PRECLINICAL PHARMACOKINETIC REPORT

Developmental Biology and Solid Tumor Program

P-PKSR Study 128058-1341154

STUDY TITLE:

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

SHORT TITLE:	**Selumetinib Screening Plasma Tumor PK (SPTPK)**
TEST ARTICLE:	Selumetinib sulfate
SECTION:	Nonclinical Pharmacokinetics (Non-GLP)
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SJCRH SRM2 O/R:	128058-1341154 Preclinical Pharmacokinetic Shared Resource 124312-1298567
REFERENCE STUDY NUMBERS:	NA NA
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REPORT FORMAT:	Study Summary
REPORT STATUS:	FINAL
DATE:	2020-04-16

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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 selumetinib were conducted in female Athymic nude mice (Charles River Laboratories, Frederick, MD) and are summarized below.

The first selumetinib PK study (SRM2 O/R 124312-1298567, SPPK) was a survival plasma PK evaluation using non-tumor bearing Athymic nude mice. Selumetinib sulfate was suspended in 1% hydroxyethylcellulose (MW 720,000), 0.25% Tween 80, and ~0.05% simethicone at 1 mg/mL free base equivalents and administered as a 10 mL/kg oral gavage for a 10 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 selumetinib PK study (SRM2 O/R 128058-1341154, SPTPK), the plasma and tumor PK were evaluated after a single oral dose of the selumetinib sulfate 10 mg/kg suspension. Female Athymic nude mice bearing rhabdomyosarcoma (MAST 39) 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, selumetinib 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 selumetinib (sulfate salt, Abmole, Lot # NA, purity 100%) 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 7.25 ng/mL LY3023414 (ADOOQ, Lot # L16126B001, purity 96.6%) in acetonitrile as an internal

standard. A 3 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 Phenomenex Kinetex EVO (2.6 µm C18 100Å, 50 x 2.1 mm) column maintained at 50 °C with gradient elution at a flow rate of 0.5 mL/min. The binary mobile phase consisted of water-acetonitrile-200 mM ammonium acetate pH 6.0 (90:10:10 v/v/v) in reservoir A and acetonitrile-water-200 mM ammonium acetate pH 6.0 (90:10:10 v/v/v) in reservoir B. The initial mobile phase consisted of 10% B with a linear increase to 100% B in 4 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 7 min. Under these conditions, the analyte and IS eluted at 1.64 and 1.36 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: 457.00 -> 395.00 for selumetinib and 407.20 -> 319.10 for LY3023414.

The method qualification and bioanalytical runs all passed 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 0.9993. 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 ≤ 6.23% CV and 95.3% to 97.6%, respectively.

1.3 Pharmacokinetic (PK) Analysis

The resultant selumetinib 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 selumetinib 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 selumetinib 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 selumetinib of 25 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.

The plasma and tumor PK of selumetinib was well-behaved in our mice, demonstrating low Ct CV% values, and exposure was within 2.5-fold of that reported by Denton [3]. Penetration to the tumor was relatively slow and poor, with tumor only achieving ~14% of plasma exposure. At the RP2D of 25 mg/m^2 PO BID in a typical child, the plasma AUCtau was 3210 hr-ug/L [2], with an estimated AUCu of 36.6 hr-ug/L (Fu,p,h = 0.0114). Our measured mouse Fu,p was similar at 0.0109. The mouse plasma AUCinf at 10 mg/kg was 42000 hr-ug/L, yielding an AUCu of 458 hr-ug/L. A strict CRD would therefore be 0.8 mg/kg PO BID. However, given the low tumor penetration, a higher dose of 1.25 mg/kg was suggested, which at ~60% higher than the target clinical exposure still meets the within 2-fold criteria.

3.0 REFERENCES

1. Romer J, Bickel MH. A method to estimate binding constants at variable protein concentrations. J Pharm Pharmacol. 1979;31(1):7–11.

