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ORIGINAL ARTICLE

A phase I study to determine the pharmacokinetics and urinary excretion of belinostat and metabolites in patients with advanced solid tumors

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Abstract
Purpose Belinostat is an inhibitor of histone deacetylase enzymes, resulting in DNA repair inhibition and apoptosis. Present data are lacking to provide dosing recommendations in renal insufficiency. The purpose of this trial was to assess the pharmacokinetics (PK) of belinostat and belinostat metabolites in plasma and urine.
Methods This was a phase I, single-center, open-label, two-part study. In Part I, patients received single-agent belinostat 1000 mg/m^2. Blood and urine samples were collected at pre-specified time points to determine PK of belinostat and metabolites and their elimination in urine. In Part II, patients were permitted to continue belinostat in 21-day cycles on Days 1 through 5 until disease progression, unacceptable toxicity, or according to patient preference.
Results A total of nine patients with advanced solid tumors were treated. Median t_{max} for belinostat was observed 10 min after the start of infusion. Concentrations of belinostat rapidly declined with a $t_{1/2}$ of 2.9 h. The mean fraction of belinostat excreted unchanged in urine was 0.926 %. The metabolites belinostat glucuronide and 3-ASBA represented the largest fractions of belinostat dose excreted in urine (30.5 and 4.61 %, respectively), while renal excretion appeared to be a minor route of elimination for the parent belinostat (<1 %). The most common adverse events were nausea, fatigue, and diarrhea. One Grade 3 adverse event (constipation) was thought to be treatment related.
Conclusions Urinary elimination of parent belinostat was minimal, although a combined 36.7 % of belinostat metabolites were excreted in urine. Since these metabolites are primarily inactive, belinostat may not require dosage adjustment in renal dysfunction.

Keywords Belinostat · PXD101 · HDAC inhibitor · Pharmacokinetics · Metabolites · Elimination

Introduction

Belinostat is a potent hydroxamate-type low molecular weight histone deacetylase inhibitor of several enzymes including classes I, II, and IV [1]. HDACs are involved in epigenetic modification through regulation of acetylation of both histone and nonhistone proteins. Deacetylation of lysine residues on histones by HDACs leads to closure of chromatin structure and subsequent gene repression [2]. Loss of acetylation has been reported in cancer development including cancer initiation and progression [3]. HDAC inhibition results in a variety of cellular responses including DNA damage, cell cycle arrest, and ultimately cell apoptosis [4].

Currently, belinostat is FDA approved for the treatment of relapsed or refractory peripheral T-cell lymphoma [5]. In preclinical trials, belinostat has also shown activity in both solid and hematologic malignancies including acute myeloid leukemia [6], acute lymphoblastic leukemia [6], acute promyelocytic leukemia [7, 8], bladder cancer [9], breast cancer [10], chronic lymphocytic leukemia [11], colon cancer [10, 12, 13], head and neck cancer [14], hepatocellular cancer [15, 16], mantle cell lymphoma [17], multiple

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Guru Reddy: Conducted pharmacokinetics analysis.

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myeloma [18], non-small cell lung cancer [19], ovarian cancer [10, 20], pancreatic cancer [15, 21, 22], prostate cancer [23–25], renal cancer [26, 27], and thyroid cancer [28–30]. Clinical trials have demonstrated the potential utility of belinostat in cutaneous T-cell lymphoma [31], ovarian cancer [32], peripheral T-cell lymphoma [31, 33], and thymic epithelial tumors [34].

Previous studies have demonstrated metabolism as the main route of belinostat elimination [35]. The major metabolites of belinostat are belinostat glucuronide, 3-(anilinosulfonyl)-benzenecarboxylic acid (3-ASBA), belinostat amide, belinostat acid, and methyl belinostat [36]. These metabolites of belinostat are inactive or very weekly active in clonogenic assays.

Present data are lacking to provide specific dosing recommendations for belinostat in patients with Cockcroft–Gault estimated creatinine clearance below 40 mL/min. The purpose of this trial was to assess the pharmacokinetics of belinostat and its metabolites in plasma. In addition, urinary elimination of belinostat and belinostat metabolites was measured. Finally, we assessed progression-free survival in all patients.

Materials and methods

Patient selection

To be eligible for study inclusion, patients were required to be 18 years of age or older and have a histologically confirmed diagnosis of malignancy. Eligible patients had to have a documented Eastern Cooperative Oncology Group performance status of ≤ 2 and a 3-month or longer life expectancy. Patients could not have concurrent serious medical conditions and were required to have normal baseline hepatic and renal function (creatinine clearance ≥ 45 mL/min). Other pertinent inclusion criteria were: QTc interval ≤ 450 ms, absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, serum potassium within normal range, and fasting blood glucose $\leq 1.5 \times$ upper limit of normal.

Patients were required to demonstrate adequate recovery from prior anticancer treatments. Patients were considered ineligible if they had received anticancer therapy or underwent a major surgery within two weeks of study initiation. Our study required a minimum washout period of four weeks from any previous investigational agent. Use of a reliable contraceptive method was required for women of childbearing potential, as well as male patients with female partners capable of conceiving.

The study was approved by the Huntsman Cancer Institute Clinical Cancer Investigations Committee and the University of Utah Institutional Review Board (IRB). The study met all criteria depicted by the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. Written informed consent was obtained by all study patients in accordance with the University of Utah IRB.

