CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206256Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA (SDN)	206256 (1)
Submission Date(s):	12/09/2013
Brand Name:	Beleodaq
Generic Name:	Belinostat
Submission Type; Code:	NME NDA; Standard review
PUDFA Date:	8/9/2014
Sponsor:	Spectrum Pharmaceuticals Inc
Formulation; Strength(s):	lyophilized powder, 500 mg/vial
Proposed Indication:	Relapsed or Refractory Peripheral T-Cell Lymphoma(PTCL)
OND Division:	DHP
OCP Division:	DCP5

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1 EXECUTIVE SUMMARY

Beleodaq® (belinostat) is a pan-histone deacetylase (HDAC) inhibitor proposed for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). The proposed dose is 1000 mg/m^2 administered over 30 minutes by intravenous (IV) infusion on days 1-5 of a 21-day cycle.

Based on the data submitted in this NDA, it is reasonable to label belinostat for PTCL at the proposed dose of 1000 mg/m^2. The 1000 mg/m^2 dose given on days 1 to 5 of a 21-day cycle was determined to be the MTD. However, using the submitted data, we could not determine whether the proposed dose of 1000 mg/m^2 is the optimal dose. The dose/exposure response properties of belinostat were assessed for effectiveness, safety, and pharmacodynamic (PD) endpoints using data from two phase 1 dose escalation trials and one phase 2 pivotal trial. Dose-response analyses for effectiveness and safety using dose escalation data showed that increasing the dose of belinostat from 150 to 1200 mg/m^2 increased the rates of Grade 3 or worse (Grade 3+) adverse events while the rate of clinical response (effectiveness) stayed flat across all studied doses. On the other hand, the levels of histone acetylation (PD marker for HDAC activity), increased with dose and appeared to plateau at doses of 900 mg/m^2 and above, providing supporting evidence for the adequacy of 1000 mg/m^2 dose. It is worth noting that the relationship with the PD biomarker and the clinical outcome is not known. In the phase 2 pivotal trial exposure-response relationships for efficacy or safety were not evident at the proposed dose of 1000 mg/m^2.

The sponsor did not conduct a human ADME study, but human urine excretion study indicated that 40% of the administered drug was excreted in the urine primarily metabolites. Mass balance (ADME) and liver impairment studies are currently ongoing.

Belinostat undergoes extensive metabolism in the liver, primarily by UGT1A1. As such, strong inhibitors of UGT1A1 are expected to increase systemic exposure to belinostat. In addition, genetic variation in UGT1A1 may influence belinostat metabolism, and this possibility is supported by a recent article by Wang et al. (PMID: 23382909). Since the 1000 mg/m^2 recommended dose is also the MTD of belinostat, factors that increase systemic exposure to belinostat could lead to intolerable adverse events.

The sponsor will be asked to submit all of their ongoing trials as post marketing requirements (see Section 1.2). In addition, the sponsor will be asked to evaluate the influence of UGT1A1 inhibitors, UGT1A1 polymorphism, and renal impairment on the PK and safety of belinostat in patients with cancer.

1.1 Recommendation

This NDA is acceptable from a clinical pharmacology perspective.

Decision	Acceptable to OCP?			Comment
Overall	Yes ☒	No ☐	NA ☐	
Evidence of Effectiveness†	Yes ☒	No ☐	NA ☐	1 positive registration trial
Proposed dose for general population	Yes ☒	No ☐	NA ☐	1000 mg/m^2 IV daily x 5, q21 days
Proposed dose selection for others	Yes ☒	No ☐	NA ☐	
Pivotal BE	Yes ☐	No ☐	NA ☒	IV administration
Labeling	Yes ☒	No ☐	NA ☐	

†Clinical Pharmacology perspective; although dose-response was not apparent, belinostat has similar response rates as currently marketed drugs with favorable safety profile.

1.2 Post Marketing Requirements

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

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1.3 Summary of Important Clinical Pharmacology Findings

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

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

In vitro, belinostat is primarily (≈ 80-90%) metabolized by UGT1A1 and to a lesser extent by CYP2A6, CYP2C9, and CYP3A4. However, the exact contribution of each enzyme in the biotransformation of belinostat has not been determined.

The sponsor did not conduct human drug-drug interaction studies to evaluate the influence of liver enzyme inhibitors of UGT1A1, CYP2A6, CYP2C9, and CYP3A4 on the systemic exposure of belinostat. Available data indicate UGT1A1 inhibitors will likely produce meaningful belinostat exposure increases that could lead to dose limiting toxicities. Since the proposed starting dose (1000 mg/m^2) is also the MTD and 3 out of 5 patients treated with 1200 mg/m^2 developed dose limiting toxicities (including grade 3 fatigue, atrial fibrillation, and diarrhea), even modest exposure increases due to a DDI could lead to dose limiting toxicities.

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

In vitro, belinostat inhibited CYP2C8 and 2C9. A human PK study was conducted in patients following the administration of the CYP2C9 substrate warfarin in the absence and presence of belinostat. The exposure of S-warfarin was not increased to a meaningful extent.

The sponsor did not conduct a human ADME study to determine the excretion routes of belinostat. Limited data suggest that 40% of the administered dose was excreted in urine, mostly in the form of metabolites. Since the renally excreted metabolite, belinostat glucuronide, is an active metabolite with cell killing activities, very high accumulation of this metabolite in patients with renal impairment may produce non-specific adverse events. The sponsor stated that human mass balance and hepatic impairment studies are ongoing. A post-marketing trial in patients with renal impairment will be requested.

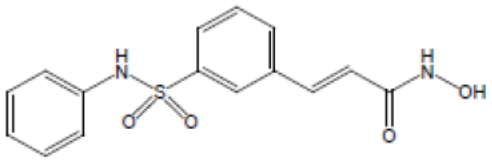
2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Belinostat has the following physical and chemical characteristics:

- Established name: belinostat
- Molecular Formula: C15H14N2O4S
- Molecular Weight: 318.35 g/mol
- Chemical Name (CAS):(2E)-*N*-hydroxy-3-[3-(phenylsulfamoyl)phenyl]prop-2-enamide
- Structural formula:



Belinostat is supplied as a sterile lyophilized yellow solid containing belinostat and L-Arginine, USP.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Belinostat is a pan-histone deacetylase (HDAC) inhibitor. Histone deacetylase enzymes catalyze the removal of acetyl groups from the lysine residues of histones (and non-histone proteins such as transcription factors). Histone deacetylation leads to chromatin compacting and the repression of gene transcription. In some cancer cells, there is aberrant expression of HDAC enzymes. Belinostat inhibits the enzymatic activity of histone deacetylases (b) (4) (Class I) (b) (4) (Class II) (b) (4) (Class 1V) (b) (4)

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed dose of belinostat is 1000 mg/m^2 administered over 30 minutes by intravenous (IV) infusion on days 1-5 of a 21-day cycle. Cycles can be repeated every 21 days until disease progression or unacceptable toxicity.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Several clinical trials were conducted in cancer patients to support the PTCL indication at the proposed dose (**Table 1**). Two dose escalation trials (TT20 and TT30) were used to assess dose limiting toxicities and clinical activities of belinostat. These two studies assessed the dose-response properties of belinostat in two different cancer populations:

- TT20 evaluated belinostat doses of 150, 300, 600, 900, 1000, 1200 mg/m^2 given as a 30-min IV infusion on day 1 to 5 of a 21-day treatment cycle in patients with advanced solid tumors
- TT30 evaluated belinostat doses of 600, 900 and 1000 mg/m^2 given as a 30-min IV infusion on day 1 to 5 of a 21-day treatment cycle in patients with advanced hematological malignancies

To demonstrate clinical efficacy, the sponsor conducted an open-label, single-arm, multicenter phase 2 trial (CLN-19) in 129 refractory peripheral T-cell lymphoma (PTCL) patients. Belinostat at 1000 mg/m^2 was administered as 30-minute intravenous infusion on days 1 to 5 of a 21-day treatment cycle. Patients received treatment until disease progression or death.