2. Patel Y, Daryani V, Patel P, Zhou D, Fangusaro J, Carlile D, Martin P, Aarons L, Stewart C. Population Pharmacokinetics of Selumetinib and Its Metabolite N-desmethyl-selumetinib in Adult Patients With Advanced Solid Tumors and Children With Low-Grade Gliomas. CPT Pharmacomet Syst Pharmacol. 2017 May 1;6(5):305–14.

3. Denton CL, Gustafson DL. Pharmacokinetics and pharmacodynamics of AZD6244 (ARRY-142886) in tumor-bearing nude mice. Cancer Chemother Pharmacol. 2011 Feb 1;67(2):349–60.

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4.0 TABLES, LISTINGS, AND FIGURES (TLFS)

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

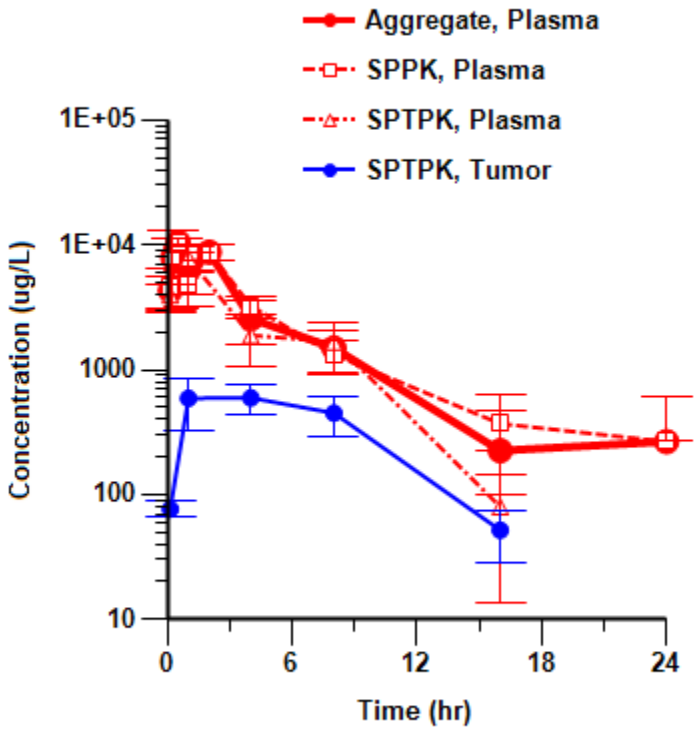

Table 4.1: NCA PK Parameter Estimates of Selumetinib by Group

		Analyte			
		Selumetinib			
		Study			
		Aggregate	SPPK	SPTPK	
		Group	Group	Group	
		Plasma	Plasma	Plasma	Tumor
Parameter	Units	Estimate			
Cmax	ug/L	10500	10500	7830	595
Tmax	hr	0.500	0.500	1.00	4.00
AUClast	hr*ug/L	40300	41900	29200	5620
AUCinf	hr*ug/L	42000	44100	29600	5900
Kel	1/hr	0.108	0.100	0.280	0.213
T1/2	hr	6.42	6.92	2.47	3.26
CL/F	L/hr/kg	0.238	0.227	0.338	1.70
Vz/F	L/kg	2.20	2.26	1.21	7.97

		Analyte			
		Selumetinib			
		Study			
		Aggregate	SPPK	SPTPK	
		Group	Group	Group	
		Plasma	Plasma	Plasma	Tumor
Parameter	Units	Estimate			
Clast	ug/L	265	265	79.9	51.8
Tlast	hr	24.0	24.0	16.0	16.0
Kp,tumor*	-	*	-	-	0.141