Study design and treatment

Our study was a single-center, open-label, two-part study that evaluated the pharmacokinetics of belinostat and its metabolites. In Part I of the study, patients received a single dose of belinostat 1000 mg/m^2 intravenously (IV) over 30 min, and the urinary excretion of belinostat and its metabolites was recorded (Fig. 1).

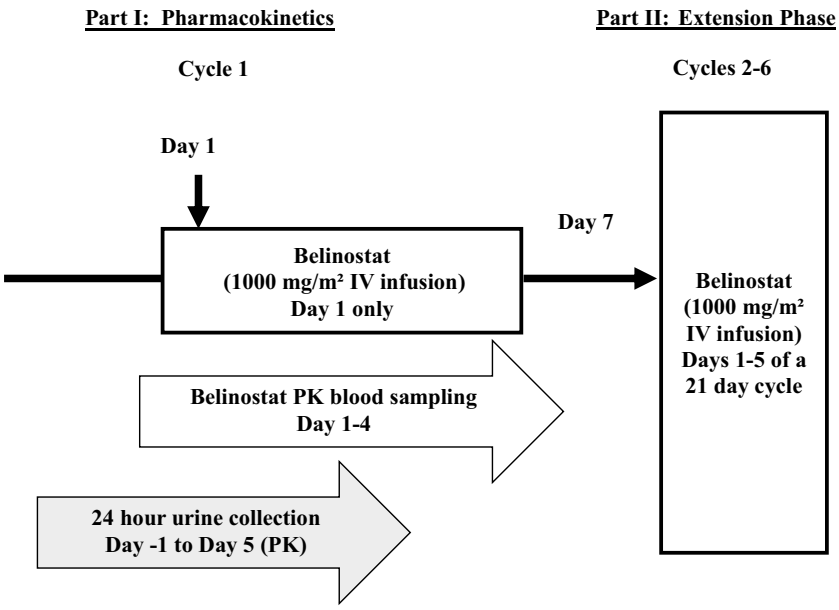

Fig. 1 Study design

In Part II (extension phase), patients were permitted to continue belinostat therapy as determined by the study investigators. As early as 7 days after the initial belinostat administration in Cycle 1, eligible patients were permitted to begin the next cycle of belinostat. In Part II, belinostat 1000 mg/m^2 or a reduced dose was administered IV in 21-day cycles on Days 1 through 5. Belinostat treatment continued until disease progression, unacceptable toxicity, or according to patient preference (Fig. 1). Study participants were scheduled for the end-of-treatment (EOT) visit 30 days after the last belinostat dose.

The dose of belinostat was recalculated for weight changes of 10 % or more. Belinostat dose reductions for hematologic adverse events (AEs) were permitted based on ANC and platelet counts measured at the start of each new cycle. Hematologic treatment parameters required patients to have an ANC $\geq 1.5 \times 10^9$/L and a platelet count $\geq 100 \times 10^9$/L prior to the start of each new cycle. Treatment cycles were delayed up to three weeks until hematologic treatment parameters were met. After the first incidence of hematologic toxicity, belinostat was restarted at full dose; however, the second incidence of hematologic toxicity necessitated a 25 % reduction in dose. Belinostat therapy was deferred for any therapy-related non-hematologic toxicity until return to Grade ≤ 1. For the first or second incidence of a Grade ≥ 3 non-hematologic toxicity, belinostat was restarted after a 25 % reduction in dose. The third incidence of a Grade ≥ 3 non-hematologic toxicity required permanent therapy discontinuation. Therapy was also deferred for a QTc prolongation of greater than 500 ms, and belinostat was restarted when the QTc interval returned to <450 ms. For the first or second occurrence of QTc interval >500 ms, belinostat was restarted after a 25 % dose reduction. Following the third incidence of QTc interval >500 ms or for Grade 4 QTc interval prolongation, belinostat was permanently discontinued.

Safety and efficacy assessments

To be included in safety and efficacy analyses, patients had to have been administered at least one or more dose(s) of belinostat.

At baseline, physical examinations were conducted and subsequently reevaluated at the start of each new cycle. In addition, 12-lead electrocardiograms (ECGs) were initially completed and later repeated on Days 1 through 5 of Cycle 1, on Day 5 of the following cycles, and at EOT visit. Hematology and chemistry laboratory tests were performed at baseline and were repeated on Days 1 and 5 of each cycle (Parts I and II) and at EOT.

The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.02 was utilized to assess therapy-associated AEs. This study established a serious adverse event (SAE) as an AE that led to any of the following: hospitalization, life-threatening event, death, significant disability, birth defect, or a major condition.

Standard of care assessments for treatment efficacy were conducted until disease progression or in the event a subsequent anticancer therapy was started. Progression-free survival (PFS) was defined as the time following the initial belinostat dose to progressive disease or death from any cause. If progressive disease was not documented, patients were censored at the most recent disease assessment. Alive patients without disease assessments after baseline were censored from the initial date of administration of belinostat therapy.

