PRECLINICAL PHARMACOKINETIC REPORT

Developmental Biology and Solid Tumor Program

P-PKSR Study 130292-1364586

STUDY TITLE:

SCREENING PLASMA AND TUMOR PHARMACOKINETICS (SPTPK) OF LY3023414 IN FEMALE ATHYMIC NUDE MICE AFTER A SINGLE ORAL DOSE

SHORT TITLE:	**LY3023414 Screening Plasma Tumor PK (SPTPK)**
TEST ARTICLE:	LY3023414
SECTION:	Nonclinical Pharmacokinetics (Non-GLP)
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SJCRH SRM2 O/R:	130292-1364586 Preclinical Pharmacokinetic Shared Resource 124312-1298566
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 LY3023414 were conducted in female Athymic nude mice (Charles River Laboratories, Frederick, MD) and are summarized below.

The first LY3023414 PK study (SRM2 O/R 124312-1298566, SPPK) was a survival plasma PK evaluation using non-tumor bearing Athymic nude mice. LY3023414 was suspended in 1% hydroxyethylcellulose (MW 720,000), 0.25% Tween 80, and ~0.05% simethicone at 1.5 mg/mL and administered as a 10 mL/kg oral gavage for a 15 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 LY3023414 PK study (SRM2 O/R 130292-1364586, SPTPK), the plasma and tumor PK were evaluated after a single oral dose of the LY3023414 15 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, LY3023414 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 LY3023414 (ADOOQ, Lot # L16126B001, purity 96.6%) 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 selumetinib (Abmole, Lot # NA, purity 100%) 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 1.37 and 1.65 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: 407.20 -> 319.10 for LY3023414 and 457.00 -> 395.00 for selumetinib.

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 0.9995. 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 ≤ 4.18% CV and 96.8% to 104.0%, respectively.

1.3 Pharmacokinetic (PK) Analysis

In the SPPK study, to compare sampling techniques at termination, a retro-orbital bleed and cardiac puncture was obtained from each mouse. All observations were used in the summary and PK analyses.

The resultant LY3023414 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 LY3023414 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 LY3023414 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 LY3023414 of 200 mg PO BID [2,3]. 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.

When comparing the retro-orbital bleed to the paired cardiac puncture (n=6 above LLOQ observations) in the SPPK study, the retro-orbital bleeds tended to produce a lower result, -5.19% on average. The smallest deviation was -3.62%, and the largest was -49.5%. Similar bias between ROB and cardiac puncture results was previously observed (RPT.124103-1295433). The cause for this bias remains uncertain, but could be technique- or device- related, or represent a difference in drug distribution at sampling sites. The bias remains within 15%, and such is within assay error, and can be considered negligible.

LY3023414 demonstrated rapid absorption (Tmax = 0.25 hr) and a favorable PK profile in our mice. Tumor penetration was modest with a Kp,inf of 0.529. In adults, at the RP2D of 200 mg PO BID, the plasma AUCtau was 3670 hr-ug/L [2,3], yielding an AUCu of 456 hr-ug/L (Fu,p,h = 0.124). Mice demonstrated an AUCinf of 5800 hr-ug/L at 15 mg/kg PO, and an AUCu of 696 hr-ug/L. A strict calculated CRD with our data would be 10 mg/kg; however, as the literature reported free fraction in plasma in humans is higher (Fu,p,h = 0.17) [4], and since 15 mg/kg is the was a commonly applied mouse dosage in publications, the proposed CRD was 15 mg/kg PO BID.

3.0 REFERENCES

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4.0 TABLES, LISTINGS, AND FIGURES (TLFS)