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

Table 4.2: Full Summary Statistics of Selumetinib Ct Data by Group

		Analyte			
		Selumetinib			
		Study			
		Aggregate	SPPK	SPTPK	
		Group	Group	Group	
		Plasma	Plasma	Plasma	Tumor
Time (hr)		Concentration (ug/L)			
0.125	N	6	3	3	3
	Mean	4300	4640	3960	76.6
	SD	1300	1770	851	10.9
	Min	3290	3290	3420	65.8
	Median	3760	4000	3520	76.4
	Max	6650	6650	4940	87.6
	CV%	30.1	38.1	21.5	14.2
	Geometric Mean	4160	4440	3910	76.0
	CV% Geometric Mean	27.8	37.5	20.7	14.4
0.250	N	3	3		
	Mean	7980	7980		
	SD	4870	4870		
	Min	3710	3710		
	Median	6940	6940		
	Max	13300	13300		
	CV%	61.0	61.0		
	Geometric Mean	6990	6990		
	CV% Geometric Mean	70.8	70.8		
0.500	N	3	3		
	Mean	10500	10500		
	SD	610	610		
	Min	10100	10100		
	Median	10200	10200		
	Max	11200	11200		
	CV%	5.79	5.79		
	Geometric Mean	10500	10500		
	CV% Geometric Mean	5.71	5.71		
1.000	N	6	3	3	3

Selumetinib Screening Plasma Tumor PK (SPTPK)

		Analyte			
		Selumetinib			
		Study			
		Aggregate	SPPK	SPTPK	
		Group	Group	Group	
		Plasma	Plasma	Plasma	Tumor
Time (hr)		Concentration (ug/L)			
	Mean	6270	4720	7830	591
	SD	2270	1510	1830	263
	Min	3210	3210	5870	409
	Median	6050	4690	8130	471
	Max	9490	6240	9490	893
	CV%	36.2	32.1	23.4	44.5
	Geometric Mean	5910	4550	7680	556
	CV% Geometric Mean	40.3	34.2	24.9	43.5
2.000	N	3	3		
	Mean	8740	8740		
	SD	1270	1270		
	Min	7280	7280		
	Median	9370	9370		
	Max	9570	9570		
	CV%	14.5	14.5		
	Geometric Mean	8680	8680		
	CV% Geometric Mean	15.3	15.3		
4.000	N	6	3	3	3
	Mean	2570	3250	1890	595
	SD	1000	655	827	162
	Min	951	2870	951	411
	Median	2690	2870	2190	658
	Max	4010	4010	2520	716
	CV%	39.0	20.2	43.8	27.2
	Geometric Mean	2360	3210	1740	579
	CV% Geometric Mean	51.9	19.4	56.6	30.6
8.000	N	6	3	3	3
	Mean	1490	1320	1670	449
	SD	566	410	734	163
	Min	900	1050	900	293
	Median	1430	1110	1750	437
	Max	2360	1790	2360	618
	CV%	37.9	31.1	43.9	36.3
	Geometric Mean	1410	1280	1550	429
	CV% Geometric Mean	39.2	29.9	52.6	38.8
16.000	N	6	3	3	3
	Mean	225	370	79.9	51.8
	SD	236	269	66.3	23.0
	Min	28.7	182	28.7	26.4
	Median	169	249	56.1	57.9
	Max	678	678	155	71.2
	CV%	105	72.8	83.0	44.4

		Analyte			
		Selumetinib			
		Study			
		Aggregate	SPPK	SPTPK	
		Group	Group	Group	
		Plasma	Plasma	Plasma	Tumor
Time (hr)		Concentration (ug/L)			
	Geometric Mean	140	313	62.9	47.8
	CV% Geometric Mean	158	77.5	103	56.1
24.000	N	3	3		
	Mean	265	265		
	SD	345	345		
	Min	1.37	1.37		
	Median	139	139		
	Max	655	655		
	CV%	130	130		
	Geometric Mean	50.0	50.0		
	CV% Geometric Mean	17300	17300		