Pharmacokinetic plasma and urine sampling

Blood and urine samples were collected for PK assessments of belinostat and its metabolites. On Day 1 to Day 4, blood samples were obtained immediately prior to a single belinostat dose, 10 min after the start of infusion, 1 min prior to the end of infusion, and then 0.25, 0.5, 1, 3, 5, 7, 24, 48, and 72 h after the end of infusion. Belinostat 24-h urine sampling was performed from Day 1 to Day 5.

Statistical analysis

Up to 15 patients with advanced solid tumors were intended to be enrolled. It was estimated that six evaluable patients would be adequate for measurement of the urine concentration of belinostat and its metabolites. Formal calculations of sample size were not done. Part I and II data are combined for safety analysis.

Results

Baseline characteristics

Nine patients were eligible for study inclusion and received belinostat therapy during Part I of the study. In Part II, six patients continued belinostat therapy. Baseline patient characteristics are listed in Table 1. Multiple tumor types were included; however, urothelial carcinoma was the most common ($n = 6$, 66.7 %). Seven patients (77.8 %) received ≥ 2 prior chemotherapy regimens. Platinum-based chemotherapy was the most common type of prior chemotherapy.

Pharmacokinetics

PK data for belinostat and its metabolites are listed in Table 2. Median t_{max} for belinostat in the six patients

Table 1 Baseline characteristics

Characteristic	Number of patients (%) $n = 9$
Gender	
Male	5 (55.6)
Female	4 (44.4)
Race	
Caucasian	9 (100.0)
Age (years)	
Median (range)	74 (38, 79)
ECOG performance status	
0	3 (33.3)
1	5 (55.6)
2	1 (11.1)
Cancer diagnosis	
Prostate adenocarcinoma	1 (11.1)
Thymus	1 (11.1)
Urothelial carcinoma	6 (66.7)
Uterine leiomyosarcoma	1 (11.1)
Prior therapy	
Radiation therapy	1 (11.1)
Systemic therapy	8 (88.9)

n number of patients, *ECOG* Eastern Cooperative Oncology Group

with evaluable data was observed approximately 10 min after the start of infusion. Belinostat concentrations rapidly fell with a $t_{1/2}$ of 2.9 h (Fig. 2). The mean fraction of the dose excreted in urine as unchanged parent drug was 0.926 %.

Concentration–time profiles for each belinostat metabolite are shown in Figs. 3, 4, 5, 6, and 7. Methyl belinostat was detected in plasma approximately 40 min post-infusion and declined quickly with a mean $t_{1/2}$ of 1.88 h; the mean fraction of the dose excreted as methyl belinostat in urine was 0.623 %. Belinostat amide was rapidly detected in plasma approximately 15 min post-infusion and declined rapidly with a mean $t_{1/2}$ of 9.47 h; the mean fraction of the dose excreted as belinostat amide in urine was 0.0929 %. Belinostat acid appeared rapidly in plasma, approximately 1 h post-infusion, and fell rapidly with a mean $t_{1/2}$ value of 6.98 h; the mean fraction of the dose excreted as belinostat acid in urine was 0.925 %. Belinostat glucuronide was rapidly detected in plasma approximately 15 min post-infusion and fell rapidly with a mean $t_{1/2}$ of 5.57 h; the mean fraction of the dose excreted as belinostat glucuronide in urine was 30.5 %. 3-ASBA was detected in plasma approximately 3 h post-infusion and fell rapidly with a mean $t_{1/2}$ of 8.50 h; the mean fraction of the dose excreted as 3-ASBA in urine was 4.61 %.

AUC values for belinostat amide were similar to those observed for belinostat. Methylated belinostat and belinostat acid had approximately threefold lower AUC compared with belinostat, and the metabolites 3-ASBA and belinostat glucuronide had approximately twofold and 11-fold higher AUC values, respectively, compared with belinostat.

Safety and tolerability

Belinostat therapy was well tolerated. One patient (11.1 %) withdrew from further belinostat therapy due to an AE (Grade 2 fatigue). Six patients (66.7 %) stopped therapy due to disease progression. Two patients (22.2 %) discontinued treatment at the investigator's discretion. Two patients (22.2 %) received one dose reduction by 25 %, and two patients (22.2 %) experienced a delay in the start of a cycle by more than 7 days.

Treatment-related AEs are listed in Table 3. The majority of therapy-related AEs were nausea ($n = 7$, 77.8 %), fatigue ($n = 6$, 66.7 %), and diarrhea ($n = 4$, 44.4 %). The majority of AEs were Grades 1 or 2. There was one Grade 3 therapy-related AE (constipation). Two patients experienced SAEs, none of which were considered therapy-related by the study investigator.

