PRECLINICAL PHARMACOKINETIC REPORT

Developmental Biology and Solid Tumor Program

P-PKSR Study 133410-1396203

STUDY TITLE:

SCREENING PLASMA AND TUMOR PHARMACOKINETICS (SPTPK) OF TAZEMETOSTAT IN FEMALE ATHYMIC NUDE MICE AFTER A SINGLE ORAL DOSE

SHORT TITLE:	**Tazemetostat Screening Plasma Tumor PK (SPTPK)**
TEST ARTICLE:	Tazemetostat
SECTION:	Nonclinical Pharmacokinetics (Non-GLP)
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SJCRH SRM2 O/R:	133410-1396203 Preclinical Pharmacokinetic Shared Resource 124312-1298569
REFERENCE STUDY NUMBERS:	NA NA
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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

Two separate PK studies of tazemetostat were conducted in female Athymic nude mice (Charles River Laboratories, Frederick, MD) and are summarized below.

The first tazemetostat PK study (SRM2 O/R 124312-1298569, SPPK) was a survival plasma PK evaluation using non-tumor bearing Athymic nude mice. Tazemetostat was suspended in 1% hydroxyethylcellulose (MW 720,000), 0.25% Tween 80, and ~0.05% simethicone at 20 mg/mL and administered as a 10 mL/kg oral gavage for a 200 mg/kg dose. A batch sampling design was implemented where 3 samples were collected per mouse. Mice were divided into 3 groups for sample collection. Mice from group 1 were sampled at 0.125, 1, and 16 hr post-dose. Mice from group 2 were sampled at 0.25, 2, and 24 hr, and mice from group 3 were sampled at 0.5, 4, and 8 hr post-dose. Blood samples (~ 50 µL) were collected by retro-orbital eye bleed technique using Minivette POCT 50 µL capillary devices containing K3EDTA (Sarstedt AG, Germany). Terminal samples at the last time point were collected by cardiac puncture using a 1 mL syringe, and the blood placed in a Sarstedt Microvette K3EDTA 500 µL tube.

In the second tazemetostat PK study (SRM2 O/R 1133410-1396203, SPTPK), the plasma and tumor PK were evaluated after a single oral dose of the tazemetostat 200 mg/kg suspension. Female Athymic nude mice bearing rhabdoid (A204) orthotopic xenografts in the quadriceps were sacrificed using an IACUC-approved method at 0.125, 1, 4, 8, 16 hr post-dose (3 mice per timepoint). Blood was collected by cardiac puncture, after which the carcass was perfused with PBS, the tumor extracted, rinsed, and placed in a microcentrifuge tube.

In all instances, blood samples were immediately centrifuged to plasma. Plasma and tumor samples were temporarily placed on dry ice until transfer to a deep freezer, and samples were stored at -80 °C until analysis.

Additionally, tazemetostat fraction unbound in mouse and human plasma (Fu,p,m and Fu,p,h), and patient derived rhabdomyosarcoma tumor homogenate (Fu,t) was determined using rapid equilibrium dialysis (RED, Pierce Biotechnology, ThermoFisher Scientific, Waltham, MA). Briefly, blank mouse plasma and tumor homogenates, diluted with PBS, were spiked with compounds in triplicate achieving final concentrations of 10 µM, placed in donor wells of RED apparatus, and permitted to equilibrate for 4-6 hours at 37 °C. Compounds were assayed in donor and receiver well samples using LC-MS, with the fraction unbound calculated as the ratio of concentration in receiver to donor adjusted for any dilution [1]. These experiments were conducted fully by SJCRH Chemical Biology and Therapeutics (CBT) Analytical Technologies Center (ATC) personnel under the direction of Lei Yang.

1.2 Bioanalysis

Frozen tumor samples were weighed in tared 15 mL Lysing Matrix D tubes (MP Biomedical, Santa Ana, CA) and diluted with a 5:1 volume of ultra-pure water. The tumor samples were then homogenized with a FastPrep-24 system (MP Biomedicals, Santa Ana, CA). The homogenization consisted of four 6.0 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.