Table 1. Clinical Pharmacology and Clinical trials conducted to support marketing approval of Belinostat

Study No (N)	Type of Study	Dosing Regimen Evaluated	PK Subset
TT20 (46)	Phase 1, dose escalation in patients with refractory solid tumors	150, 300, 600, 900, 1000, 1200 mg/m² 30-min IV, Day 1-5 (q21d)	41
TT30 (16)	Phase 1, dose escalation in patients with refractory hematologic malignancies	600, 900 and 1000,mg/m² 30-min IV, Day 1-5 (q21d)	-
CLN-9 (121)	Phase 1 dose escalation trial in patients with refractory hematologic malignancies	250-500 mg/day PO continuous 500-1250 mg/day PO Days 1-14 q21d 1000-2000 mg/day PO Days 1-5 q21 days 750-2000 mg/day PO Day 1-14 q21d	89
CLN-19 (129) (Pivotal trial)	Phase 2, Open label, single-arm train in patients with Relapsed or refractory Peripheral T-cell Lymphoma (PTCL)	1000 mg/m² 30-min IV, Day 1-5 q21 days	123
CLN-20 (27)	Phase 1 DDI study vs. Warfarin.	1000 mg/m² 30- min IV, Day 1-5	17
CLN-6 (53)	Phase 2 study in patients with recurrent or refractory cutaneous and PTCL	1000 mg/m² 30-min IV, Day 1-5 q21 days	-

The sponsor also conducted a population PK analysis using data from seven studies as described in **Table 2** below. The sponsor collected belinostat plasma concentrations data following single and multiple doses of belinostat.

Table 2. Trials contributing to population pharmacokinetics

Study (Phase)	Dosing Regimen	PK Sampling	PK Samples (N)
CLN-19 (2)	1000 mg/m² 30-min IV, Days 1-5 q21 days	C1D1(EOI, 2, and 4 post dose); C1D4 (EOI, 2-6 hours post dose)	123
TT20 (1)	150 to 1200 mg/m^2 30-min IV, Days 1-5 q21 days	C1D1: predose,during infusion, end of infusion (EOI), 0 – 6 hours post dose); C1D5: Predose	41
301-G (2)	900 to 1000 mg/m^2 30-min IV, Days 1-5 q21 days	C1D1 & C3D2: predose, during infusion, EOI, 0 – 6 hours post dose; C1D2, C1D3, C3D3, C3D4: Predose	6
CLN-4 (1)	300 to 1000 mg/m^2 30-min IV, Days 1-5 q21 days	C1D1: predose, EOI, 0 - 6 hours post dose C1D2, C1D3, C1D4: Predose	22
CLN-8 (1/2)	600 to 1000 mg/m^2 30-min IV, Days 1-5 q21 days	C1D1: predose, EOI, 0 - 6 hours post dose C1D2, C1D3, C1D4: Predose	22
CLN-15 (1)	1000 mg/m² 30-min IV, Days 1-5 q21 days	C1D1: predose, EOI, 0 - 6 hours post dose	18
CLN-20 (1)	1000 mg/m² 30-min IV, Days 1-5 q21 days	C1D1, C1D2, C1D3: Predose C1D4: predose, during infusion, EOI, 0 – 24 hours post dose);	17

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

Efficacy Endpoint

In the pivotal phase 2 study, the primary endpoint was ORR, as determined by an independent review committee (IRC), in the response evaluable population. The study was to be deemed successful if the 95% CI for ORR contained an ORR of 20%. A sample size of at least 100 patients was needed to detect a 20% response rate. The study enrolled 129 patients from 119 sites in 17 countries across the US, Canada, Europe, Russia, Israel, and South Africa from May 2009 to August 2011. Median age was 63.0 years (range: 29, 81 years). Mean weight was 75 kg (range: 40, 149 kg). In patients that received at least one belinostat dose and had a confirmed diagnosis of PTCL (N=120), the IRC-determined ORR was 25.8% (95% CI: 18.3, 34.6)]. There were 31 responders (13 CR and 18 PR) as detailed in **Table 3**.

Table 3. Summary of belinostat Efficacy (sponsor's analysis)

Patient Population	Efficacy Analysis Dataset (N=120) n (%)
Objective Response Rate	
Objective Response Rate (CR+PR)	31 (25.8)
95% CI*	18.3 - 34.6
Complete Response	13 (10.8)
95% CI*	5.9 - 17.8
Best Tumor Response	
Complete Response	13 (10.8)
Partial Response	18 (15.0)
Stable Disease	18 (15.0)
Progressive Disease	47 (39.2)
Not Evaluable	24 (20)

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

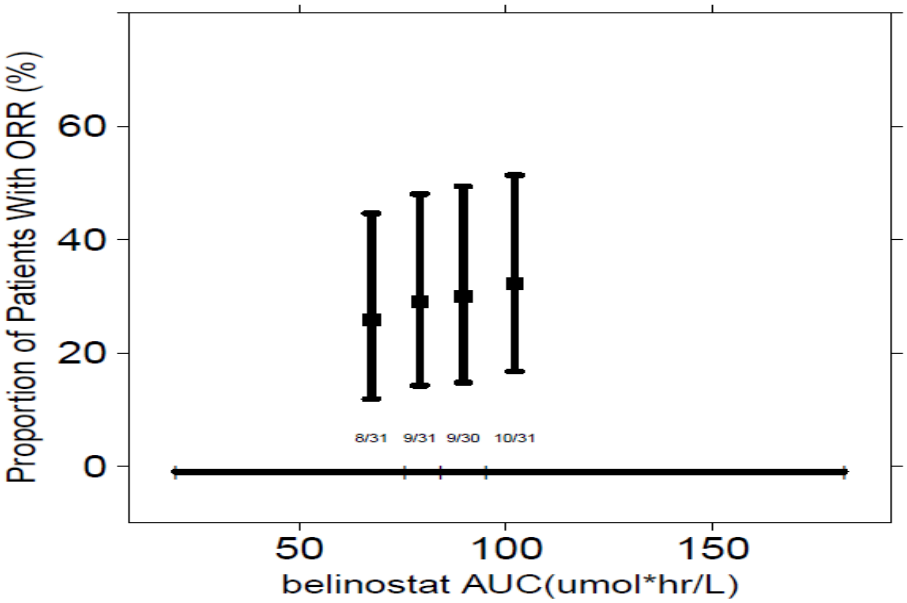
Yes. The sponsor collected PK samples from 7 studies (see **Table 2**).

2.2.4 Exposure-Response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

Exposure-response relationships were not identified for belinostat efficacy based on available data. Area under the curve (AUC) estimates that were provided by the sponsor were used for exposure-efficacy and exposure-safety analyses. Exposure-response analyses were performed to determine whether AUC influenced the primary efficacy endpoint, ORR, following belinostat doses of 1000 mg/m^2 daily on days 1-5 of a 21-day treatment cycle. **Figure 1** below shows there is a slight trend of increasing ORR with increasing AUC however this was not significantly meaningful.

Figure 1. Proportion of objective response rate (ORR) is not influenced by AUC.