Table 2 Pharmacokinetics of belinostat and metabolites in plasma

PK parameters (units)	Belinostat $n = 6$	Belinostat glucuronide $n = 6$	3-ASBA $n = 6$	Belinostat amide $n = 6$	Belinostat acid $n = 6$	Methyl belinostat $n = 6$
C_{max} (μM)	131 ± 31.6	263 ± 23.5	17.8 ± 7.74	7.65 ± 1.81	7.07 ± 2.01	7.98 ± 1.96
t^{a}_{max} (h)	0.483 (0.483, 0.683)	0.75 (0.75, 1.2)	3.5 (1.72, 3.58)	0.75 (0.75, 1.72)	1.54 (1.48, 3.5)	1.14 (0.75, 1.5)
$t_{1/2}$ (h)	2.9 ± 4.51	5.57 ± 1.81	8.5 ± 1.50	9.47 ± 5.21	6.98 ± 4.69	1.88 ± 1.26
AUC_{0-t} (μM h)	86.8 ± 21.7	987 ± 315	153 ± 67.3	80.4 ± 108	33.2 ± 12.1	25 ± 9.05

3-ASBA 3-(anilinosulfonyl)-benzenecarboxylic acid, C_{max} maximum plasma concentration, t_{max} time to C_{max}, AUC_{0-t} area under the concentration time curve from time of administration to the last measurable concentration, *PK* pharmacokinetic

[a] Median (minimum, maximum). Data are expressed as mean (standard deviation) unless noted otherwise

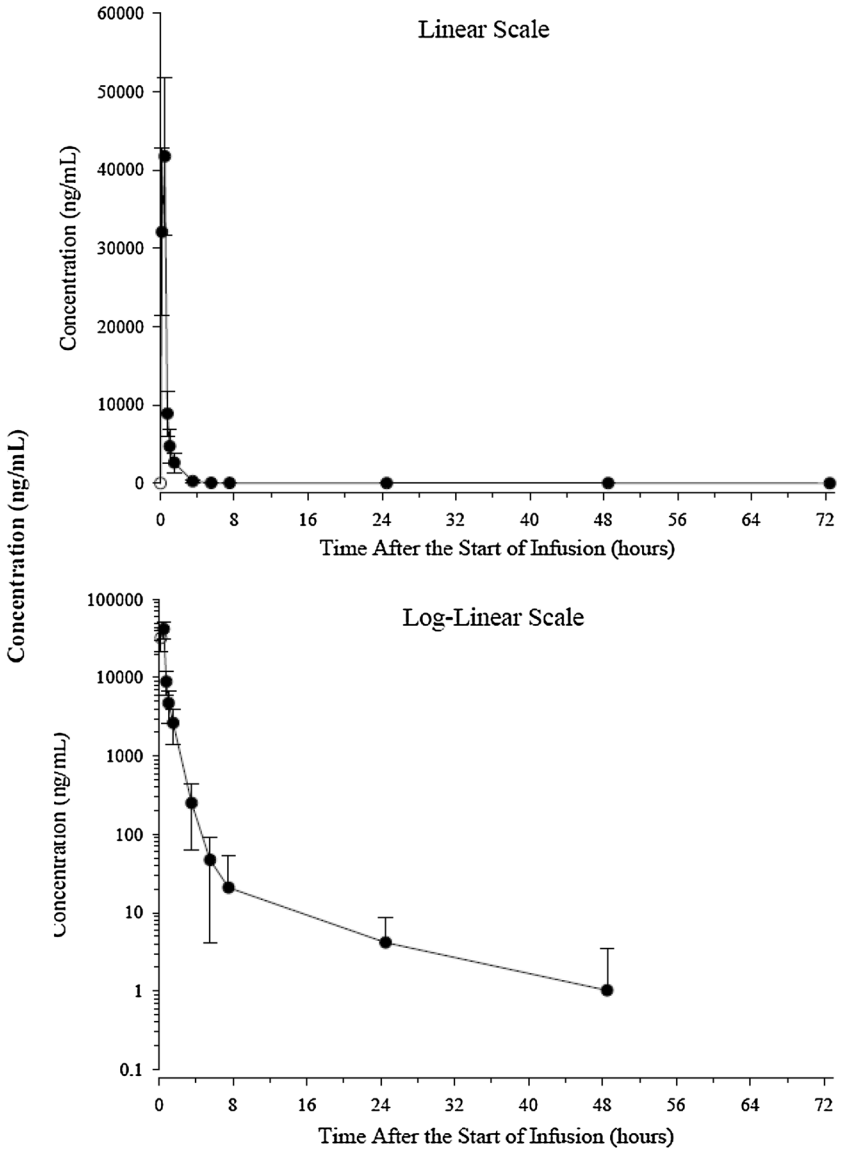

Fig. 2 Mean (SD) concentration–time profile for belinostat

Preliminary activity

Study participants represented a variety of malignancies, including urothelial carcinoma, prostate cancer, leiomyosarcoma, and thymus cancer. The median number of belinostat cycles administered was five (range 2–11). The relative dose intensity was 94.3 % (range 64.8–98.2 %). No objective responses were seen. The best responses in the nine patients were as follows: stable disease in seven patients and progressive disease in two patients (Table 4). The PFS ranged from 0.8 to 7.4 months. Notably, of the six patients with urothelial carcinoma, PFS was 1.6–7.4 months with a median PFS of 3.6 months.

