PRECLINICAL PHARMACOKINETIC REPORT

Developmental Biology and Solid Tumor Program

P-PKSR Study 19516-89512

STUDY TITLE:

SCREENING PLASMA AND TISSUE PHARMACOKINETICS (SPTPK) OF PANOBINOSTAT IN FEMALE CD1 NU/NU MICE AFTER A SINGLE INTRAPERITONEAL DOSE

SHORT TITLE:	**Panobinostat Screening Plasma Tissues PK (SPTPK)**
TEST ARTICLE:	Panobinostat
SECTION:	Nonclinical Pharmacokinetics (Non-GLP)
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Quality Statement

This non-GLP study was conducted using sound scientific principles and established techniques in accordance with the relevant guidelines and standard operating procedures (SOPs) of the Preclinical Pharmacokinetic Shared Resource (P-PKSR) and St. Jude Children's Research Hospital (SJCRH), Memphis, TN, USA. This report accurately reflects the data obtained during the course of this study.

These results represent part of an early phase preclinical pharmacology program. This study has been conducted to provide preliminary insights into the pharmacokinetic (PK) properties of the compound(s) in the indicated preclinical model(s). This study and its results are not intended to provide a comprehensive PK evaluation of the compound(s). The applied bioanalytical method was validated/qualified to support this specific study and discovery-style sample analyses.

Substantial study-to-study and inter-animal variability in preclinical PK exists. Such variability depends upon the in vivo scientists' experience, variations in compound purity and formulation, animal strains, sex and age, and other situational fixed effects (i.e. husbandry conditions, chow constituents, presence or absence of disease, concomitant drugs). As such, the actual PK, plasma or tissue compound concentrations, or equivalent dose in other studies or preclinical models may vary significantly from that reported herein.

1.0 METHODS

1.1 In Vivo Pharmacokinetic (PK) Study

The total plasma and tissue PK of panobinostat in female CD1 nu/nu mice (Jax Laboratories, aged 8-16 weeks) was assessed after a single intraperitoneal (IP) injection of 20 mg/kg. Panobinostat (LC Labs, Lot PNB-101, purity >99%, MolWt 349.43) was suspended as the free base form in dextrose 5% for injection, USP (D5W, Baxter) at a nominal concentration of 2 mg/mL for a 10 mL/kg injection volume. The IP route was chosen given the low oral bioavailability reported in rodents [1,2], and as it appeared to be the preferred route in reviewed mouse studies [3–5]. Mice were sacrificed using an IACUC-approved method at 15 min, 40 min, 2.25, 8, and 24 hr post-dose, with 3 mice per time point. Whole blood was collected with sodium heparin via cardiac puncture, immediately centrifuged to plasma, and stored on dry ice for remainder of study. Mice were then perfused with PBS via the aorta, the rhabdomyosarcoma (MAST 39) orthotopic xenografts and tissues excised, rinsed with PBS, and placed on dry ice. At the end of the in vivo procedures, all samples were transferred from dry ice and placed at -80 °C until analysis.

1.2 Bioanalysis

Total plasma and tissue homogenate panobinostat concentrations were assessed using a sensitive and specific liquid chromatography, tandem mass spectrometry assay. First, tissue samples were macerated, diluted with a 5:1 volume (for tumor and brain) or a 3.1-7.0:1 volume (for varying masses retina and vitreous) of ultrapure water, and homogenized with a bead-based technique [6] on a FastPrep-24 system (MP Biomedicals, Santa Ana, CA). Ceramic lysing matrix beads (MP Biomedicals, Lysing Matrix D, 10 mg per mg of tissue) were added to the microcentrifuge tubes containing samples. The samples were then subjected to three 60 M/S vibratory cycles of 1 min each on the FastPrep-24 system. To prevent over-heating due to friction, samples were placed on wet ice for 5 min between each cycle. The homogenates were then stored at -80 °C until analysis.