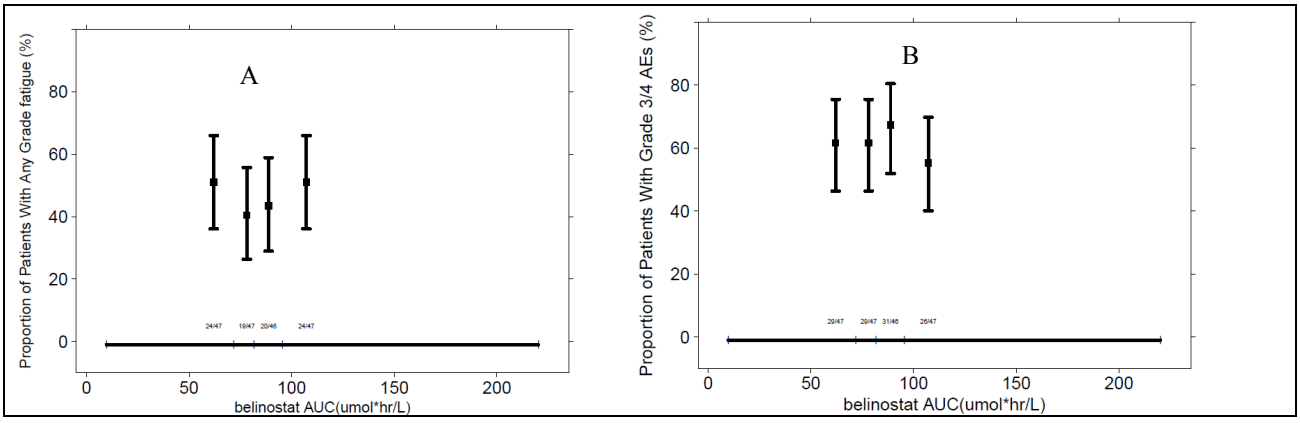


2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

In regards to safety, exposure-response relationships were not identified for belinostat based on the available data. Safety and PK data were available from 187 patients with cancer who received belinostat as monotherapy in studies 301G, CLN19, CLN20, and TT2. During the phase 2 clinical trial, seven patients (5.4%), had grade 3 or more (Grade 3+) fatigue and 41 patients (31.8%) had Grade 1+ fatigue. Since there were only seven patients with Grade 3+

fatigue, exposure-response analysis was conducted using data from patients with Grade 1+ fatigue. Although the data are limited, the proportion of patients with Grade 1+ fatigue does not increase with increasing belinostat AUC (**Figure 2A**). A similar analysis using all patients with overall Grade 3+ adverse events showed that the rates of Grade 3+ adverse events do not increase with increasing belinostat AUC (**Figure 2B**). Since the frequencies of specific Grade 3+ adverse events were relatively low during the phase 2 trial, occurring at rates of < 11%, exposure-response analyses for specific Grade 3+ AE was deemed unreliable.

Figure 2. Proportion of patients with Grade 1+ fatigue (A) and overall Grade 3+ adverse events (B) do not increase with increasing AUC.



2.2.4.3 *Does this drug prolong the QT or QTc interval?* (You must answer this question, unless this is addressed in the question above.)

The FDA's Interdisciplinary Review Team (IRT) for QT Studies evaluated the QTc data from 529 patients and concluded that belinostat is unlikely to cause QTc prolongations. The IRT review is available in DARRTS (J Liu, 04/07/2014).

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

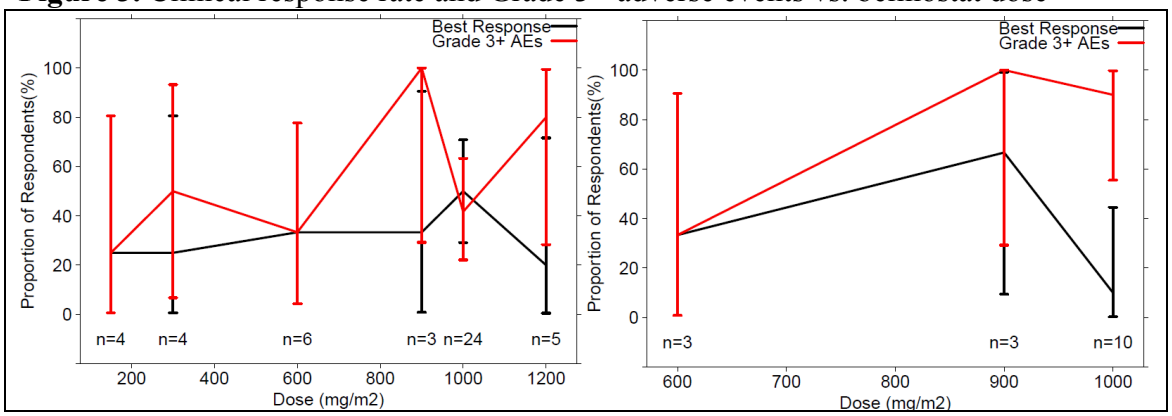
Dose response analyses using safety and clinical response data from the two dose escalation trials showed increasing the dose of belinostat increased the rates Grade 3+ adverse events while clinical response remained flat across all dose levels (**Figure 3**). In the draft labeling, the proposed dosing regimen is 1000 mg/m^2 given on days 1 to 5 of a 21-day treatment cycle. The proposed dosing regimen was selected based on results of two phase 1 dose escalation trials:

- Study TT20 (n=48) evaluated doses of 300 to 1200 mg/m^2 in patients with solid tumors
- Study TT30 (n=17) evaluated doses of 600 to 1200 mg/m^2 in patients with hematological malignancies

Both studies used the same dosing schedule (daily x5 q21 days). In the dose escalation trials, all of the clinical responses were stable disease (there were no partial or complete responders) while the safety endpoints were Grade 3+ adverse events. The lack of dose response trends over the studied dose range could be because of sample size limitations or the drug is already at the

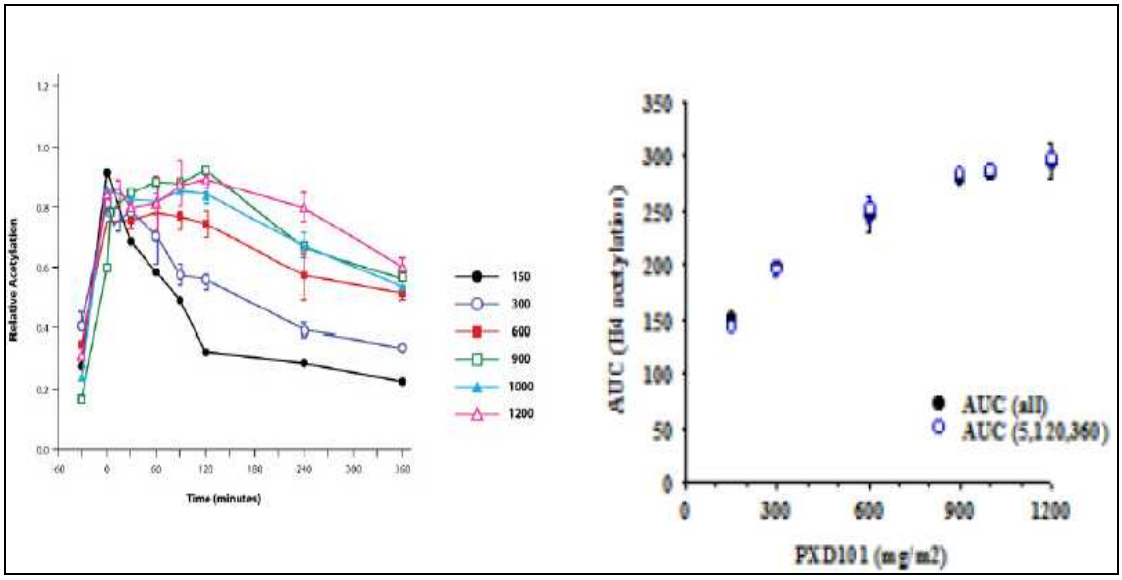
plateau part of the dose response curve (i.e., potentially efficacious lower doses were not evaluated, or the drug lacks selectivity for therapeutic and toxic activities).

Figure 3. Clinical response rate and Grade 3+ adverse events vs. belinostat dose



Study TT20 also assessed the pharmacodynamic (PD) properties of belinostat by characterizing the acetylation levels of the histones. Since belinostat inhibits the enzyme HDAC, the presence of belinostat is expected to increase the levels of histone acetylation. The PD responses measured in subjects enrolled in study TT20 showed dose-dependent increase of acetylation in peripheral blood mononuclear cells (PBMC) (**Figure 4**). Dose-dependent acetylation was observed after the first dose and appeared to plateau approximately at doses of 900 mg/m^2 and above. Although no analysis was conducted to correlate levels of acetylation with clinical activity, the PD data provide supportive evidence for the proposed 1000 mg/m^2 dose.