Plasma and tumor samples were analyzed for tazemetostat (ADOOQ, Lot # L12712B002, purity 99.7%) with a qualified liquid chromatography – tandem mass spectrometry (LC-MS/MS) assay. Plasma calibrators and quality controls were spiked with solutions, corrected for salt content, prepared in acetonitrile. Plasma and tumor homogenate samples, 25 µL each, were protein precipitated with 100 µL of 100 ng/mL GSK126 (ADOOQ, Lot # B006) in acetonitrile 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 XP (2.5 µm 75 x 2.1 mm) column maintained at 50 °C with gradient elution at a flow rate of 0.6 mL/min. The binary mobile phase consisted of water: 20 mM ammonium acetate; formic acid (950:50:0.25 v/v/v) in reservoir A and acetonitrile: 20 mM ammonium acetate; formic acid (950:50:0.25 v/v/v) in reservoir B. The initial mobile phase consisted of 30% B with a linear increase to 100% B in 1.25 min. The column was then rinsed for 1 min at 100% B and then equilibrated at the initial conditions for 2.0 min for a total run time of 4.25 min. Under these conditions, the analyte and IS eluted at 0.94 and 1.08 min, respectively. Analyte and IS were detected with tandem mass spectrometry using a SCIEX API 5500 Q-TRAP in the positive ESI mode with the following mass transitions were monitored: 573.30 -> 486.30 for tazemetostat and 527.30 -> 392.20 for GSK126.

The method qualification and bioanalytical runs all passed P-PKSR's acceptance criteria for non-GLP assay performance. A linear model ($1/X^2$ weighting) fit the calibrators across the 1 to 500 ng/mL range, with a correlation coefficient (R) of 0.9985. 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 1 ng/mL. Sample dilution integrity was confirmed. For the plasma matrix, the intra-run precision and accuracy was ≤ 5.81% CV and 93.6% to 99.3%, respectively.

1.3 Pharmacokinetic (PK) Analysis

The resultant tazemetostat concentration-time (Ct) data were grouped by study, 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 were generated, and the tazemetostat arithmetic mean Ct data for 1) each study and matrix, and for 2) plasma as an aggregate across studies (Study = Aggregate), was subjected to noncompartmental pharmacokinetic analysis (NCA).

The extravascular (Model 202) was applied, and area under the Ct curve (AUC) values were estimated using the "linear up log down" trapezoidal rule. 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) + predicted Clast/Ke.

Other NCA parameters estimated included the observed maximum concentration (Cmax), time of Cmax (Tmax), concentration at the last observed time point (Clast), time of Clast (Tlast), apparent oral clearance (CL/F = Dose/AUCinf), and apparent terminal volume of distribution (Vz/F). The apparent partition coefficient of tazemetostat 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 dosage (CRD) for mice, the resultant mouse plasma unbound AUCinf was compared with the reported pediatric unbound plasma PK value at the recommended phase 2 dose (RP2D) of tazemetostat of 1200 mg/m^2 PO BID [2]. All inferences were made under the assumption of time-independent, linear and dose-proportional PK in mice and humans.

2.0 RESULTS

The PK results for individual studies and as an aggregate for plasma across all the studies are presented in Section 4.0. The aggregate plasma results are being referenced for overall inferences, including the

clinically relevant dose (CRD) derivations. However, the plasma PK results between the two PK studies were fairly similar and within two-fold for most paramters.

Plasma and tumor PK of tazemetostat demonstrated low-to-moderate variability, with tumor concentrations approaching unity with plasma (Kp,inf = 0.717). RED plasma protein binding studies revealed fraction unbound values of 0.0361 and 0.0726 respectively for mice and humans. Children were found to tolerate higher doses of tazemetostat versus adults, with an estimated RP2D of 1200 mg/m^2 PO BID. This yielded a ~4-fold higher exposure in children than observed at the adult RP2D of 800 mg PO BID [2]. The reported total plasma AUCtau at 800 mg BID was 3340 hr-ug/L in adults [3]. Therefore, the estimated total and unbound plasma AUCtau is 13400 and 973 hr-ug/L respectively for children. In mice, the unbound plasma AUC was estimated at 715 hr-ug/L at 200 mg/kg PO, and a CRD of 225 mg/kg PO BID was recommended. However, doses in mice ranging from 200 to 300 mg/kg BID could be considered clinically relevant by AUCu.