Panobinostat (LC Labs, Lot PNB-101, purity >99%) stock solutions were prepared in methanol and used to spike matrix calibrators and quality controls. Plasma and tissue homogenate samples, 25 µL each, were protein precipitated with 100 µL of 240 ng/mL panobinostat-d8 hydrochloride salt (Toronto Research Chemicals, Inc., P180502, Lot 5-KSS-175-5, purity 96%) in methanol as an internal standard. A 2 µL aliquot of the extracted supernatant was injected onto a Shimadzu LC-20ADXR high performance liquid chromatography system via a LEAP CTC PAL autosampler. The LC separation was performed using a Waters XBridge BEH C18 LC column (2.5 µm, 75 mm x 2.1 mm) maintained at 60 °C with gradient elution at a flow rate of 0.35 mL/min. The binary mobile phase consisted of ultra-pure water - 100 mM ammonium formate, pH=3.0 – methanol (850:50:100 v/v) in reservoir A and methanol – acetonitrile – 100 mM ammonium formate, pH=3.0 (475:475:50 v/v) in reservoir B. The initial mobile phase consisted of 42.5% B and was maintained for 1.6 minutes. The column was then rinsed for 1.4 minutes at 100% B and then equilibrated at the initial conditions for 2 minutes for a total run time of 5 minutes. Under these conditions, the analyte and IS eluted at 0.85 and 0.83 minutes, respectively.

Analyte and IS were detected with tandem mass spectrometry using a SCIEX API 5500 Q-TRAP in the positive ESI mode with monitoring of the following mass transitions: panobinostat 350.18 -> 158.18, panobinostat-d8 357.91 -> 147.19.

The experimental bioanalytical runs were all found to be acceptable for the purpose of a singlicate non-GLP, preclinical PK assessment. A linear model ($1/X^2$ weighting) fit the calibrators across the 5 to 1000 ng/mL range, with a correlation coefficient (R) of ≥0.99. The lower limit of quantitation (LLOQ), defined as a peak area signal-to-noise ratio of 5 or greater verses a matrix blank with IS, was 5 ng/mL for plasma and 30 ng/mL for tissues due to the dilution factor. The intra-run precision and accuracy was < 0.312% CV and 99.4% to 113%, respectively for plasma, brain, retina, and vitreous. Tumor matrix demonstrated less-favorable precision and accuracy, with values of < 1.79% CV and 108% to 119%, respectively.

1.3 Pharmacokinetic (PK) Analysis

The resultant panobinostat concentration-time (Ct) data were grouped by matrix and time point, and manual imputation of data below the lower limit of quantitation (BLOQ) was as follows: IF at any time point ≥ 2/3rds of the Ct results were above the LLOQ, the BLOQ data were replaced with a value of ½ LLOQ, ELSE the entire time point's data were treated as missing. Then, using Phoenix WinNonlin 6.4 (Certara USA, Inc., Princeton, NJ), Ct data summary statistics (arithmetic mean, standard deviation, %CV, minimum, median, maximum) were generated, and the panobinostat arithmetic mean Ct data for each matrix was subjected to noncompartmental pharmacokinetic analysis (NCA). The extravascular model (Model 202) was applied, and area under the Ct curve (AUC) values were estimated using the linear trapezoidal method and the sparse sampling option. The terminal phase was defined as the three time points at the end of the Ct profile, and the elimination rate constant (Ke) was estimated using an unweighted log-linear regression of the terminal phase. The terminal elimination half-life (T1/2) was estimated as 0.693/Ke, and the AUC from time 0 to infinity (AUCinf) was estimated as the AUC to the last time point (AUClast) + Clast/Ke.

Other NCA parameters estimated included observed maximum concentration (Cmax), time of Cmax (Tmax), concentration at the last observed time point (Clast), time of Clast (Tlast), apparent clearance (CL/F = Dose/AUCinf), and apparent terminal volume of distribution (Vz/F). The average concentration over a dosing interval (Cavg) was estimated as AUCinf / dosing interval in hours. The apparent partition coefficient of panobinostat from the plasma to the tissue of interest (Kp,*tissue*) was estimated as the ratio of the AUCinf, tissue to AUCinf plasma when available. To estimate a clinically relevant mouse dosage, the resultant mouse plasma AUCinf and Cavg was compared with the reported human plasma PK values at the putative single agent panobinostat maximum tolerated dose or the FDA-approved dose. All inferences were made under the assumption of time-independent, linear and dose-proportional PK in mice and humans.

