostat and lung masses as related to belinostat. Three days after starting Cycle 27 ([REDACTED] (b) (6)), therapy with belinostat was discontinued due to disease progression. On Day 16 after last study dose the patient was hospitalized due to massive pulmonary hemorrhage and expired 2 days later. The Investigator assessed the event of massive pulmonary hemorrhage as unrelated to belinostat.

Patient 534-002 was a 69 year old female with medical history significant for autoimmune pneumonitis with pulmonary fibrosis and chronic bronchitis, on multiple concomitant medications. Patient started Cycle 1 of belinostat on [REDACTED] (b) (6) and received a total of 30 cycles. The patient required 2 dose reductions due to prolonged QTc. On [REDACTED] (b) (6) (Cycle 10, Day 11), following administration of IV contrast media, the patient developed wheezing, shortness of breath, decreased oxygen saturation (84%) and fever, and was admitted to the hospital the same day with a possible diagnosis of grade 3 sepsis. The patient was treated with antibiotics, steroids, fluid support and heparin anticoagulation. On [REDACTED] (b) (6), the event was considered resolved and the patient was discharged home. Cycle 11 was delayed due to sepsis.

On [REDACTED]<sup>(b) (6)</sup> Cycle 11, Day 18), the patient was hospitalized with complaints of pain and swelling of the right lower extremity. Doppler ultrasound of the lower extremities confirmed the diagnosis of grade 3 thrombosis (of right lower extremity deep veins) and a CT scan of the chest ruled out pulmonary embolism. The patient was started on anticoagulant therapy, the event resolved and the patient was discharged home on [REDACTED]<sup>(b) (6)</sup>. On [REDACTED]<sup>(b) (6)</sup> (Cycle 27, Day 26), the patient was hospitalized with complaints of cough and dyspnea. Physical examination revealed slight hyperemia of the pharyngeal structures and tonsils, emphysematous chest, rough cellular breathing sounds with extensive whistling and throbbing, and bronchitis on both sides. Admission laboratory work revealed markedly elevated CRP levels and a chest X-ray was negative for pneumonia. The patient was diagnosed with acute exacerbation of chronic bronchitis (grade 3) and responded well to treatment with IV hydration and antibiotics. On [REDACTED]<sup>(b) (6)</sup> the event was considered resolved and the patient was discharged home. On [REDACTED]<sup>(b) (6)</sup> the patient was hospitalized with complaints of fever (38 C), cough, expectoration and dyspnea. An admission chest X-ray was performed and the patient was diagnosed with Grade 3 bronchopneumonia. The patient improved on antibiotic therapy, her condition improved and she was subsequently discharged home. On [REDACTED]<sup>(b) (6)</sup> (Cycle 29, Day 24), the patient was hospitalized once again due to weakness and low grade fever, and diagnosed with grade 2 dehydration; treatment included intravenous fluids. The patient also experienced tachycardia (non-serious event) during hospitalization, which was treated by increasing the dose of ongoing bisoprolol. On [REDACTED]<sup>(b) (6)</sup>, the event was considered resolved and the patient was discharged to another hospital for a pre-arranged appointment. On [REDACTED]<sup>(b) (6)</sup> (Cycle 30, Day 22), the patient was hospitalized with complaints of dyspnea at rest, weakness, chest pain and abdominal pain. She was dehydrated and was treated with IV antibiotics and hydration. While in the hospital, the patient experienced fever and cultures revealed gram negative rods. The patient was started on meropenem and amikacin. On [REDACTED]<sup>(b) (6)</sup>, the patient was diagnosed with disease progression, reported as a serious adverse event, and withdrawn from study. The patient expired the same day. The Investigator assessed all the events as unrelated to belinostat.

Four patients experienced SAEs: patient 220-002: pneumonia, 516-004: pulmonary hemorrhage, 534-002: dehydration and disease progression, and 541-001: pulmonary embolism. Other than the two patients who died due to SAEs, patient 541-001 discontinued treatment due to the SAE.