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

Study	Subject	Analyte	Time (hr)	Group	Concentration (ug/L)
Aggregate	1.00	Selumetinib	0.13	Plasma	6646.42
Aggregate	1.00	Selumetinib	1.00	Plasma	6238.86
Aggregate	1.00	Selumetinib	16.00	Plasma	182.48
Aggregate	2.00	Selumetinib	0.13	Plasma	3996.15
Aggregate	2.00	Selumetinib	1.00	Plasma	4694.65
Aggregate	2.00	Selumetinib	16.00	Plasma	677.99
Aggregate	3.00	Selumetinib	0.13	Plasma	3291.65
Aggregate	3.00	Selumetinib	1.00	Plasma	3212.99
Aggregate	3.00	Selumetinib	16.00	Plasma	248.58
Aggregate	4.00	Selumetinib	0.25	Plasma	13276.30
Aggregate	4.00	Selumetinib	2.00	Plasma	9572.33
Aggregate	4.00	Selumetinib	24.00	Plasma	1.37
Aggregate	5.00	Selumetinib	0.25	Plasma	6943.36
Aggregate	5.00	Selumetinib	2.00	Plasma	7284.06
Aggregate	5.00	Selumetinib	24.00	Plasma	139.19
Aggregate	6.00	Selumetinib	0.25	Plasma	3711.33
Aggregate	6.00	Selumetinib	2.00	Plasma	9366.28
Aggregate	6.00	Selumetinib	24.00	Plasma	655.42
Aggregate	7.00	Selumetinib	0.50	Plasma	11237.82
Aggregate	7.00	Selumetinib	4.00	Plasma	2869.35
Aggregate	7.00	Selumetinib	8.00	Plasma	1049.49
Aggregate	8.00	Selumetinib	0.50	Plasma	10130.06
Aggregate	8.00	Selumetinib	4.00	Plasma	2870.26
Aggregate	8.00	Selumetinib	8.00	Plasma	1112.30
Aggregate	9.00	Selumetinib	0.50	Plasma	10239.66

Selumetinib Screening Plasma Tumor PK (SPTPK)

Study	Subject	Analyte	Time (hr)	Group	Concentration (ug/L)
Aggregate	9.00	Selumetinib	4.00	Plasma	4005.10
Aggregate	9.00	Selumetinib	8.00	Plasma	1788.80
Aggregate	10.00	Selumetinib	0.13	Plasma	4942.74
Aggregate	11.00	Selumetinib	0.13	Plasma	3520.02
Aggregate	12.00	Selumetinib	0.13	Plasma	3422.89
Aggregate	13.00	Selumetinib	1.00	Plasma	9491.86
Aggregate	14.00	Selumetinib	1.00	Plasma	5866.55
Aggregate	15.00	Selumetinib	1.00	Plasma	8133.63
Aggregate	16.00	Selumetinib	4.00	Plasma	2515.85
Aggregate	17.00	Selumetinib	4.00	Plasma	950.78
Aggregate	18.00	Selumetinib	4.00	Plasma	2194.43
Aggregate	19.00	Selumetinib	8.00	Plasma	1750.60
Aggregate	20.00	Selumetinib	8.00	Plasma	899.54
Aggregate	21.00	Selumetinib	8.00	Plasma	2361.26
Aggregate	22.00	Selumetinib	16.00	Plasma	28.71
Aggregate	23.00	Selumetinib	16.00	Plasma	154.74
Aggregate	24.00	Selumetinib	16.00	Plasma	56.14
SPPK	1.00	Selumetinib	0.13	Plasma	6646.42
SPPK	1.00	Selumetinib	1.00	Plasma	6238.86
SPPK	1.00	Selumetinib	16.00	Plasma	182.48
SPPK	2.00	Selumetinib	0.13	Plasma	3996.15
SPPK	2.00	Selumetinib	1.00	Plasma	4694.65
SPPK	2.00	Selumetinib	16.00	Plasma	677.99
SPPK	3.00	Selumetinib	0.13	Plasma	3291.65
SPPK	3.00	Selumetinib	1.00	Plasma	3212.99
SPPK	3.00	Selumetinib	16.00	Plasma	248.58
SPPK	4.00	Selumetinib	0.25	Plasma	13276.30
SPPK	4.00	Selumetinib	2.00	Plasma	9572.33
SPPK	4.00	Selumetinib	24.00	Plasma	1.37
SPPK	5.00	Selumetinib	0.25	Plasma	6943.36
SPPK	5.00	Selumetinib	2.00	Plasma	7284.06
SPPK	5.00	Selumetinib	24.00	Plasma	139.19
SPPK	6.00	Selumetinib	0.25	Plasma	3711.33
SPPK	6.00	Selumetinib	2.00	Plasma	9366.28
SPPK	6.00	Selumetinib	24.00	Plasma	655.42
SPPK	7.00	Selumetinib	0.50	Plasma	11237.82
SPPK	7.00	Selumetinib	4.00	Plasma	2869.35
SPPK	7.00	Selumetinib	8.00	Plasma	1049.49
SPPK	8.00	Selumetinib	0.50	Plasma	10130.06
SPPK	8.00	Selumetinib	4.00	Plasma	2870.26
SPPK	8.00	Selumetinib	8.00	Plasma	1112.30
SPPK	9.00	Selumetinib	0.50	Plasma	10239.66
SPPK	9.00	Selumetinib	4.00	Plasma	4005.10
SPPK	9.00	Selumetinib	8.00	Plasma	1788.80
SPTPK	10.00	Selumetinib	0.13	Plasma	4942.74
SPTPK	10.00	Selumetinib	0.13	Tumor	87.57
SPTPK	11.00	Selumetinib	0.13	Plasma	3520.02