2.0 RESULTS

Panobinostat concentrations showed appreciable variability, demonstrating average coefficients of variation of 33.0% to 86.7% for plasma across the sampling time points. The earliest time points through Cmax, during the putative absorption and distribution phases, exhibited the most variability. This is likely due to an inadequately solubilized formulation. After sonicating the panobinostat in D5W for 30 minutes in a water bath, the compound did not dissolve but instead formed a homogenous, hazed suspension. Tumor penetration appeared to be very rapid and extensive, with a Kp,tumor value of 12.2. Also, panobinostat appeared to readily distribute to the mouse vitreous and retina, demonstrating Kp values of 4.59 and 4.84, respectively. All brain concentrations were BLOQ, except for the three observations at the 8 hr time point. As such, NCA parameters could not be estimated for brain. The apparent T1/2 of panobinostat in the plasma was 43.1 hr. In this instance of administering a suspension IP, this long half-life is thought to result from a dissolution-limited, absorption-driven "flip-flop" phenomenon [7]. Apparent tissue half-lives were also long and Kp values high, indicating high tissue distribution and affinity.

In two Phase 1 studies of single agent panobinostat as either IV or oral therapy, the maximum tolerated doses were 20 mg/m^2 IV weekly [8] and 60 mg PO Q MWF weekly or biweekly [9]. The FDA-approved dosage for panobinostat in multiple myeloma is 20 mg PO Q MWF for 2 weeks every 21 days [10]. The major adverse event is thrombocytopenia and myelosuppression; however, some cardiac events (QTc prolongation) have been noted at higher IV doses, and seem to be related to Cmax. The total plasma AUCs for these clinical regimens were extracted from the literature – the estimates ranged from 125 hr-ng/mL to 1040 hr-ng/mL (**Table 2.1**). The fraction of panobinostat unbound in plasma (Fu,p) values for mice and humans were obtained from the FDA Drug Approval Package [2], and were ~0.4 and 0.1 for mouse and human, respectively. Therefore, based on the most precise inter-species derivation for a pharmacokinetically equivalent dose, i.e. unbound plasma AUCs, the strict recommended MED range is 0.41 to 3.4 mg/kg IP as a suspension in D5W. Given these PK findings, and considering other pharmacology information available for panobinostat in mouse models, the selected MED was 3 mg/kg IP (suspended in D5W) TIW.

Table 2.1 Estimated Panobinostat Plasma AUC Values in Humans from Literature Sources

Study	Dose	AUC	Unbound AUC	MED est.
Sharma et al. [8]	20 mg/m^2 IV	1040 hr-ng/mL	104 hr-ng/mL	3.4 mg/kg
DeAngelo et al. [9]	60 mg PO (Day 15)	349 hr-ng/mL	34.9 hr-ng/mL	1.1 mg/kg
Shapiro et al. [11]	20 mg PO	144 – 176 hr-ng/mL	14.4 – 17.6 hr-ng/mL	0.47 – 0.58 mg/kg
Population PK model [12,13]	20 – 80 mg PO	125 – 500 hr-ng/mL	12.5 – 50.0 hr-ng/mL	0.41 – 1.6 mg/kg

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4.0 TABLES, LISTINGS, AND FIGURES (TLFS)