Discussion

In this phase I trial, we evaluated the pharmacokinetics of belinostat and its metabolites in plasma and urine. Given the small sample size, our study did not have a formal statistical plan. After administration, concentrations of belinostat declined in a multi-exponential manner, falling quickly after the end of infusion and then transitioning to a more gradual decline. Levels of belinostat metabolites swiftly rose in plasma and were eliminated with slightly varying terminal half-lives. For all analytes, excretion of belinostat and its metabolites in urine generally occurred within the first 24 h

Table 3 Treatment-related adverse events

MedDRA SOC and preferred term	Number of patients (%), $n = 9$		
	Any grade	G1–2	G3
Gastrointestinal disorders			
Nausea	7 (77.8)	7 (77.8)	–
Vomiting	3 (33.3)	3 (33.3)	–
Diarrhea	4 (44.4)	4 (44.4)	
Constipation	2 (22.2)	1 (11.1)	1 (11.1)
General disorders			
Fatigue	6 (66.7)	6 (66.7)	–
Psychiatric disorders			
Insomnia	2 (22.2)	2 (22.2)	–
Vascular disorders			
Hypotension	2 (22.2)	2 (22.2)	–

No Grade 4 treatment-related adverse events were reported

MedDRA SOC Medical Dictionary for Regulatory Activities System Organ Class, *n* number of patients

after dose administration. The metabolites belinostat glucuronide and 3-ASBA represented the largest fractions of the belinostat dose excreted in urine (30.5 and 4.61 %, respectively), while renal excretion appeared to be a minor route of elimination for the parent belinostat (<1 %). The results of our study are consistent with previously reported data, indicating metabolism as the primary route of belinostat elimination [37]. Current data are insufficient to recommend dosage adjustments for belinostat for Cockcroft–Gault estimated creatinine clearance of 39 mL/min and below. However, we propose that since belinostat metabolites are mostly inactive, it is unlikely that belinostat will require dose modification for renal dysfunction.

Belinostat therapy appeared to be safe. The majority were Grade 1 and 2 AEs and included nausea, fatigue, and diarrhea. One patient experienced a Grade 3 AE of constipation. No unforeseen safety alerts were noted as a result of this study.

During the study, we investigated preliminary efficacy of belinostat. Based on the results of the study, belinostat seemed to demonstrate antitumor activity in the setting of chemotherapy refractory metastatic urothelial carcinoma. Among six patients with metastatic urothelial carcinoma, the median PFS was 3.6 months (range 1.6–7.4 months). This suggests that belinostat may have clinically relevant efficacy in a subset of patients with urothelial carcinoma, although our sample size was small. Increased expression of histone deacetylases has been demonstrated in urothelial carcinoma and may represent an attractive therapeutic target using HDAC inhibitors [38]. Vorinostat, another HDAC inhibitor, has been evaluated in a phase II trial in patients with advanced urothelial cancer. Median disease-free survival and overall survival were 1.1 months and 4.3 months, respectively. However, five out of 14 patients had Grade 4/5 toxicity [39]. As single-agent belinostat seems to be well tolerated, further trials evaluating its use in patients with urothelial carcinoma may be warranted. Studies of other HDAC inhibitors in patients with urothelial carcinoma are ongoing [40, 41].

In conclusion, the results of our study are indicative of metabolism being the main route of belinostat elimination. Following administration, belinostat appeared quickly in plasma with a subsequent rapid decline in belinostat concentration and a median half-life of 2.9 h. Urinary elimination accounted for excretion of approximately 40 % of

Table 4 Progression-free survival

Patient	Tumor diagnosis	Best response	Duration of best response (weeks)	PFS (months)	PFS status
1	Uterine leiomyosarcoma	PD	0	0.8	Event
2	Urothelial carcinoma	SD	24	5.1	Event
3	Thymus	SD	10	1.5	Censored
4	Urothelial carcinoma	PD	0	1.6	Event
5	Urothelial carcinoma	SD	30	7.4	Event
6	Urothelial carcinoma	SD	16	3.0	Censored
7	Prostate Adenocarcinoma	SD	16	2.9	Censored
8	Urothelial carcinoma	SD	14	3.3	Censored
9	Urothelial carcinoma	SD	18	3.8	Event

PD progressive disease, *PFS* progression-free survival, *SD* stable disease, *n* number of patients

belinostat metabolites with less than 1 % of parent compound excreted in urine. Based on these results, we suggest that belinostat will unlikely require dosage adjustment in the setting of renal insufficiency.

Acknowledgments Spectrum Pharmaceuticals, Inc., and Topotarget provided funding for the study.

Compliance with ethical standards

Conflict of interest Guru Reddy and Gajanan Bhat are employees of Spectrum Pharmaceuticals. There are no other conflicts of interest reported by the remaining authors.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Appendix

See Figs. 3, 4, 5, 6, and 7.