Figure 4. Maximal histone acetylation observed at 900 mg/m^2

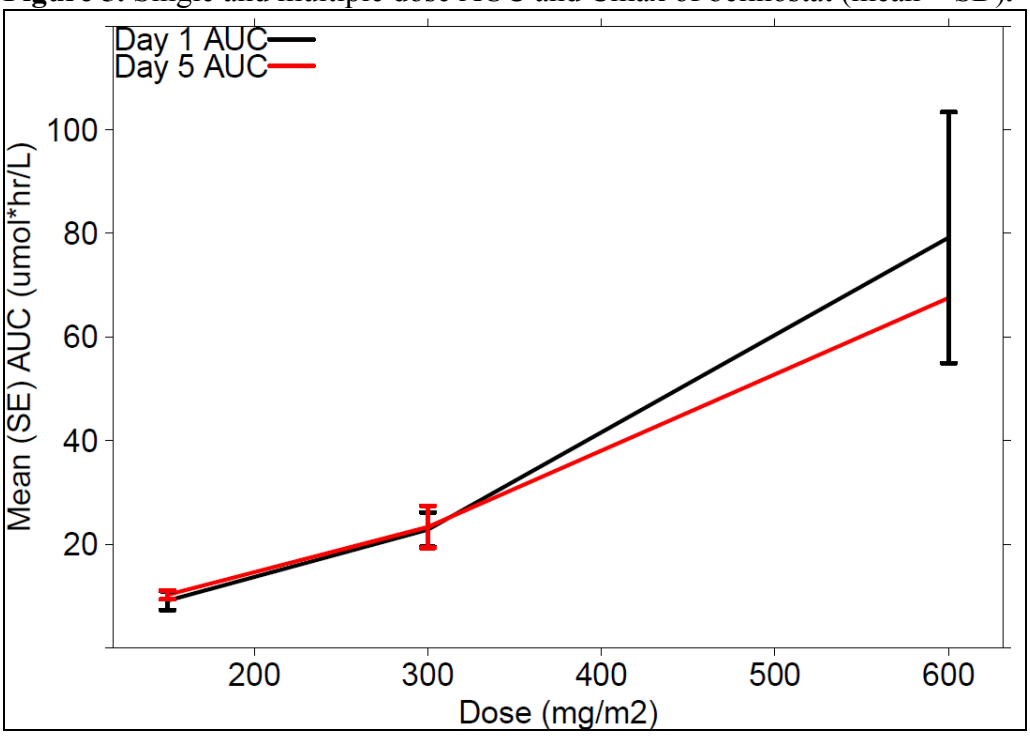


2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose PK parameters?

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

Figure 5. Single and multiple dose AUC and Cmax of belinostat (mean ± SD).



2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

All of the submitted PK data were collected in patients with cancer. Therefore, PK comparison between healthy volunteers and patients cannot be conducted.

2.2.5.3 What are the characteristics of drug absorption?

Belinostat is formulated for intravenous administration.

2.2.5.4 What are the characteristics of drug distribution?

The plasma protein binding (PPB) characteristics of belinostat were evaluated in two in vitro studies ((b) (4) & Topotarget studies) in human plasma. The protein binding results in human plasma were 93.4% in the (b) (4) study and 94.1% in the Topotarget study. The average level

of protein biding was determined to be about 94%, which is considered a moderate level of protein binding. This level of protein binding is consistent with mean steady-state volume of distribution (Vss) of 11 to 15 L as determined using non-compartmental analysis in study CLN4.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

The sponsor did not conduct a human ADME study. The sponsor conducted excretion study in dogs following IV doses of 25 and 50 mg/kg (**Table 4**). The mean overall recovery of radioactivity following IV infusion in dogs was 95.94% of the administered dose over 0-168 hours post-dose. The primary route of excretion was via the feces, which accounted for 63.73% of the dose. Urinary recovery was 30%, with a further 1.65% recovered in cage washings, probably from urine that had dried onto the internal surfaces of the cages (**Table 4**). A rat study showed urinary and fecal routes accounted for 53% and 39% of the administered dose.

Table 4. Excretion routes of belinostat in dogs after single IV and oral doses of belinostat

	Mean Recovery (% Administered Dose)			
	Intravenous (25 mg/kg)		Oral (50 mg/kg)	
Sample	Males	Females	Males	Females
Urine	28.30	31.69	21.69	17.54
Feces	64.85	62.60	71.94	76.43
Cage wash	2.058	1.239	2.104	1.068
Cage debris	0.626	0.408	0.220	0.084
Residual water	NS	NS	0.019	ND
Swabs	0.030	0.080	0.147	0.106
Total	95.86	96.02	96.12	95.22

Human urinary excretion of belinostat and its metabolites were also measured in study CLN20 following treatment with 1000 mg/m^2 doses of belinostat. The urinary excretion assessment indicated less than 1% of unchanged belinostat was excreted in the urine. Belinostat glucuronide and 3-ASBA had the highest fractions of the belinostat dose excreted in urine, representing 30.5% and 4.6% of the administered dose, respectively (**Table 5**). In total, it appears about 40% of the administered dose is excreted in urine, primarily in the form of metabolites.

Table 5. Urine excretion profiles of belinostat and its metabolites

Metabolite	N	Percent of Belinostat Dose	
		Mean	SD
Belinostat	5	0.926	0.428
Belinostat Glucuronide	5	30.5	4.36
Methyl Belinostat	5	0.632	0.142
Belinostat Amide	5	0.0929	0.0724
Belinostat Acid	5	0.925	0.387
3-ASBA	5	4.61	1.15

2.2.5.6 What are the characteristics of drug metabolism?

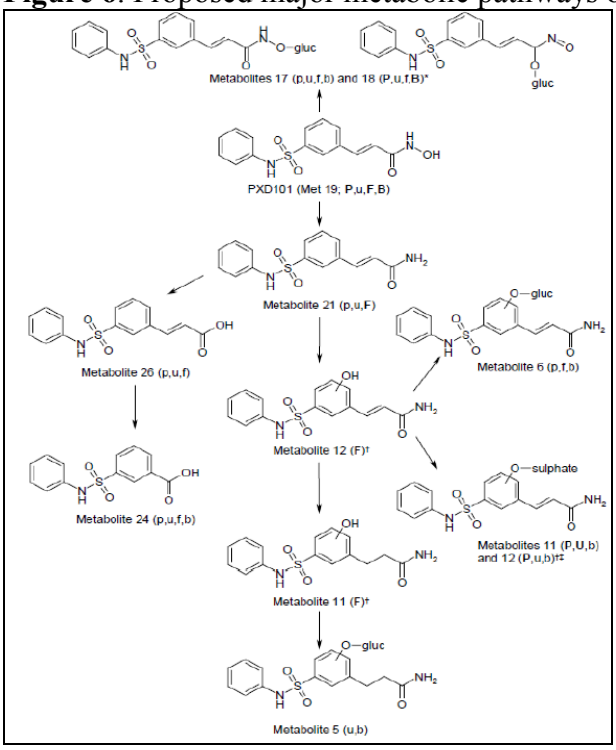
In patients with cancer who were treated with belinostat at doses of 1000 mg/m^2, five human metabolites were identified and characterized (study CLN8). The primary metabolite, belinostat glucuronide, which has 16-fold higher AUC than the parent drug, is formed primarily by

UGT1A1 enzyme (**Table 6**). The other two metabolites (belinostat amide and belinostat acid) are formed by multiple CYP P450 enzymes (**Table 6**). Using data from the rat ADME study the sponsor proposed the metabolism pathways for many of the major metabolites (**Figure 6**).