Figure 4.1: Mean (SD) Ct Profiles of Panobinostat by Tissue

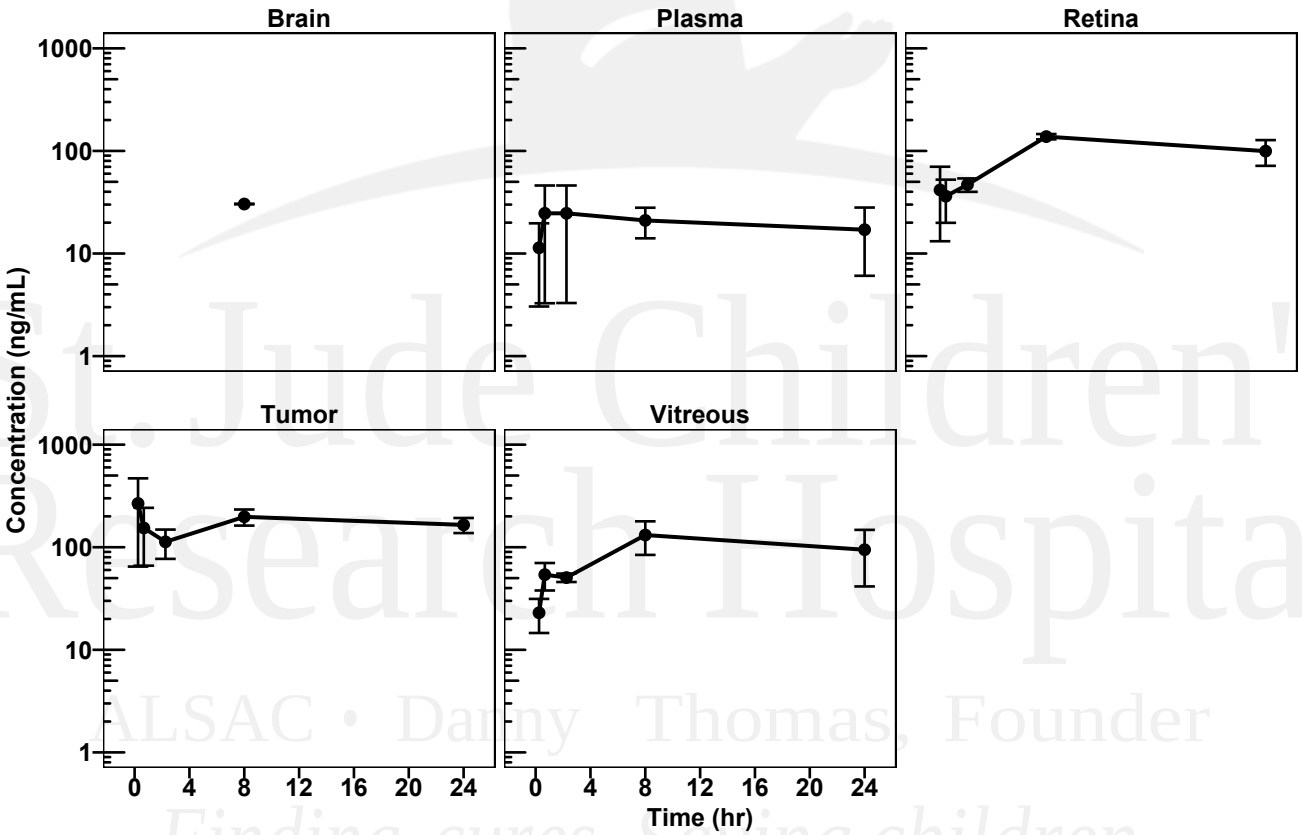

Table 4.1: NCA PK Parameter Estimates of Panobinostat by Tissue

Parameter	Units	Plasma	Tumor	Retina	Vitreous	Brain
Cmax	ng/mL	24.7	267	138	132	30.4
Tmax	hr	2.25	0.25	8	8	8
AUClast	hr-ng/mL	484	4130	2520	2430	NE
Kel	1/hr	0.0161	0.0113	0.0204	0.0206	NE
AUCinf	hr-ng/mL	1530	18700	7410	7020	NE
T1/2	hr	43.1	61.2	34.0	33.6	NE
Clast	ng/mL	17.1	165	99.6	94.5	30.4
Tlast	hr	24	24	24	24	8
CL/F	L/hr/kg	13.0	1.07	2.70	2.85	NE
Vz/F	L/kg	811	94.4	133	138	NE
Cavg (48 hr interval)	ng/mL	31.9	390	154	146	NE
Kp,*tissue*	-	-	12.2	4.84	4.59	NE

NE: not estimated

Table 4.2: Full Summary Statistics of Panobinostat Ct Data by Group=Tissue

		Analyte				
		Panobinostat				
		Group				
		Brain	Plasma	Retina	Tumor	Vitreous
Time (hr)		Concentration (ug/L)				
0.250	N	0	3	3	3	3
	Mean		11.4	41.7	267	23.0
	SD		8.33	28.5	202	8.38
	Min		2.50	15.6	64.8	16.9
	Median		12.6	37.2	267	19.5
	Max		19.0	72.1	469	32.5
	CV%		73.2	68.4	75.7	36.5
	Geometric Mean		8.43	34.8	201	22.0
	CV% Geometric Mean		147	89.4	135	35.5
0.670	N	0	3	3	3	3
	Mean		24.6	36.2	154	54.0
	SD		21.4	16.3	88.0	16.2
	Min		8.83	25.8	75.8	36.0
	Median		16.1	27.9	137	59.0
	Max		49.0	54.9	249	67.1
	CV%		86.7	45.0	57.1	29.9
	Geometric Mean		19.1	34.0	137	52.2