## 8 Postmarket Experience

Belinostat is a new molecular entity and is not approved for marketing in any country at this time. There is no post-marketing experience with belinostat.

## 9 Appendices

### 9.1 Literature Review/References

1. Mak V, Hamm J, Chhanabhai M, et al. Survival of patients with peripheral T-cell lymphoma after first relapse or progression: Spectrum of disease and rare long-term survivors. *J Clin Oncol* 2013;31(16):1970-1976.
2. O’Leary HM, Savage K. Novel therapies in peripheral T-cell lymphomas. *Current Oncology Reports* 2008;10:404-411.
3. Foss F, Luigi Zinzani P, Vose J, et al. Peripheral T-cell lymphoma. *Blood* 2011;117(25):6756-6767.
4. Foss F. Evolving therapy of peripheral T-cell lymphoma: 2010 and beyond. *Ther Adv Hematol* 2011;2(3):161-173.
5. Weisenburger DD, Savage KJ, Harris NL, et al. Peripheral T-cell lymphoma, not otherwise specified: a report of 340 cases from the International Peripheral T-cell Lymphoma Project. *Blood* 2011;117(12):3402-3408.
6. Chen A, Advani R. Beyond the guidelines in the treatment of peripheral T-cell lymphoma: New drug development. *J Natl Compr Canc Netw* 2008;6:428-435.
7. NCCN Guidelines. Peripheral T-Cell Lymphomas. Version 1.2014.

### 9.2 Labeling Recommendations

The label is under development. Refer to the final version of the label.

### 9.3 Advisory Committee Meeting

This application was not taken to ODAC (Oncologic Drugs Advisory Committee) because the protocol (CLN-19) was under Special Protocol Assessment agreement, the Division is familiar with the trial design/endpoints, and an agreement on the Post-Marketing Requirement trial was completed before the application review was completed.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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HYON-ZU LEE  
05/16/2014

VIRGINIA E KWITKOWSKI  
05/16/2014

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA Number: 206256**

**Applicant: Spectrum  
Pharmaceuticals, Inc.**

**Stamp Date: December 9, 2013**

**Drug Name: Beleodaq (belinostat) NDA Type: NME**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Section 2.5.6 Clinical Overview
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(1)
<b>DOSE</b>					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: TT20 Study Title: A Phase 1 Clinical Study of PXD101 in Patients with Advanced Cancer Sample Size: 48 Arms: Single arm trial Location in submission: Module 5.3.3.2  Study Number: TT30 Study Title: A Phase I Clinical Study of PXD101 in Patients with Advanced Hematological Neoplasia Sample Size: 16	X			

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Arms: Single arm trial Location in submission: Module 5.3.5.2				
<b>EFFICACY</b>					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?  Pivotal Study #1: PXD101-CLN-19 Study title: A Multi-center, Open-Label Trial of Belinostat in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma. Sample Size: 129 Arms: Single arm trial Location in submission: Module 5.3.5.2 Indication: Treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL).  Pivotal Study #2: None.	X			In general, two adequate and well-controlled trials are required. However, Congress amended section 505(d) to allow FDA to consider single pivotal trial and confirmatory evidence (FDAMA).
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		In the pivotal trial (CLN-19), 29% of patients were from US.
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	Orphan designation for PTCL received on 9/3/2009.
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		In the pivotal trial (CLN-19), 29% of patients were from US.
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
<b>FINANCIAL DISCLOSURE</b>					

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
38.	Has the applicant submitted the required Financial Disclosure information?	X			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes**

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

- 1) Provide the number of investigators in the CLN-19 trial who are sponsor employees (including both full-time and part-time employees).

Hyon-Zu Lee	January 22, 2014
Reviewing Medical Officer	Date

Virginia Kwitkowski	January 22, 2014
Clinical Team Leader	Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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HYON-ZU LEE  
01/22/2014

VIRGINIA E KWITKOWSKI  
01/22/2014