Table 6. Metabolite characteristics of belinostat metabolites

Compound (ID)	Mol weight (g/mol)	AUC inf (ng/ml*hr) (Mean)	AUC inf (uM*hr) (Mean)	Relative Exposure (Fold)	Formation Pathway
Belinostat	318	12500	39	1.0	0
Belinostat glucuronide (M18)	494	315000	638	16.2	UGT1A1
Methylated belinostat	332	15000	45	1.1	Not determined
Belinostat amide (M21)	302	11800	39	1.0	CYP2A6 (62.6%), CYP3A4 (18.4%), CYP2C9 (13.0%)
3-ASBA (M24)	277	29000	105	2.7	Not determined
Belinostat acid (M26)	303	6500	21	0.5	CYP2A6 (43.1%), CYP3A4 (20.4%), CYP2C9 (17.4%)

Figure 6. Proposed major metabolic pathways of belinostat in the rat



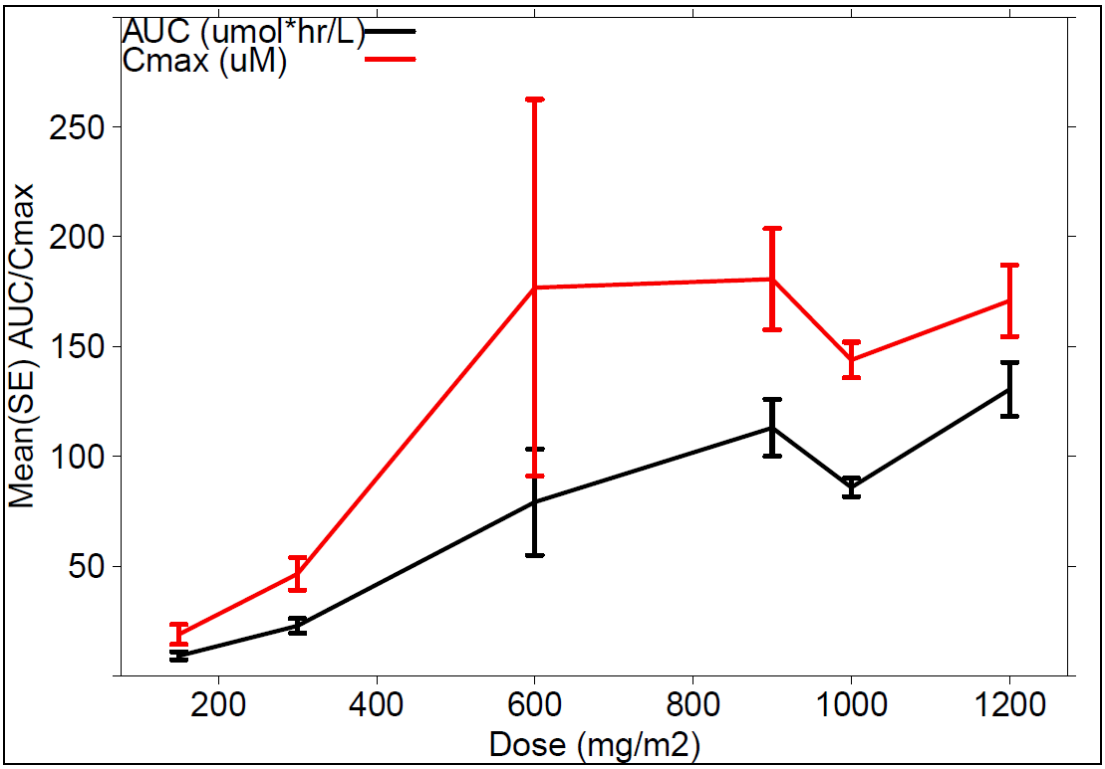
2.2.5.7 What are the characteristics of drug excretion?

Animal studies show that belinostat is rapidly converted to multiple metabolites. Those metabolites are excreted by the urine and feces. Human excretion studies were not conducted for belinostat. See section 2.2.5.5 for more detail.

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Overall, the AUC and Cmax of belinostat increase in proportion with dose. Intensive single dose plasma concentration data were collected in a dose escalation study (TT20) at doses ranging from 150 to 1200 mg/m^2. As shown in **Figure 7** below, AUC and Cmax generally increased in proportion with dose.

Figure 7. Dose-proportionality assessment of belinostat using dose escalation study data.



2.2.5.9 How do the PK parameters change with time following chronic dosing?

As described in section 2.2.5.1, the Cmax and AUC of belinostat do not change following multiple dosing. Because belinostat has very short half-life, little accumulation takes place following multiple dose administration.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Table 7 below summarizes the population PK parameter estimates and associated inter- and

intra-individual PK variability. The inter-individual variabilities for clearance (CL) and volume of distribution (V1) were 27% and 69%, respectively. Residual or intra-individual variability for log transformed belinostat concentrations was 0.349 µmol/L. Height was determined to be the main source of inter-individual variability on clearance. Height is not a physiologically plausible covariate that typically influences drug dispositions.

Table 7. Summary of belinostat PK parameter estimates

Parameter	Estimate	%RSE
CL (L/h)	69.7	3.46
V1 (L)	12.7	8.90
V2 (L)[a]	1	-
Q3 (L/h)	17.4	8.10
V3 (L)	11.9	5.59
Q4 (L/h)	1.94	8.45
V4 (L)	53.6	17.5
$Fmet_{oat}$ (L^{-1})	0.0659	4.78
CLM	0.461	5.49
HGT on CL	1.25	23.7
IIV (variances and %CV)		
IIV-CL	0.0722 (26.9)	23.0
IIV-V1	0.477 (69.1)	27.5
IIV-CLM	0.106 (32.6)	23.7
RV (log error)		
Belinostat (µmol/L)	0.349	12.7
Belinostat Glucuronide (µmol/L)	0.386	20.2

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The sponsor conducted population PK analysis using data from 249 patients who took part in seven clinical trials (**Table 8**). Population PK analysis was used to evaluate the influence of intrinsic factors on belinostat PK. Patient covariates such as age, weight, height, body surface area, creatinine clearance (CrCL), gender, ethnicity, degree of hepatic impairment (mild/moderate/severe), total bilirubin, liver enzymes, platelet, absolute neutrophil count, and potassium were used to evaluate the influence of intrinsic factors on belinostat PK (**Table 8**). Population PK analysis revealed that height influences the clearance of belinostat. Since height is a primary component of BSA calculations, the inclusion of height in the population PK model was thought to be an artifact of the BSA based dosing. Furthermore, plot of BSA vs. AUC shows consistent exposure across all sizes groups indicating that the BSA based dosing is appropriate (**Figure 8**).

Figure 8. Belinostat AUC vs. BSA

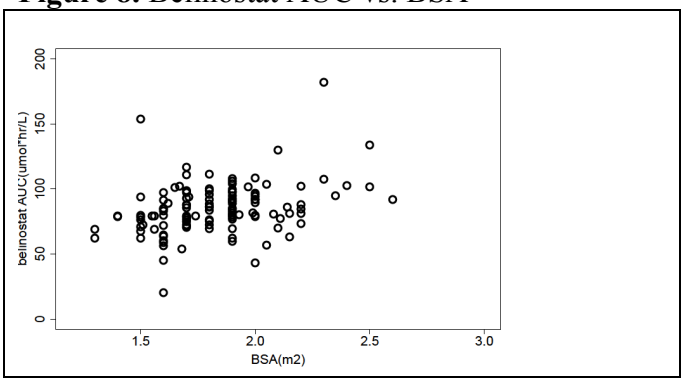


Table 8. Summary of patient characteristics that were part of the population pharmacokinetics analysis

	Continuous					
	Mean	SD	Median	Min	Max	N
Age (y)	61.2	11.0	62.0	28.0	81.0	249
Height (cm)	169	9.66	168	146	193	249
Weight, (kg)	74.6	17.5	72.0	40.0	149	249
Body Surface Area (m^2)	1.84	0.245	1.81	1.30	2.60	249
Creatinine Clearance (mL/min)	91.7	33.3	89.1	35.7	236	249
Total Bilirubin (mg/dL)	0.583	0.361	0.526	0.100	3.02	249
Alanine Aminotransferase (U/L)	30.0	25.6	22.0	4.00	168	249
Aspartate Aminotransferase (U/L)	31.9	24.4	25.0	5.00	163	249
Absolute Neutrophil Count (1.0^9/L)	5.37	5.14	4.22	0.000	62.0	249
Platelet (1.0^9/L)	222	121	209	4.00	579	249
Potassium (mmol/dL)	4.07	0.440	4.00	2.80	6.30	249
Prothrombin Intl. Normalized Ratio[a]	1.08	0.258	1.00	0.700	2.90	186
Activated Partial Thromboplastin Time (s)[b]	30.8	8.31	29.2	0.700	79.0	227
	Categorical					
Sex, n (%)	Male, 142 (57.0)					
	Female, 107 (43.0)					
Race, n (%)[c]	White, 230 (92.4)					
	Black, 7 (2.81)					
	Asian, 3 (1.20)					
	Latin,5 (2.01)					
	Other, 4 (1.61)					
Hepatic dysfunction	Normal, 186 (74.7)					
	Mild, 59 (23.7)					
	Moderate, 2 (0.803)					
	Severe, 1 (0.402)					
	Missing , 1 (0.402)					
CM[d]	Non_UGT1A1 Inhibitor, 249 (100)					

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups?