		Analyte				
		Panobinostat				
		Group				
		Brain	Plasma	Retina	Tumor	Vitreous
Time (hr)		Concentration (ug/L)				
	CV% Geometric Mean		106	43.5	65.2	33.8
2.250	N	0	3	3	3	3
	Mean		24.7	46.9	113	50.6
	SD		21.4	7.02	35.8	4.77
	Min		10.5	39.2	78.2	46.2
	Median		14.3	48.7	110	49.9
	Max		49.2	52.9	150	55.6
	CV%		86.6	15.0	31.8	9.44
	Geometric Mean		19.5	46.6	109	50.4
	CV% Geometric Mean		97.7	15.6	33.4	9.40
8.000	N	3	3	3	3	3
	Mean	30.4	21.0	138	198	131
	SD	0.203	6.94	8.19	35.4	47.3
	Min	30.2	15.3	131	177	98.2
	Median	30.3	19.0	136	178	111
	Max	30.6	28.7	147	239	186
	CV%	0.668	33.0	5.94	17.9	36.0
	Geometric Mean	30.4	20.3	138	196	126
	CV% Geometric Mean	0.667	32.9	5.89	17.2	34.9
24.000	N	0	3	2	3	3
	Mean		17.1	99.5	165	94.5
	SD		11.0	28.0	27.7	53.1
	Min		9.11	79.8	134	59.3
	Median		12.5	99.5	175	68.8
	Max		29.6	119	186	156
	CV%		64.5	28.1	16.8	56.1
	Geometric Mean		15.0	97.6	163	85.9
	CV% Geometric Mean		67.2	29.1	17.7	55.7

Table 4.3: Panobinostat Ct Data Listings by Subject, Analyte, Group=Tissue, and Time

Subject	Analyte	Group	Time (hr)	Concentration (ug/L)
M1	Panobinostat	Brain	24.00	

Panobinostat Screening Plasma Tissues PK (SPTPK)

Subject	Analyte	Group	Time (hr)	Concentration (ug/L)
M1	Panobinostat	Plasma	24.00	9.11
M1	Panobinostat	Retina	24.00	79.76
M1	Panobinostat	Tumor	24.00	133.82
M1	Panobinostat	Vitreous	24.00	68.77
M2	Panobinostat	Brain	24.00	
M2	Panobinostat	Plasma	24.00	12.46
M2	Panobinostat	Retina	24.00	119.34
M2	Panobinostat	Tumor	24.00	174.89
M2	Panobinostat	Vitreous	24.00	59.28
M3	Panobinostat	Brain	24.00	
M3	Panobinostat	Plasma	24.00	29.62
M3	Panobinostat	Retina	24.00	
M3	Panobinostat	Tumor	24.00	186.47
M3	Panobinostat	Vitreous	24.00	155.58
M4	Panobinostat	Brain	8.00	30.21
M4	Panobinostat	Plasma	8.00	28.72
M4	Panobinostat	Retina	8.00	135.65
M4	Panobinostat	Tumor	8.00	177.99
M4	Panobinostat	Vitreous	8.00	185.69
M5	Panobinostat	Brain	8.00	30.30
M5	Panobinostat	Plasma	8.00	19.03
M5	Panobinostat	Retina	8.00	147.00
M5	Panobinostat	Tumor	8.00	176.85
M5	Panobinostat	Vitreous	8.00	110.57
M6	Panobinostat	Brain	8.00	30.60
M6	Panobinostat	Plasma	8.00	15.26
M6	Panobinostat	Retina	8.00	131.08
M6	Panobinostat	Tumor	8.00	238.64
M6	Panobinostat	Vitreous	8.00	98.24
M7	Panobinostat	Brain	2.25	
M7	Panobinostat	Plasma	2.25	14.26
M7	Panobinostat	Retina	2.25	52.91
M7	Panobinostat	Tumor	2.25	110.41
M7	Panobinostat	Vitreous	2.25	49.92
M8	Panobinostat	Brain	2.25	
M8	Panobinostat	Plasma	2.25	49.24
M8	Panobinostat	Retina	2.25	48.69
M8	Panobinostat	Tumor	2.25	78.23
M8	Panobinostat	Vitreous	2.25	46.16
M9	Panobinostat	Brain	2.25	
M9	Panobinostat	Plasma	2.25	10.49