3.0 REFERENCES

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2. Chi S, Fouladi M, Shukla N, Bourdeaut F, Margol A, Makin G, McCowage G, Wetmore C, Macy M, Laetsch T, Hargrave D, Pinto N, Yi J, Ebb D, Robinson G, Roche M, Suttle B, Clawson A, Ho P, Rodstrom J, Daigle S, Nysom K. Abstract A175: Phase 1 study of the EZH2 inhibitor, tazemetostat, in children with relapsed or refractory INI1-negative tumors including rhabdoid tumors, epithelioid sarcoma, chordoma, and synovial sarcoma. Mol Cancer Ther. 2018 Jan 1;17(1 Supplement):A175–A175.

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4.0 TABLES, LISTINGS, AND FIGURES (TLFS)

Figure 4.1: Mean (SD) Ct Profile of Tazemetostat by Group

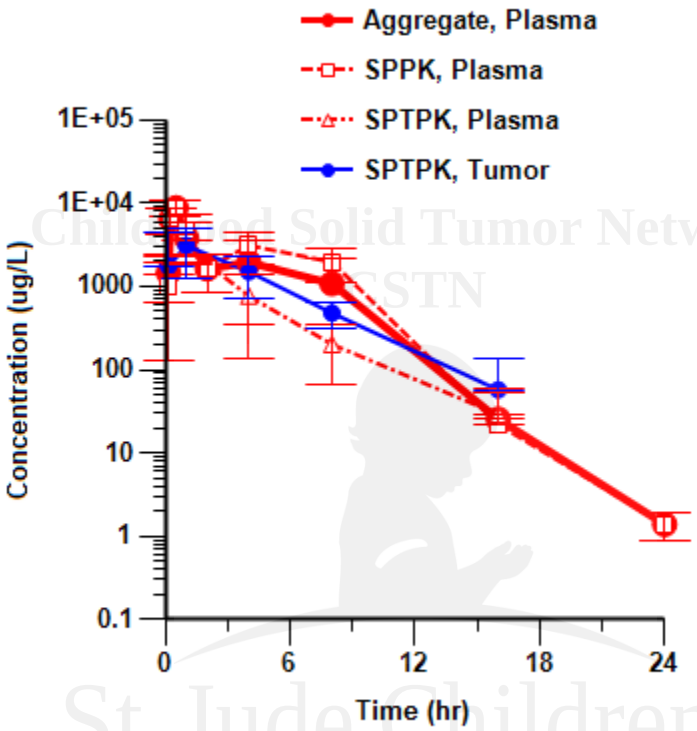

Table 4.1: NCA PK Parameter Estimates of Tazemetostat by Group

		Analyte			
		Tazemetostat			
		Study			
		Aggregate	SPPK	SPTPK	
		Group	Group	Group	
		Plasma	Plasma	Plasma	Tumor
Parameter	**Units**	**Estimate**			
Cmax	ug/L	8820	8820	2940	3090
Tmax	hr	0.500	0.500	1.00	1.00
AUClast	hr*ug/L	19800	26900	9510	14000
AUCinf	hr*ug/L	19800	26900	9620	14200
Kel	1/hr	0.416	0.413	0.268	0.271
T1/2	hr	1.67	1.68	2.58	2.55
CL/F	L/hr/kg	10.1	7.45	20.8	14.0

		Analyte			
		Tazemetostat			
		Study			
		Aggregate	SPPK	SPTPK	
		Group	Group	Group	
		Plasma	Plasma	Plasma	Tumor
Parameter	Units	Estimate			
Vz/F	L/kg	24.2	18.0	77.5	51.8
Clast	ug/L	1.39	1.39	29.1	57.4
Tlast	hr	24.0	24.0	16.0	16.0
Kp,tumor*	-	*	-	-	0.717