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

2.3.2.1 Elderly

In the population PK analysis, age (range: 28 to 81) was not shown to influence the disposition of belinostat.

2.3.2.2 Pediatric patients. Also, what is the status of pediatric studies and/or any pediatric plan for study?

The applicant has not conducted clinical studies with belinostat in pediatric patients and has not shared their pediatric development program. Because belinostat was granted orphan designation on 3/09/2009 and orphan drugs are not required to comply with PREA requirements, the sponsor is not required to provide pediatric development plans.

2.3.2.3 Gender

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

2.3.2.4 Race, in particular differences in exposure and/or response in Caucasians, African-Americans, and/or Asians

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

2.3.2.5 Renal impairment

The sponsor did not conduct a renal impairment study.

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

2.3.2.6 Hepatic impairment

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

2.3.2.7 Pharmacogenetics

Belinostat is metabolized primarily by UGT1A1 (80 - 90%), a known polymorphic enzyme with allelic variants that influence enzymatic activity. UGT1A1 alleles that reduce enzyme activity are expected to decrease the metabolism of belinostat, thereby increasing belinostat exposure. The applicant cited a literature reference (PMID: 23382909) that showed in vitro formation of belinostat glucuronide was reduced by 26% and 53% in subjects heterozygous and homozygous for UGT1A1*28 (a reduced function allele), respectively. Among Caucasians, approximately

40% and 10% of individuals are heterozygous and homozygous for UGT1A1*28, respectively (PMID: 18518849). However, the applicant did not conduct any clinical studies to assess the influence of UGT1A1*28 or other known reduced function alleles on the systemic exposure of belinostat. The FDA PBPK reviewer conducted physiologically-based pharmacokinetic modeling and simulations to assess the impact of UGT1A1 polymorphism on the exposure of belinostat. The simulations suggest that subjects homozygous for UGT1A1*28 may have 20% higher belinostat AUC than subjects homozygous for UGT1A1*1.

2.3.2.8 What pregnancy and lactation use information is there in the application?

The effect of belinostat in lactating and pregnant women has not been evaluated. The proposed belinostat package insert states that belinostat is genotoxic and targets rapidly dividing cells, indicating that belinostat could cause fetal harm when administered to pregnant women and women should avoid pregnancy while taking belinostat. No further pregnancy and lactation information is provided in the proposed label. Pharmacology and toxicology reviewers will address pregnancy and lactation related issues in greater depth.

2.3.2.9 Other human factors that are important to understanding the drug's efficacy and safety?

There are no other known important human factors to the understanding of belinostat safety and efficacy.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

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

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

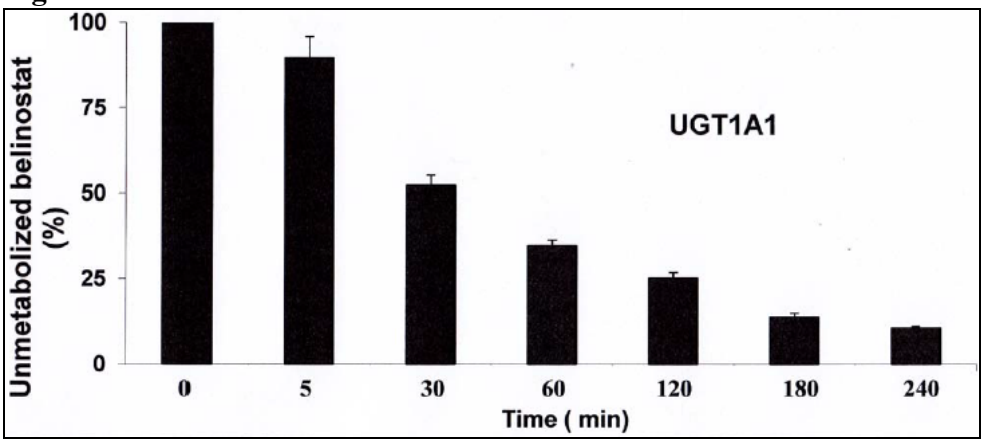
Yes, the drug is metabolized by multiple liver enzymes including UGT1A1, CYP2A6, CYP3A4, and CYP3C9 as detailed in **Table 6**. However, the sponsor did not determine the percentage contributions of each enzyme in the biotransformation of belinostat. In an vitro drug-drug interaction study, belinostat and its metabolites were shown to moderately inhibit CYP2C8 and CYP2C9. The sponsor also reported belinostat increased the enzymatic activities CYP1A2 by up to 3-fold, indicating belinostat could be a modest CYP1A2 inducer.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Yes, belinostat is metabolized by UGT1A1 and multiple CYP (CYP2A6, CYP3A4, and CYP3C9) enzymes (**Table 6).** While the primary metabolizing enzyme appears to be UGT1A1, there was no reliable quantification of the contribution of each enzyme in the biotransformation

of belinostat**.** The sponsor cited a literature reference (Wang et al, 2013) indicating that, in vitro, UGT1A1 metabolized approximately 80 to 90% of belinostat in 4 hours (**Figure 9**). However, the validity and reliability of the cited literature is uncertain since we were not able to assess and verify the design, data collection, and analysis procedures of the in vitro study. Also see section 2.3.2.7.

Figure 9. UGT1A1 mediated metabolism of belinostat in vitro



(Source**:** Wang et al. PLoS One. 2013;8(1))

In study CLN-4, the PK properties of belinostat were evaluated following the administration of belinostat alone and belinostat in combination with 5-FU at nominal doses of 1000 mg/m^2. When given in combination with 5-FU the Cmax and AUC of belinostat increased by 15 to 26% and 10 to 15%, respectively (**Table 9**). The mechanisms of 5-FU mediated exposure increases are not clear but literature reports suggest 5-FU may decrease the expression of P450 enzymes.

Table 9. Mean (SD) PK parameters of belinostat following treatment with belinostat alone and combination with 5-FU.

Dose mg/m^2	Cycle and Day	N	C_{max} (ng/mL)	$AUC_{0-\infty}$ (h•ng/mL	$t_{½}$ (h)	CL (L/h/m^2)	Vd_{ss} (L/m^2)
300	C2D1	4	15,300.0 (6,749.8)	11,277.5 (4,068.2)	1.4 (0.4)	48.3 (42.9)	24.7 (28.3)
300	C2D5	3	19,466.7 (2,914.3)	13,304.9 (644.4)	1.8 (0.9)	22.6 (1.10)	8.8 (1.5)
600	C2D1	4	23,725.0 (13,039.3)	15,087.3 (5527.4)	1.1 (0.5)	43.9 (15.8)	19.4 (11.3)
600	C2D5	4	27,125.0 (6,679.0)	16,821.0 (3,312.3)	1.2 (0.1)	36.7 (6.9)	13.2 (2.6)
1,000	C2D1	14	42,657.1 (11,281.2)	29,004.6 (9,295.3)	1.0 (0.3)	37.6 (10.9)	16.5 (4.9)
1,000	C2D5	13	49,500.0 (16,626.2)	33,295.0 (10,676.0)	1.2 (0.3)	30.1 (13.8)	13.5 (7.3)

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

CYP Enzyme Inhibition

In an in vitro study, belinostat and three of its metabolites were shown to inhibit human CYP2C8 and CYP2C9 (**Table 10**). For belinostat, the IC_{50} values for the in vitro inhibition of CYP2C8 and CYP2C9 were estimated to be 100 and 60 µM in human liver microsomes, respectively. In study TT20, the clinical Cmax of belinostat following treatment with 1000 mg/m^2 was determined to be 100 µM (32 µg/mL). Therefore, the belinostat inhibitory IC_{50}s were around Cmax. Cmax values for all of the metabolites at the clinical dose were not determined. However, the clinical DDI study using warfarin as a substrate of CYP2C9 will provide definitive information on the effect of belinostat and its metabolite on the metabolic activity of CYP2C9.