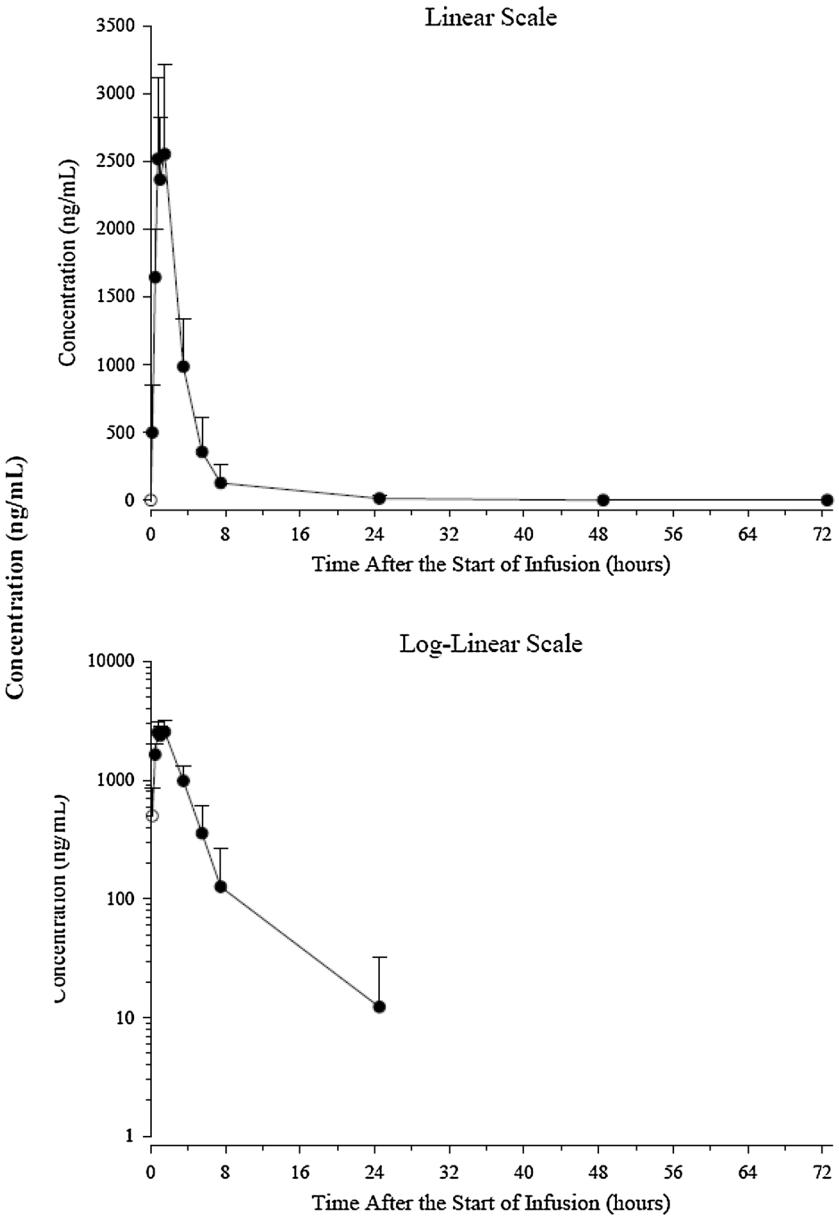

Fig. 3 Mean (SD) concentration–time profile for methyl belinostat

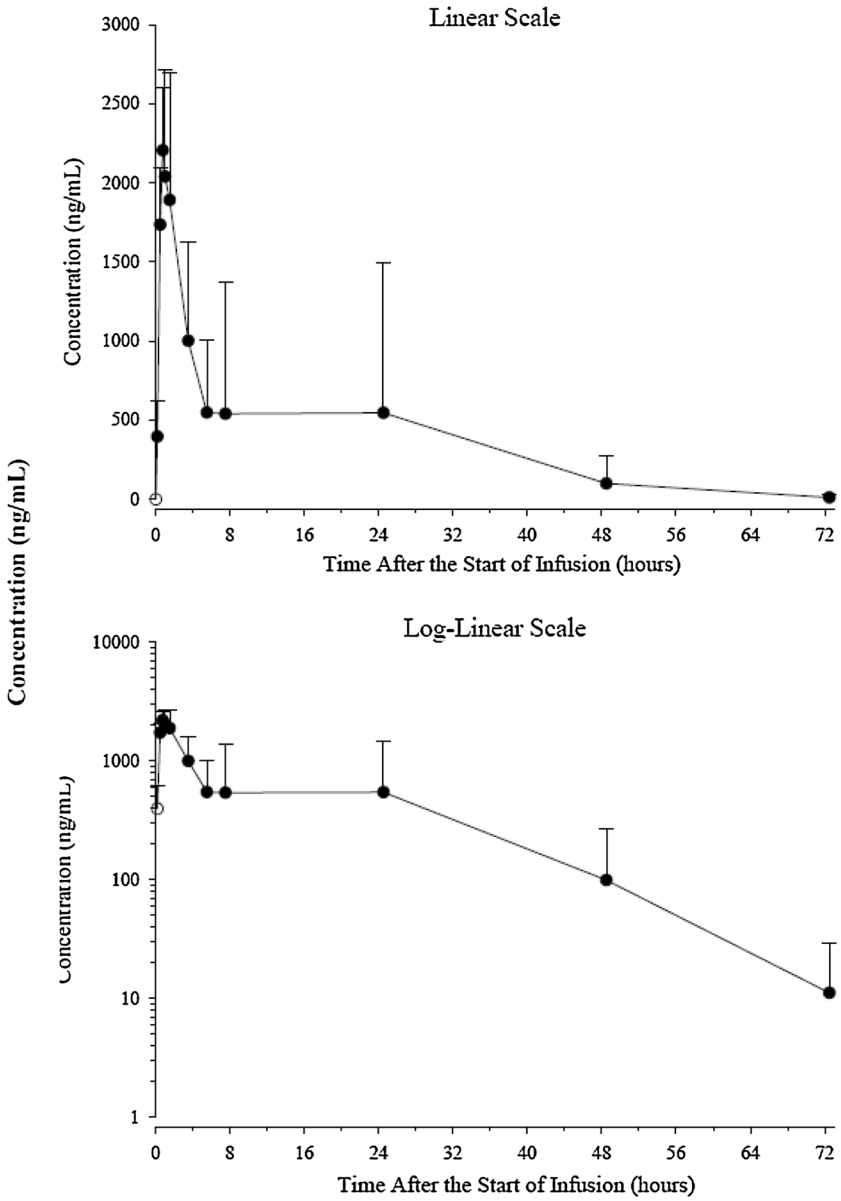

Fig. 4 Mean (SD) concentration–time profile for belinostat amide