Subject	Analyte	Group	Time (hr)	Concentration (ug/L)
M9	Panobinostat	Retina	2.25	39.21
M9	Panobinostat	Tumor	2.25	149.75
M9	Panobinostat	Vitreous	2.25	55.64
M10	Panobinostat	Brain	0.67	
M10	Panobinostat	Plasma	0.67	16.15
M10	Panobinostat	Retina	0.67	25.75
M10	Panobinostat	Tumor	0.67	137.13
M10	Panobinostat	Vitreous	0.67	59.00
M11	Panobinostat	Brain	0.67	
M11	Panobinostat	Plasma	0.67	8.83
M11	Panobinostat	Retina	0.67	27.87
M11	Panobinostat	Tumor	0.67	75.79
M11	Panobinostat	Vitreous	0.67	35.96
M12	Panobinostat	Brain	0.67	
M12	Panobinostat	Plasma	0.67	48.96
M12	Panobinostat	Retina	0.67	54.93
M12	Panobinostat	Tumor	0.67	249.35
M12	Panobinostat	Vitreous	0.67	67.09
M13	Panobinostat	Brain	0.25	
M13	Panobinostat	Plasma	0.25	12.59
M13	Panobinostat	Retina	0.25	37.23
M13	Panobinostat	Tumor	0.25	469.31
M13	Panobinostat	Vitreous	0.25	32.51
M14	Panobinostat	Brain	0.25	
M14	Panobinostat	Plasma	0.25	19.02
M14	Panobinostat	Retina	0.25	72.08
M14	Panobinostat	Tumor	0.25	266.99
M14	Panobinostat	Vitreous	0.25	19.51
M15	Panobinostat	Brain	0.25	
M15	Panobinostat	Plasma	0.25	2.50
M15	Panobinostat	Retina	0.25	15.65
M15	Panobinostat	Tumor	0.25	64.78
M15	Panobinostat	Vitreous	0.25	16.86

Table 4.4: Panobinostat Ct Summary (Mean, SD, N) by Group=Tissue

Variable	Units	Analyte	Group	Time (hr)	Mean (ug/L)	SD (ug/L)	N
Concentration	ug/L	Panobinostat	Brain	0.25			0.00
Concentration	ug/L	Panobinostat	Brain	0.67			0.00
Concentration	ug/L	Panobinostat	Brain	2.25			0.00

Variable	Units	Analyte	Group	Time (hr)	Mean (ug/L)	SD (ug/L)	N
Concentration	ug/L	Panobinostat	Brain	8.00	30.37	0.20	3.00
Concentration	ug/L	Panobinostat	Brain	24.00			0.00
Concentration	ug/L	Panobinostat	Plasma	0.25	11.37	8.33	3.00
Concentration	ug/L	Panobinostat	Plasma	0.67	24.65	21.37	3.00
Concentration	ug/L	Panobinostat	Plasma	2.25	24.66	21.37	3.00
Concentration	ug/L	Panobinostat	Plasma	8.00	21.01	6.94	3.00
Concentration	ug/L	Panobinostat	Plasma	24.00	17.06	11.00	3.00
Concentration	ug/L	Panobinostat	Retina	0.25	41.65	28.48	3.00
Concentration	ug/L	Panobinostat	Retina	0.67	36.19	16.27	3.00
Concentration	ug/L	Panobinostat	Retina	2.25	46.93	7.02	3.00
Concentration	ug/L	Panobinostat	Retina	8.00	137.91	8.19	3.00
Concentration	ug/L	Panobinostat	Retina	24.00	99.55	27.99	2.00
Concentration	ug/L	Panobinostat	Tumor	0.25	267.03	202.27	3.00
Concentration	ug/L	Panobinostat	Tumor	0.67	154.09	88.01	3.00
Concentration	ug/L	Panobinostat	Tumor	2.25	112.80	35.82	3.00
Concentration	ug/L	Panobinostat	Tumor	8.00	197.83	35.35	3.00
Concentration	ug/L	Panobinostat	Tumor	24.00	165.06	27.67	3.00
Concentration	ug/L	Panobinostat	Vitreous	0.25	22.96	8.38	3.00
Concentration	ug/L	Panobinostat	Vitreous	0.67	54.02	16.15	3.00
Concentration	ug/L	Panobinostat	Vitreous	2.25	50.58	4.77	3.00
Concentration	ug/L	Panobinostat	Vitreous	8.00	131.50	47.34	3.00
Concentration	ug/L	Panobinostat	Vitreous	24.00	94.55	53.07	3.00

5.0 ATTACHED FILES

Attached File 5.1 Panobinostat Plasma Tumor PK Study.docx– *Final in vivo study plan as executed*

Attached File 5.2 Panobinostat RMS PK for Burgess.xlsx– *Submitted in vivo study digital data collection form (DCF)*

Attached File 5.3 Panobinostat Screening Plasma Tissues PK TLFs.docx – *Report TLFs as a Word document for manipulation, plotting, and further presentation*