* Kp,tumor calculated as AUCinf,tumor / AUCinf,plasma,Aggregate

Table 4.2: Full Summary Statistics of Tazemetostat Ct Data by Study and Group

		Analyte			
		Tazemetostat			
		Study			
		Aggregate	SPPK	SPTPK	
		Group	Group	Group	
		Plasma	Plasma	Plasma	Tumor
Time (hr)		Concentration (ug/L)			
0.125	N	6	3	3	3
	Mean	1470	1010	1920	1760
	SD	828	885	552	2730
	Min	225	225	1340	63.9
	Median	1650	840	2000	306
	Max	2440	1970	2440	4900
	CV%	56.4	87.5	28.7	155
	Geometric Mean	1160	720	1870	458
	CV% Geometric Mean	109	152	31.2	1120
0.250	N	3	3		
	Mean	6470	6470		
	SD	2380	2380		
	Min	4280	4280		
	Median	6130	6130		
	Max	9000	9000		
	CV%	36.7	36.7		
	Geometric Mean	6180	6180		
	CV% Geometric Mean	38.5	38.5		
0.500	N	3	3		

Tazemetostat Screening Plasma Tumor PK (SPTPK)

		Analyte			
		Tazemetostat			
		Study			
		Aggregate	SPPK	SPTPK	
		Group	Group	Group	
		Plasma	Plasma	Plasma	Tumor
Time (hr)		Concentration (ug/L)			
	Mean	8820	8820		
	SD	1800	1800		
	Min	6840	6840		
	Median	9260	9260		
	Max	10400	10400		
	CV%	20.4	20.4		
	Geometric Mean	8690	8690		
	CV% Geometric Mean	21.8	21.8		
1.000	N	6	3	3	3
	Mean	3800	4660	2940	3090
	SD	2010	2740	665	1850
	Min	1970	1970	2200	1550
	Median	3310	4570	3140	2590
	Max	7440	7440	3480	5150
	CV%	53.0	58.7	22.6	59.9
	Geometric Mean	3420	4060	2890	2740
	CV% Geometric Mean	51.9	75.5	24.5	66.3
2.000	N	3	3		
	Mean	1630	1630		
	SD	777	777		
	Min	763	763		
	Median	1870	1870		
	Max	2260	2260		
	CV%	47.6	47.6		
	Geometric Mean	1480	1480		
	CV% Geometric Mean	63.2	63.2		
4.000	N	6	3	3	3
	Mean	1950	3120	768	1510
	SD	1590	1320	633	811
	Min	183	2330	183	716
	Median	1890	2380	681	1470
	Max	4650	4650	1440	2340

Tazemetostat Screening Plasma Tumor PK (SPTPK)

		Analyte			
		Tazemetostat			
		Study			
		Aggregate	SPPK	SPTPK	
		Group	Group	Group	
		Plasma	Plasma	Plasma	Tumor
Time (hr)		Concentration (ug/L)			
	CV%	81.7	42.4	82.4	53.8
	Geometric Mean	1290	2960	564	1350
	CV% Geometric Mean	166	40.8	140	65.3
8.000	N	6	3	3	3
	Mean	1080	1970	202	480
	SD	1100	833	136	174
	Min	51.0	1040	51.0	285
	Median	676	2210	240	535
	Max	2650	2650	316	619
	CV%	102	42.4	67.4	36.3
	Geometric Mean	535	1820	157	455
	CV% Geometric Mean	298	53.0	127	43.1
16.000	N	6	3	3	3
	Mean	25.5	21.9	29.1	57.4
	SD	27.6	30.3	30.7	81.6
	Min	3.28	3.28	9.71	7.31
	Median	11.4	5.44	13.2	13.2
	Max	64.4	56.9	64.4	152
	CV%	108	139	105	142
	Geometric Mean	14.2	10.0	20.2	24.5
	CV% Geometric Mean	185	303	134	350
24.000	N	3	3		
	Mean	1.39	1.39		
	SD	0.494	0.494		
	Min	1.03	1.03		
	Median	1.19	1.19		
	Max	1.95	1.95		
	CV%	35.6	35.6		
	Geometric Mean	1.34	1.34		
	CV% Geometric Mean	34.6	34.6		