Study	Subject	Analyte	Time (hr)	Group	Concentration (ug/L)
SPTPK	11.00	Selumetinib	0.13	Tumor	76.38
SPTPK	12.00	Selumetinib	0.13	Plasma	3422.89
SPTPK	12.00	Selumetinib	0.13	Tumor	65.75
SPTPK	13.00	Selumetinib	1.00	Plasma	9491.86
SPTPK	13.00	Selumetinib	1.00	Tumor	892.56
SPTPK	14.00	Selumetinib	1.00	Plasma	5866.55
SPTPK	14.00	Selumetinib	1.00	Tumor	408.69
SPTPK	15.00	Selumetinib	1.00	Plasma	8133.63
SPTPK	15.00	Selumetinib	1.00	Tumor	471.23
SPTPK	16.00	Selumetinib	4.00	Plasma	2515.85
SPTPK	16.00	Selumetinib	4.00	Tumor	716.32
SPTPK	17.00	Selumetinib	4.00	Plasma	950.78
SPTPK	17.00	Selumetinib	4.00	Tumor	411.08
SPTPK	18.00	Selumetinib	4.00	Plasma	2194.43
SPTPK	18.00	Selumetinib	4.00	Tumor	658.30
SPTPK	19.00	Selumetinib	8.00	Plasma	1750.60
SPTPK	19.00	Selumetinib	8.00	Tumor	618.04
SPTPK	20.00	Selumetinib	8.00	Plasma	899.54
SPTPK	20.00	Selumetinib	8.00	Tumor	292.50
SPTPK	21.00	Selumetinib	8.00	Plasma	2361.26
SPTPK	21.00	Selumetinib	8.00	Tumor	437.34
SPTPK	22.00	Selumetinib	16.00	Plasma	28.71
SPTPK	22.00	Selumetinib	16.00	Tumor	26.42
SPTPK	23.00	Selumetinib	16.00	Plasma	154.74
SPTPK	23.00	Selumetinib	16.00	Tumor	71.20
SPTPK	24.00	Selumetinib	16.00	Plasma	56.14
SPTPK	24.00	Selumetinib	16.00	Tumor	57.92