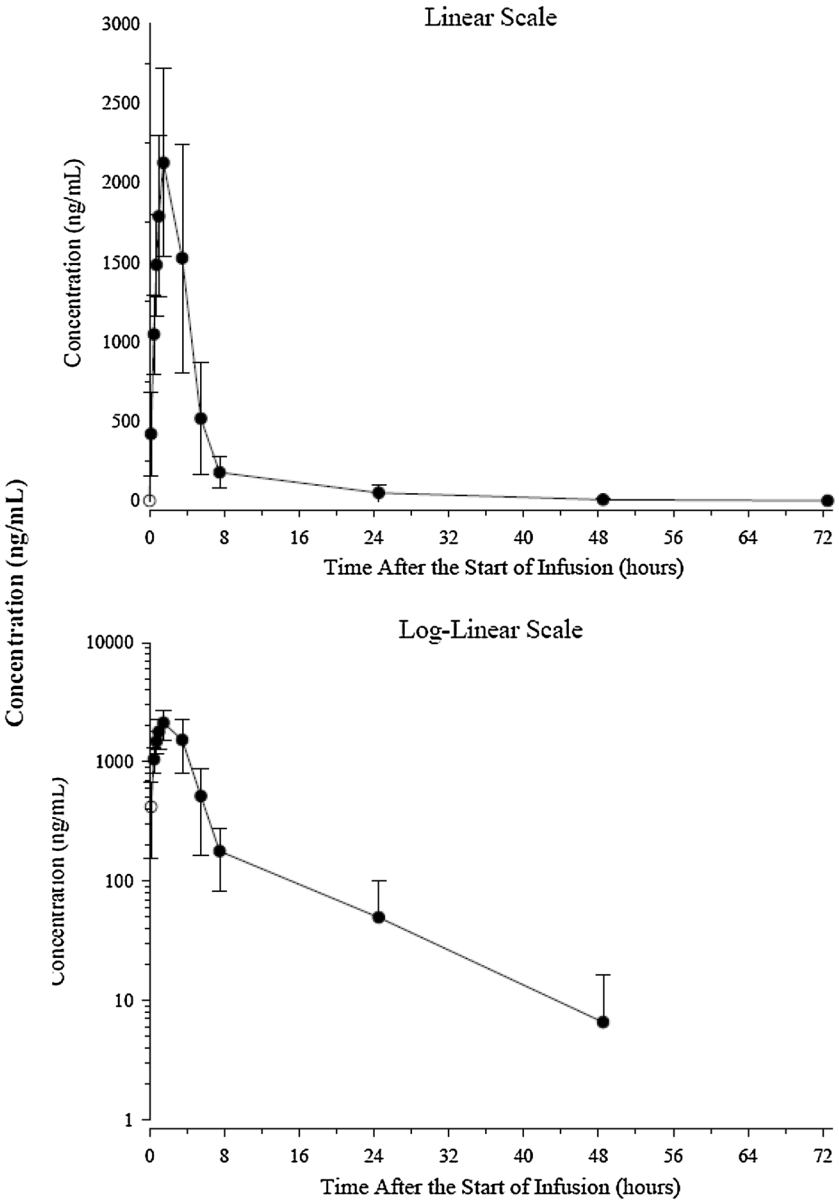

Fig. 5 Mean (SD) concentration–time profile for belinostat acid

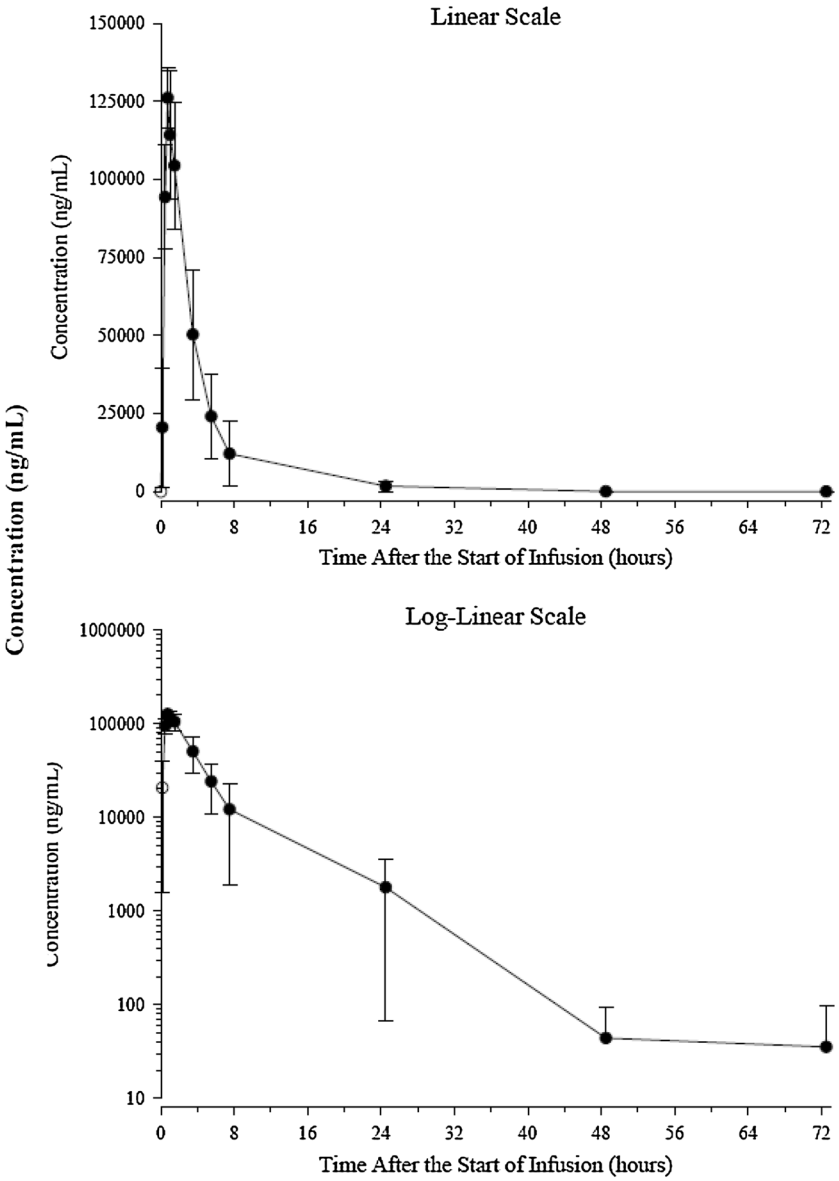