Table 4.3: Tazemetostat Ct Data Listings by Subject, Analyte, Group, and Time

Study	Subject	Analyte	Group	Time (hr)	Concentration (ug/L)
Aggregate	97.00	Tazemetostat	Plasma	0.13	225.33
Aggregate	97.00	Tazemetostat	Plasma	1.00	7442.00
Aggregate	97.00	Tazemetostat	Plasma	16.00	5.44
Aggregate	98.00	Tazemetostat	Plasma	0.13	840.37
Aggregate	98.00	Tazemetostat	Plasma	1.00	1973.40
Aggregate	98.00	Tazemetostat	Plasma	16.00	56.88
Aggregate	99.00	Tazemetostat	Plasma	0.13	1971.00
Aggregate	99.00	Tazemetostat	Plasma	1.00	4567.60
Aggregate	99.00	Tazemetostat	Plasma	16.00	3.28
Aggregate	100.00	Tazemetostat	Plasma	0.25	9000.00
Aggregate	100.00	Tazemetostat	Plasma	2.00	1866.10
Aggregate	100.00	Tazemetostat	Plasma	24.00	1.03
Aggregate	101.00	Tazemetostat	Plasma	0.25	4282.90
Aggregate	101.00	Tazemetostat	Plasma	2.00	762.81
Aggregate	101.00	Tazemetostat	Plasma	24.00	1.19
Aggregate	102.00	Tazemetostat	Plasma	0.25	6129.70
Aggregate	102.00	Tazemetostat	Plasma	2.00	2261.50
Aggregate	102.00	Tazemetostat	Plasma	24.00	1.95
Aggregate	103.00	Tazemetostat	Plasma	0.50	6838.90
Aggregate	103.00	Tazemetostat	Plasma	4.00	2382.90
Aggregate	103.00	Tazemetostat	Plasma	8.00	2211.00
Aggregate	104.00	Tazemetostat	Plasma	0.50	9263.00
Aggregate	104.00	Tazemetostat	Plasma	4.00	2333.40
Aggregate	104.00	Tazemetostat	Plasma	8.00	1037.40
Aggregate	105.00	Tazemetostat	Plasma	0.50	10365.00
Aggregate	105.00	Tazemetostat	Plasma	4.00	4650.80
Aggregate	105.00	Tazemetostat	Plasma	8.00	2648.20
Aggregate	106.00	Tazemetostat	Plasma	0.13	1338.20
Aggregate	107.00	Tazemetostat	Plasma	0.13	1999.00
Aggregate	108.00	Tazemetostat	Plasma	0.13	2435.30
Aggregate	109.00	Tazemetostat	Plasma	1.00	2198.50
Aggregate	110.00	Tazemetostat	Plasma	1.00	3140.90
Aggregate	111.00	Tazemetostat	Plasma	1.00	3483.20
Aggregate	112.00	Tazemetostat	Plasma	4.00	1439.90
Aggregate	113.00	Tazemetostat	Plasma	4.00	183.45
Aggregate	114.00	Tazemetostat	Plasma	4.00	680.77
Aggregate	115.00	Tazemetostat	Plasma	8.00	239.75
Aggregate	116.00	Tazemetostat	Plasma	8.00	51.01
Aggregate	117.00	Tazemetostat	Plasma	8.00	315.58
Aggregate	118.00	Tazemetostat	Plasma	16.00	9.71
Aggregate	119.00	Tazemetostat	Plasma	16.00	64.45

Tazemetostat Screening Plasma Tumor PK (SPTPK)