Table 4.4: Selumetinib Ct Summary (Mean, SD, N) by Group

Variable	Units	Analyte	Study	Group	Time (hr)	Mean (ug/L)	SD (ug/L)	N
Concentration	ug/L	Selumetinib	Aggregate	Plasma	0.13	4303.31	1296.58	6.00
Concentration	ug/L	Selumetinib	Aggregate	Plasma	0.25	7977.00	4865.53	3.00
Concentration	ug/L	Selumetinib	Aggregate	Plasma	0.50	10535.85	610.39	3.00
Concentration	ug/L	Selumetinib	Aggregate	Plasma	1.00	6273.09	2273.51	6.00
Concentration	ug/L	Selumetinib	Aggregate	Plasma	2.00	8740.89	1265.85	3.00
Concentration	ug/L	Selumetinib	Aggregate	Plasma	4.00	2567.63	1000.51	6.00
Concentration	ug/L	Selumetinib	Aggregate	Plasma	8.00	1493.67	565.96	6.00
Concentration	ug/L	Selumetinib	Aggregate	Plasma	16.00	224.77	236.45	6.00
Concentration	ug/L	Selumetinib	Aggregate	Plasma	24.00	265.33	344.79	3.00
Concentration	ug/L	Selumetinib	SPPK	Plasma	0.13	4644.74	1768.93	3.00
Concentration	ug/L	Selumetinib	SPPK	Plasma	0.25	7977.00	4865.53	3.00
Concentration	ug/L	Selumetinib	SPPK	Plasma	0.50	10535.85	610.39	3.00
Concentration	ug/L	Selumetinib	SPPK	Plasma	1.00	4715.50	1513.04	3.00
Concentration	ug/L	Selumetinib	SPPK	Plasma	2.00	8740.89	1265.85	3.00
Concentration	ug/L	Selumetinib	SPPK	Plasma	4.00	3248.24	655.46	3.00

Variable	Units	Analyte	Study	Group	Time (hr)	Mean (ug/L)	SD (ug/L)	N
Concentration	ug/L	Selumetinib	SPPK	Plasma	8.00	1316.86	409.91	3.00
Concentration	ug/L	Selumetinib	SPPK	Plasma	16.00	369.69	269.04	3.00
Concentration	ug/L	Selumetinib	SPPK	Plasma	24.00	265.33	344.79	3.00
Concentration	ug/L	Selumetinib	SPTPK	Plasma	0.13	3961.88	850.83	3.00
Concentration	ug/L	Selumetinib	SPTPK	Plasma	1.00	7830.68	1831.54	3.00
Concentration	ug/L	Selumetinib	SPTPK	Plasma	4.00	1887.02	826.58	3.00
Concentration	ug/L	Selumetinib	SPTPK	Plasma	8.00	1670.47	734.15	3.00
Concentration	ug/L	Selumetinib	SPTPK	Plasma	16.00	79.86	66.28	3.00
Concentration	ug/L	Selumetinib	SPTPK	Tumor	0.13	76.57	10.91	3.00
Concentration	ug/L	Selumetinib	SPTPK	Tumor	1.00	590.83	263.17	3.00
Concentration	ug/L	Selumetinib	SPTPK	Tumor	4.00	595.23	162.10	3.00
Concentration	ug/L	Selumetinib	SPTPK	Tumor	8.00	449.29	163.10	3.00
Concentration	ug/L	Selumetinib	SPTPK	Tumor	16.00	51.85	23.00	3.00

5.0 ATTACHED FILES

Attached File 5.1 Selumetinib Screening Plasma PK.docx – *Final in vivo study plan as executed (SRM2 O/R 124312-1298570, SPPK)*

Attached File 5.2 Selumetinib Screening Plasma and Tumor PK.docx – *Final in vivo study plan as executed (SRM2 O/R 134278-1406200, SPTPK)*

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

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

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