Table 10. In vitro evaluation of belinostat and metabolites as inhibitors or inducers of CYP450 and P-gp

Metabolite (Id)	Classification in Humans Exposure	CYP450 Inhibition (IC50)	CYP450 Induction	P-gp Substrate	P-gp Induction
Belinostat	Parent	CYP2C8 (100 µM) CYP2C9 (61.8 µM)	CYP1A2 (weak induction)	Likely	unlikely
Belinostat glucuronide (M18)	Major metabolite 10-fold higher than belinostat	-	nd	nd	nd
3-ASBA (M24)	Major metabolite 1.5-fold higher than belinostat	CYP2C8 (49.1 µM)	nd	nd	nd
Belinostat amide (M21)	Major metabolite Exposure like belinostat	CYP2C8 (30.8 µM) CYP2C9 (44.4 µM)	nd	nd	nd
Belinostat acid (M26)	Major metabolite 3-fold lower than belinostat	CYP2C8 (22.1 µM)	nd	nd	nd
Methyl belinostat (PX106507)	Major metabolite 3-fold lower than belinostat	CYP2C8 (13.8 µM) CYP2C9 (11.5 µM)	nd	nd	nd

CYP Enzyme Induction

As indicated in **Table 10**, belinostat was determined to be an inducer of CYP1A2. Study 2525-018 assessed whether belinostat induces select CYP (1A2, 2B6, 2C9, C19, or 3A4) enzymes using hepatocytes from three human donors. Known inducers, as identified in the FDA's DDI guidance, were used as positive controls. The study identified belinostat as a weak inducer of CYP1A2. Compared to the positive control omeprazole that showed a mean 13.6-fold induction, belinostat showed mean fold inductions of 1.2, 2.3, and 2 at concentrations of 1.5 to 150 µM (**Table 11**). Relative to omeprazole, the induction potential of belinostat is 14%. Such a relatively modest induction is unlikely to result in a clinically meaningful drug-drug interaction.

Table 11. In vitro evaluation of belinostat as an inducer of CYP1A2

	Fold Induction			
Inducer (concentration)	**Donor 1**	**Donor 2**	**Donor 3**	**Mean**
Omeprazole (30µM)	4.0	8.8	28.0	13.6
Belinostat (1.5 µM)	1.1	1.9	0.7	1.2
Belinostat (15 µM)	1.1	3.8	2.0	2.3
Belinostat (150 µM)	1.8	1.5	3.0	2.1

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

The extent to which belinostat acts as a substrate or inhibitor of P-glycoprotein (P-gp) has been assessed in a Caco-2 monolayer system by looking at net efflux ratio of belinostat in the presence and absence of inhibitors. The efflux ratio of belinostat ranged from 2.6 to 14.15 at belinostat concentrations ranges of 2 to 50 (**Table 12**). Digoxin was used as the positive control in parallel to demonstrate the validity of the experiments. The efflux ratio of belinostat was reduced by up to 72 % in the in the presence of 60 µM verapamil (**Table 12**). Comparatively, the efflux ratio of digoxin was reduced by 92% in the presence of 60 µM verapamil (**Table 12**). It is important to notice that the baseline efflux ratio for belinostat is much smaller (3 to 4) than the efflux ratio of digoxin (11 to 16), indicating that P-gp dependent transport may not be critical in the disposition of belinostat. In a separate experiment, belinostat was shown not to influence the efflux ratio of the known P-gp substrate digoxin. Furthermore, since belinostat is given by intravenous infusion, P-gp inhibitors are not likely to have clinically meaningful influence exposure to belinostat.

Table 12. Permeability and recovery of belinostat and digoxin in Caco-2 cells

Assay	Substrate (concentration)	Inhibitor (concentration)	Efflux Ratio	Efflux Ratio Reduction[a]
Caco-2, Part 1a	Belinostat (2 µM)	NA	3.11 ± 0.04	NA
	Belinostat (10 µM)	NA	2.76 ± 0.46	NA
	Belinostat (50 µM)	NA	2.60 ± 0.50	NA
Assay	**Substrate (concentration)**	**Inhibitor (concentration)**	**Efflux Ratio**	**Efflux Ratio Reduction[a]**
Caco-2, Part 1b	Belinostat (10 µM)	NA	3.38 ± 0.27	NA
Caco-2, Part 1b – repeat	Belinostat (10 µM)	NA	4.15 ± 0.12	NA
Caco-2, Part 1b	Belinostat (10 µM)	PSC883 (10 µM)	1.80 ± 0.39	48%
Caco-2, Part 1b – repeat	Belinostat (10 µM)	PSC883 (10 µM)	2.51 ± 0.43	40%
Caco-2, Part 1b	Belinostat (10 µM)	Verapamil (60 µM)	1.41 ± 0.26	58%
Caco-2, Part 1b – repeat	Belinostat (10 µM)	Verapamil (60 µM)	1.17 ± 0.22	72%
Caco-2, Part 1b	Digoxin (10 µM)	NA	16.11 ± 0.15	NA
Caco-2, Part 1b – repeat	Digoxin (10 µM)	NA	10.89 ± 0.17	NA
Caco-2, Part 1b	Digoxin (10 µM)	PSC883 (10 µM)	0.79 ± 0.11	95%
Caco-2, Part 1b – repeat	Digoxin (10 µM)	PSC883 (10 µM)	0.79 ± 0.10	93%
Caco-2, Part 1b	Digoxin (10 µM)	Verapamil (60 µM)	1.21 ± 0.18	92%
Caco-2, Part 1b – repeat	Digoxin (10 µM)	Verapamil (60 µM)	1.24 ± 0.20	89%

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

No experiments were conducted in other metabolic or transporter systems.

2.4.2.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

Belinostat will be used as a monotherapy.

2.4.2.7 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Since in vitro drug-drug interaction (DDI) studies indicated belinostat and its metabolites inhibit CYP2C9 and CYP2C8, the sponsor conducted an in vivo DDI study in patients by administrating the known CYP2C9 substrate warfarin in the absence and presence of belinostat as outlined below. Since the IC_{50}s for the inhibition of CYP2C9 and CYP2C8 were similar, in vivo evaluation of CYP2C9 will provide information regarding the magnitude of in vivo inhibition of CYP2C8. The study design of the DDI study was as follows:

- **Period 1**: Day -14 patients (n=18) received a single oral dose of warfarin at 5 mg. PK blood samples were collected on days -14 to -7.
- **Period 2:** The same patients were treated with belinostat 1000 mg/m^2 intravenously on days 1 to 5, Warfarin at 5 mg was given on day 3 two hours before the beginning of the Belinostat infusion. Belinostat PK samples were collected on days 4-6, PK samples for warfarin were collected on days 3-10.

The AUC of S-warfarin was increased by about 10% in the presence of belinostat while the Cmax of S-warfarin was reduced by the same magnitude (**Table 13**). Although warfarin has a very narrow therapeutic window, coadministration with belinostat is unlikely to produce clinically meaningful drug-drug interaction when given in combination with belinostat.