Study	Subject	Analyte	Group	Time (hr)	Concentration (ug/L)
Aggregate	120.00	Tazemetostat	Plasma	16.00	13.17
SPPK	97.00	Tazemetostat	Plasma	0.13	225.33
SPPK	97.00	Tazemetostat	Plasma	1.00	7442.00
SPPK	97.00	Tazemetostat	Plasma	16.00	5.44
SPPK	98.00	Tazemetostat	Plasma	0.13	840.37
SPPK	98.00	Tazemetostat	Plasma	1.00	1973.40
SPPK	98.00	Tazemetostat	Plasma	16.00	56.88
SPPK	99.00	Tazemetostat	Plasma	0.13	1971.00
SPPK	99.00	Tazemetostat	Plasma	1.00	4567.60
SPPK	99.00	Tazemetostat	Plasma	16.00	3.28
SPPK	100.00	Tazemetostat	Plasma	0.25	9000.00
SPPK	100.00	Tazemetostat	Plasma	2.00	1866.10
SPPK	100.00	Tazemetostat	Plasma	24.00	1.03
SPPK	101.00	Tazemetostat	Plasma	0.25	4282.90
SPPK	101.00	Tazemetostat	Plasma	2.00	762.81
SPPK	101.00	Tazemetostat	Plasma	24.00	1.19
SPPK	102.00	Tazemetostat	Plasma	0.25	6129.70
SPPK	102.00	Tazemetostat	Plasma	2.00	2261.50
SPPK	102.00	Tazemetostat	Plasma	24.00	1.95
SPPK	103.00	Tazemetostat	Plasma	0.50	6838.90
SPPK	103.00	Tazemetostat	Plasma	4.00	2382.90
SPPK	103.00	Tazemetostat	Plasma	8.00	2211.00
SPPK	104.00	Tazemetostat	Plasma	0.50	9263.00
SPPK	104.00	Tazemetostat	Plasma	4.00	2333.40
SPPK	104.00	Tazemetostat	Plasma	8.00	1037.40
SPPK	105.00	Tazemetostat	Plasma	0.50	10365.00
SPPK	105.00	Tazemetostat	Plasma	4.00	4650.80
SPPK	105.00	Tazemetostat	Plasma	8.00	2648.20
SPTPK	106.00	Tazemetostat	Plasma	0.13	1338.20
SPTPK	106.00	Tazemetostat	Tumor	0.13	63.87
SPTPK	107.00	Tazemetostat	Plasma	0.13	1999.00
SPTPK	107.00	Tazemetostat	Tumor	0.13	4903.00
SPTPK	108.00	Tazemetostat	Plasma	0.13	2435.30
SPTPK	108.00	Tazemetostat	Tumor	0.13	305.80
SPTPK	109.00	Tazemetostat	Plasma	1.00	2198.50
SPTPK	109.00	Tazemetostat	Tumor	1.00	2588.80
SPTPK	110.00	Tazemetostat	Plasma	1.00	3140.90
SPTPK	110.00	Tazemetostat	Tumor	1.00	5147.00
SPTPK	111.00	Tazemetostat	Plasma	1.00	3483.20
SPTPK	111.00	Tazemetostat	Tumor	1.00	1545.90
SPTPK	112.00	Tazemetostat	Plasma	4.00	1439.90
SPTPK	112.00	Tazemetostat	Tumor	4.00	2336.30
SPTPK	113.00	Tazemetostat	Plasma	4.00	183.45

Study	Subject	Analyte	Group	Time (hr)	Concentration (ug/L)
SPTPK	113.00	Tazemetostat	Tumor	4.00	715.75
SPTPK	114.00	Tazemetostat	Plasma	4.00	680.77
SPTPK	114.00	Tazemetostat	Tumor	4.00	1467.60
SPTPK	115.00	Tazemetostat	Plasma	8.00	239.75
SPTPK	115.00	Tazemetostat	Tumor	8.00	535.27
SPTPK	116.00	Tazemetostat	Plasma	8.00	51.01
SPTPK	116.00	Tazemetostat	Tumor	8.00	284.99
SPTPK	117.00	Tazemetostat	Plasma	8.00	315.58
SPTPK	117.00	Tazemetostat	Tumor	8.00	619.44
SPTPK	118.00	Tazemetostat	Plasma	16.00	9.71
SPTPK	118.00	Tazemetostat	Tumor	16.00	151.54
SPTPK	119.00	Tazemetostat	Plasma	16.00	64.45
SPTPK	119.00	Tazemetostat	Tumor	16.00	13.22
SPTPK	120.00	Tazemetostat	Plasma	16.00	13.17
SPTPK	120.00	Tazemetostat	Tumor	16.00	7.31