Figure 4.1: Mean (SD) Ct Profile of LY3023414 by Group

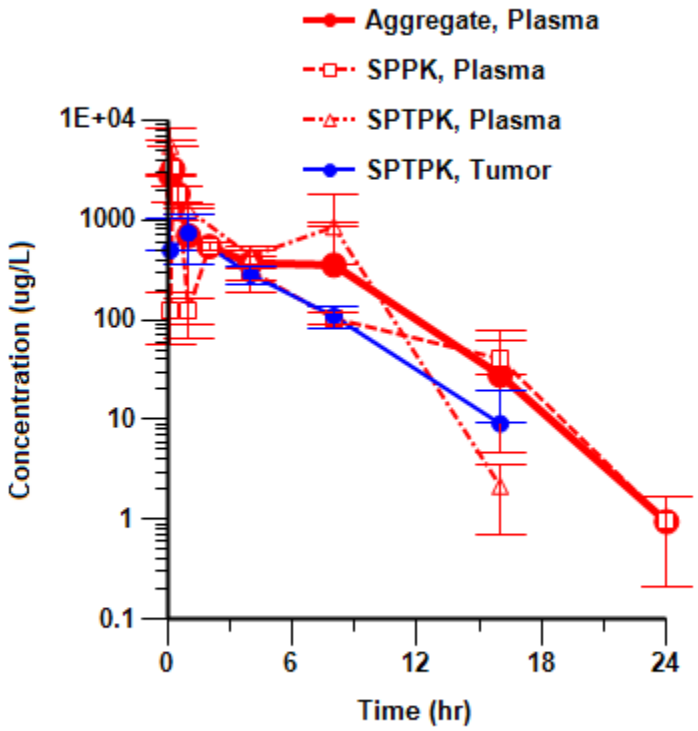

Table 4.1: NCA PK Parameter Estimates of LY3023414 by Group

		Analyte			
		LY3023414			
		Study			
		Aggregate	SPPK	SPTPK	
		Group	Group	Group	
		Plasma	Plasma	Plasma	Tumor
Parameter	Units	Estimate			
Cmax	ug/L	3230	3230	5520	738
Tmax	hr	0.250	0.250	0.125	1.00
AUClast	hr*ug/L	5800	3680	8900	3040
AUCinf	hr*ug/L	5800	3680	8910	3070
Kel	1/hr	0.370	0.293	0.485	0.290
T1/2	hr	1.87	2.37	1.43	2.39
CL/F	L/hr/kg	4.31	6.79	2.81	8.13

		Analyte			
		LY3023414			
		Study			
		Aggregate	SPPK	SPTPK	
		Group	Group	Group	
		Plasma	Plasma	Plasma	Tumor
Parameter	Units	Estimate			
Vz/F	L/kg	11.6	23.2	5.78	28.1
Clast	ug/L	0.951	0.951	2.16	9.10
Tlast	hr	24.0	24.0	16.0	16.0
Kp,tumor	-	*	-	-	0.529

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

Table 4.2: Full Summary Statistics of LY3023414 Ct Data by Group

		Analyte			
		LY3023414			
		Study			
		Aggregate	SPPK	SPTPK	
		Group	Group	Group	
		Plasma	Plasma	Plasma	Tumor
Time (hr)		Concentration (ug/L)			
0.125	N	6	3	3	3
	Mean	2820	121	5520	495
	SD	3460	65.0	2830	536
	Min	83.1	83.1	3560	31.2
	Median	1880	83.4	4240	373
	Max	8760	196	8760	1080
	CV%	123	53.8	51.3	108
	Geometric Mean	751	111	5090	233
	CV% Geometric Mean	986	52.5	50.7	513
0.250	N	3	3		
	Mean	3230	3230		
	SD	2260	2260		
	Min	877	877		
	Median	3420	3420		
	Max	5380	5380		
	CV%	70.0	70.0		
	Geometric Mean	2530	2530		
	CV% Geometric Mean	120	120		
0.500	N	3	3		

LY3023414 Screening Plasma Tumor PK (SPTPK)

		Analyte			
		LY3023414			
		Study			
		Aggregate	SPPK	SPTPK	
		Group	Group	Group	
		Plasma	Plasma	Plasma	Tumor
Time (hr)		Concentration (ug/L)			
	Mean	1820	1820		
	SD	298	298		
	Min	1520	1520		
	Median	1820	1820		
	Max	2110	2110		
	CV%	16.4	16.4		
	Geometric Mean	1800	1800		
	CV% Geometric Mean	16.7	16.7		
1.000	N	6	3	3	3
	Mean	693	125	1260	738
	SD	628	34.7	136	387
	Min	85.2	85.2	1160	323
	Median	654	144	1210	801
	Max	1410	147	1410	1090
	CV%	90.6	27.7	10.8	52.5
	Geometric Mean	391	122	1260	656
	CV% Geometric Mean	209	31.6	10.5	70.1
2.000	N	3	3		
	Mean	541	541		
	SD	58.3	58.3		
	Min	474	474		
	Median	566	566		
	Max	583	583		
	CV%	10.8	10.8		
	Geometric Mean	539	539		
	CV% Geometric Mean	11.2	11.2		
4.000	N	6	3	3	3
	Mean	370	308	433	283
	SD	119	117	100	60.9
	Min	214	214	347	237
	Median	378	271	409	259
	Max	543	439	543	352