Table 13. S-Warfarin PK after administration of 5 mg warfarin alone or in combination with belinostat

Parameter (Unit)	Treatment	N	Geometric Mean	Ratio	90 % CI	
					lower	upper
AUC0-∞ (ng•h/mL)	Reference	13	8910	111.19	104.59	118.21
	Test	13	9908			
AUC0-t (ng•h/mL)	Reference	15	8046	116.96	104.65	130.73
	Test	14	9411			
Cmax (ng/mL)	Reference	18	274	89.92	79.07	102.27
	Test	15	246			

2.4.2.8 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

There is no known mechanistic basis for PD drug-drug interactions.

2.4.2.9 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

Yes. See section 1.2.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

No.

2.5 General Biopharmaceutics

Belinostat is formulated for intravenous administration. As such, solubility, permeability and dissolution issues will not influence the exposure to belinostat.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

The in vitro pharmacologic properties of belinostat and the five human belinostat metabolites were evaluated and compared in a HeLa HDAC enzyme inhibition assay, in WST proliferation assay and in clonogenic assay for cell growth. The WST and clonogenic assays were done using HeLa (cervical cancer), HCT-116 (colon cancer) and MCF-7 (Breast cancer) cell lines. In the HDAC and WST assays, the IC_{50}s for belinostat were 0.04 and 0.7 µM, while all of the metabolites had IC50s of > 100 µM for both assays. On the other hand, for the clonogenic assay, some of the metabolites showed pharmacologic activities with IC_{50}s values that were within the range of clinically relevant concentrations (**Table 14**). However, the relative potency of even the most potent metabolite (belinostat glucuronide) is still 65-fold less potent than belinostat. Due to the reduced relative potencies, no meaningful clinical activities are expected from any of the metabolites.

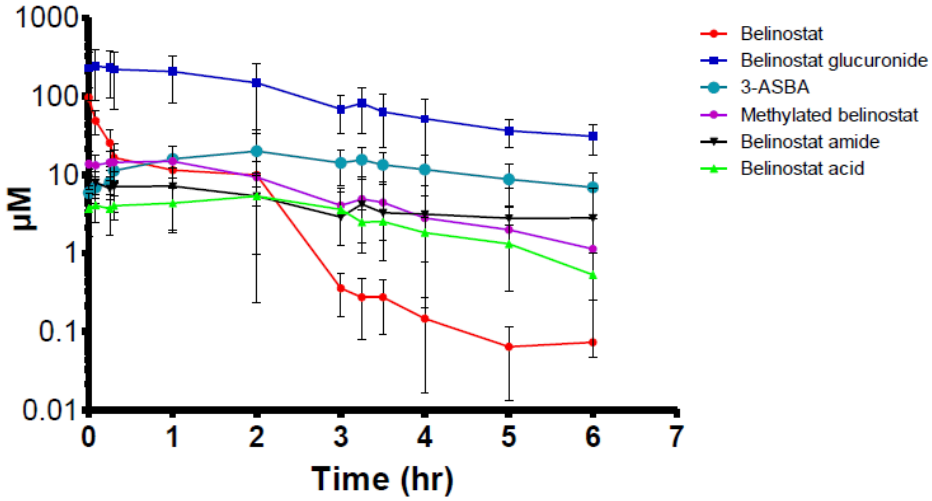
Table 14. Activity of belinostat and its metabolites in clonogenic assay.

	Metabolite exposure relative to belinostat	Clonogenic assay (cell growth) (IC_{50} µM)		
Id	Fold	HeLa	MCF-7	HCT-116
Belinostat	1.0	0.40	1.30	0.51
Belinostat glucuronide	16.2	26	>300	41
Methylated belinostat	1.1	105	54	199
Belinostat amide	1.0	97	148	224
3-ASBA	2.7	>300	>300	>300
Belinostat acid	0.5	>300	>300	>300

2.6.2 Which metabolites have been selected for analysis?

In study CLN8, plasma PK analyses were conducted for five of the metabolites listed in **Table 14** in patients with cancer following treatment with a 1000 mg/m^2 dose of belinostat. Except for belinostat acid, all of the metabolites have similar or higher exposures relative to belinostat. All of the metabolites appear to have slower clearance than the parent drug (**Figure 10**).

Figure 10. Plasma concentration profiles of belinostat and its metabolites.



2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total belinostat and metabolite plasma concentrations were measured in clinical studies.

2.6.4 What bioanalytical methods are used to assess concentrations?

A bioanalytical method was developed and validated for the determination of belinostat and its five metabolites in plasma using UPLC/MS/MS detection method. The lower limits of quantitation (LLOQ) for belinostat, methyl belinostat, belinostat amide, belinostat acid, and 3-ASBA were all 5 ng/mL. For belinostat glucuronide the LLOQ was 30 ng/mL. The calibration curves were acceptable over a range of 5-1000 ng/mL for belinostat, methyl belinostat, belinostat amide, belinostat acid, and 3-ASBA. For belinostat glucuronide the curve was acceptable over a range of 30-6000 ng/mL. Inter assay variability, expressed as relative standard deviation (%CV) were all less than 10%. For all of the analytes intra- and inter-assay results demonstrated a %CV for QC samples to be <15.0% (<20.0% at the LLOQ). The accuracy of the method was assessed by comparing the means of the measured concentrations of the QC samples (intra- and inter-assay) with their theoretical concentrations. The accuracy results of this study demonstrated calculated mean values in the range of 85.0 to 115.0% (80.0 to 120.0% at the LLOQ). It was therefore concluded that the method demonstrated acceptable accuracy in characterizing the concentrations of belinostat and its metabolites.

2.6.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies?

The ranges of the standard curves are described above in See section 2.6.4. The concentrations of the analytes are within the bounds of the standard curve ranges.

2.6.6 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

See section 2.6.5 above.

2.6.7 What are the accuracy, precision, and selectivity at these limits?

See section 2.6.4 above.

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/s/

BAHRU A HABTEMARIAM
05/13/2014

SARAH E DORFF
05/13/2014

ROSANE CHARLAB ORBACH
05/13/2014
Agree with Genomics portion.

NITIN MEHROTRA
05/14/2014

JULIE M BULLOCK
05/14/2014

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

NDA 206256 for Beleodaq™ (belinostat) was submitted on 12/06/2013.The sponsor is seeking FDA approval to use belinostat for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL).

	Information		Information
NDA/BLA Number	206256	**Brand Name**	Beleodaq
OCP Division (I, II, III, IV, V)	5	**Generic Name**	belinostat
Medical Division	DHP	**Drug Class**	Oncology
OCP Reviewer	Bahru A Habtemariam, Pharm.D	**Indication(s)**	Beleodaq is indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL
OCP Team Leader	Julie Bullock, Pharm.D	**Dosage Form**	solution
Pharmacometrics Reviewer	Bahru A. Habtemariam, Pharm.D.	**Dosing Regimen**	1000 mg/m^2 administered over 30 minutes by intravenous (IV) infusion on Days 1-5 of a 21-day cycle.
Date of Submission	12/6/2013	**Route of Administration**	Intravenous
Estimated Due Date of OCP Review	May 11, 2014	**Sponsor**	Spectrum Pharma
Medical Division Due Date	July 14, 2014	**Priority Classification**	Priority
PDUFA Due Date	August 9, 2014		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X	14	14	The sponsor submitted a total of 9 studies. One of the studies is the pivotal phase 2 study which is intended to support the proposed indication. In addition, the sponsor has submitted results of a DDI study
Tabular Listing of All Human Studies	X	14	14	
HPK Summary				
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	X			
Pharmacokinetics (e.g., Phase I) -	X	7	7	
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				

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multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	X	2	2	
Data sparse:	X	5	5	
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:			**2**	
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X	87	-	
Total Number of Studies		14	14	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	

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4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?		X		
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

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IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
Yes

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

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

Bahru A. Habtemariam, Pharm.D.	January 18, 2014
Reviewing Clinical Pharmacologist	Date
Julie Bullock, Pharm.D.	January 18, 2014
Team Leader/Supervisor	Date

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

/s/

BAHRU A HABTEMARIAM
01/26/2014

JULIE M BULLOCK
01/29/2014