Table 4.4: Tazemetostat Ct Summary (Mean, SD, N) by Study and Group

Variable	Units	Analyte	Study	Group	Time (hr)	Mean (ug/L)	SD (ug/L)	N
Concentration	ug/L	Tazemetostat	Aggregate	Plasma	0.13	1468.20	827.72	6.00
Concentration	ug/L	Tazemetostat	Aggregate	Plasma	0.25	6470.87	2376.98	3.00
Concentration	ug/L	Tazemetostat	Aggregate	Plasma	0.50	8822.30	1803.89	3.00
Concentration	ug/L	Tazemetostat	Aggregate	Plasma	1.00	3800.93	2014.42	6.00
Concentration	ug/L	Tazemetostat	Aggregate	Plasma	2.00	1630.14	776.71	3.00
Concentration	ug/L	Tazemetostat	Aggregate	Plasma	4.00	1945.20	1588.74	6.00
Concentration	ug/L	Tazemetostat	Aggregate	Plasma	8.00	1083.82	1103.57	6.00
Concentration	ug/L	Tazemetostat	Aggregate	Plasma	16.00	25.49	27.56	6.00
Concentration	ug/L	Tazemetostat	Aggregate	Plasma	24.00	1.39	0.49	3.00
Concentration	ug/L	Tazemetostat	SPPK	Plasma	0.13	1012.23	885.43	3.00
Concentration	ug/L	Tazemetostat	SPPK	Plasma	0.25	6470.87	2376.98	3.00
Concentration	ug/L	Tazemetostat	SPPK	Plasma	0.50	8822.30	1803.89	3.00
Concentration	ug/L	Tazemetostat	SPPK	Plasma	1.00	4661.00	2735.50	3.00
Concentration	ug/L	Tazemetostat	SPPK	Plasma	2.00	1630.14	776.71	3.00
Concentration	ug/L	Tazemetostat	SPPK	Plasma	4.00	3122.37	1323.89	3.00
Concentration	ug/L	Tazemetostat	SPPK	Plasma	8.00	1965.53	832.98	3.00
Concentration	ug/L	Tazemetostat	SPPK	Plasma	16.00	21.86	30.34	3.00
Concentration	ug/L	Tazemetostat	SPPK	Plasma	24.00	1.39	0.49	3.00
Concentration	ug/L	Tazemetostat	SPTPK	Plasma	0.13	1924.17	552.37	3.00
Concentration	ug/L	Tazemetostat	SPTPK	Plasma	1.00	2940.87	665.30	3.00
Concentration	ug/L	Tazemetostat	SPTPK	Plasma	4.00	768.04	632.75	3.00
Concentration	ug/L	Tazemetostat	SPTPK	Plasma	8.00	202.11	136.24	3.00
Concentration	ug/L	Tazemetostat	SPTPK	Plasma	16.00	29.11	30.65	3.00
Concentration	ug/L	Tazemetostat	SPTPK	Tumor	0.13	1757.56	2726.72	3.00

Variable	Units	Analyte	Study	Group	Time (hr)	Mean (ug/L)	SD (ug/L)	N
Concentration	ug/L	Tazemetostat	SPTPK	Tumor	1.00	3093.90	1852.92	3.00
Concentration	ug/L	Tazemetostat	SPTPK	Tumor	4.00	1506.55	810.98	3.00
Concentration	ug/L	Tazemetostat	SPTPK	Tumor	8.00	479.90	173.96	3.00
Concentration	ug/L	Tazemetostat	SPTPK	Tumor	16.00	57.36	81.62	3.00

5.0 ATTACHED FILES

Attached File 5.1 Tazemetostat Screening Plasma PK DBSTP.docx – *Final in vivo study plan as executed (SRM2 O/R 124312-1298569, SPPK)*

Attached File 5.2 Tazemetostat SPTPK A204.docx – *Final in vivo study plan as executed (SRM2 O/R 133410-1396203, SPTPK)*

Attached File 5.3 Tazemetostat PK_non tumor.docx – *Digital data collection form from SPPK in vivo study*

Attached File 5.4 Tazemetostat PK tumor bearing study sheet 2.docx – *Digital data collection form from in vivo SPTPK study*

Attached File 5.5 Tazemetostat Screening Plasma and Tumor PK TLFs.docx – *Tables, listings, and figures from SPTPK report in Word document for reformatting or manipulations*