Fig. 6 Mean (SD) concentration–time profile for belinostat glucuronide

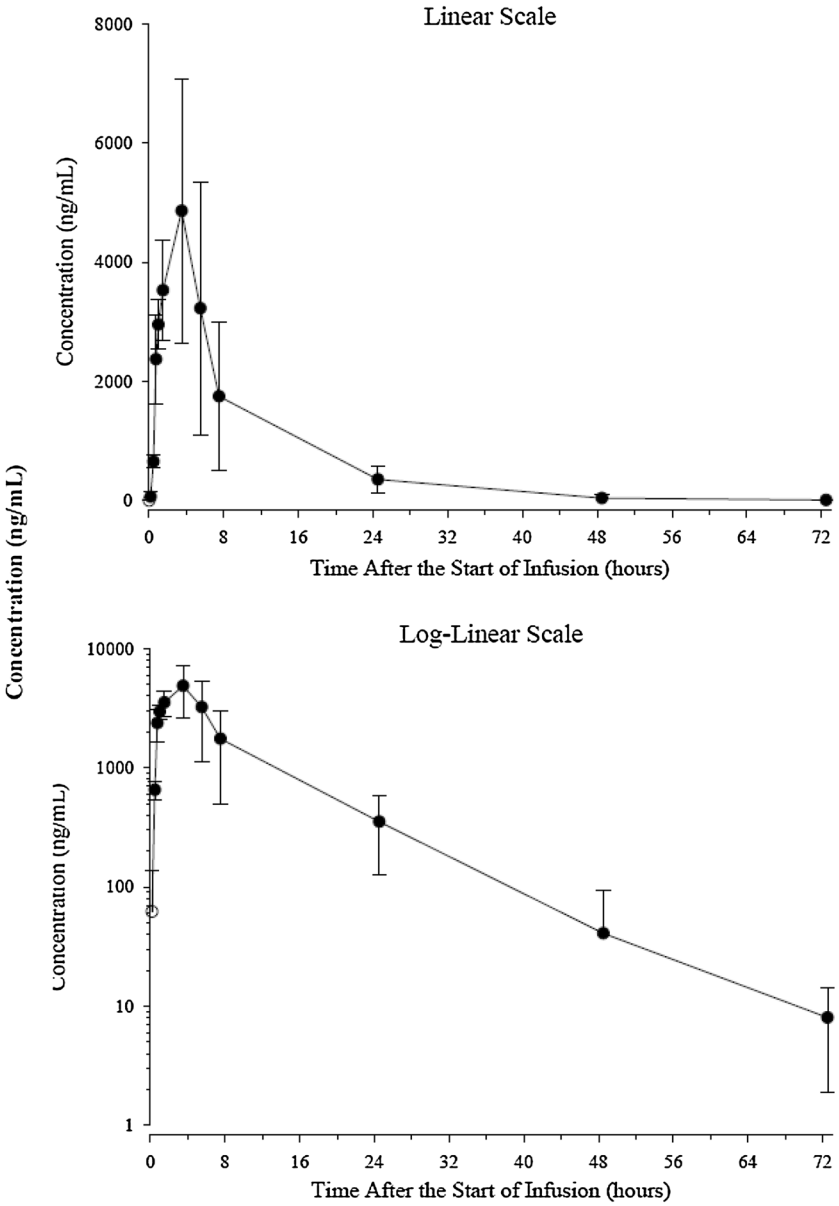

Fig. 7 Mean (SD) concentration–time profile for 3-ASBA

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