LY3023414 Screening Plasma Tumor PK (SPTPK)

		Analyte			
		LY3023414			
		Study			
		Aggregate	SPPK	SPTPK	
		Group	Group	Group	
		Plasma	Plasma	Plasma	Tumor
Time (hr)		Concentration (ug/L)			
	CV%	32.1	38.1	23.1	21.5
	Geometric Mean	354	294	425	279
	CV% Geometric Mean	35.0	38.0	22.9	20.9
8.000	N	9	6	3	3
	Mean	353	103	854	108
	SD	606	15.6	951	25.3
	Min	85.1	85.1	158	84.2
	Median	118	104	466	106
	Max	1940	119	1940	135
	CV%	172	15.1	111	23.4
	Geometric Mean	176	102	523	106
	CV% Geometric Mean	139	15.4	196	23.9
16.000	N	9	6	3	3
	Mean	27.9	40.8	2.16	9.10
	SD	34.5	36.1	1.45	10.6
	Min	0.500	0.500	0.500	3.00
	Median	3.16	41.0	2.82	3.00
	Max	84.9	84.9	3.16	21.3
	CV%	123	88.5	67.0	116
	Geometric Mean	6.13	11.8	1.65	5.77
	CV% Geometric Mean	1250	2110	138	161
24.000	N	6	6		
	Mean	0.951	0.951		
	SD	0.736	0.736		
	Min	0.500	0.500		
	Median	0.500	0.500		
	Max	2.22	2.22		
	CV%	77.4	77.4		
	Geometric Mean	0.769	0.769		
	CV% Geometric Mean	76.4	76.4		

Table 4.3: LY3023414 Ct Data Listings by Subject, Analyte, Group, and Time

Study	Subject	Analyte	Time (hr)	Group	Concentration (ug/L)
Aggregate	25.00	LY3023414	0.13	Plasma	83.10
Aggregate	25.00	LY3023414	1.00	Plasma	85.21
Aggregate	25.00	LY3023414	16.00	Plasma	76.94
					84.89
Aggregate	26.00	LY3023414	0.13	Plasma	195.78
Aggregate	26.00	LY3023414	1.00	Plasma	143.72
Aggregate	26.00	LY3023414	16.00	Plasma	37.71
					44.32
Aggregate	27.00	LY3023414	0.13	Plasma	83.40
Aggregate	27.00	LY3023414	1.00	Plasma	146.81
Aggregate	27.00	LY3023414	16.00	Plasma	0.50
					0.50
Aggregate	28.00	LY3023414	0.25	Plasma	3417.80
Aggregate	28.00	LY3023414	2.00	Plasma	582.72
Aggregate	28.00	LY3023414	24.00	Plasma	0.50
					0.50
Aggregate	29.00	LY3023414	0.25	Plasma	5380.80
Aggregate	29.00	LY3023414	2.00	Plasma	565.70
Aggregate	29.00	LY3023414	24.00	Plasma	0.50
					0.50
Aggregate	30.00	LY3023414	0.25	Plasma	877.16
Aggregate	30.00	LY3023414	2.00	Plasma	474.40
Aggregate	30.00	LY3023414	24.00	Plasma	1.49
					2.22
Aggregate	31.00	LY3023414	0.50	Plasma	2112.50
Aggregate	31.00	LY3023414	4.00	Plasma	439.22
Aggregate	31.00	LY3023414	8.00	Plasma	119.02
					85.10
Aggregate	32.00	LY3023414	0.50	Plasma	1817.50
Aggregate	32.00	LY3023414	4.00	Plasma	271.03
Aggregate	32.00	LY3023414	8.00	Plasma	113.94
					118.06
Aggregate	33.00	LY3023414	0.50	Plasma	1516.40
Aggregate	33.00	LY3023414	4.00	Plasma	213.61
Aggregate	33.00	LY3023414	8.00	Plasma	93.90
					88.52
Aggregate	34.00	LY3023414	0.13	Plasma	3557.40
Aggregate	35.00	LY3023414	0.13	Plasma	4237.10
Aggregate	36.00	LY3023414	0.13	Plasma	8762.00
Aggregate	37.00	LY3023414	1.00	Plasma	1414.70
Aggregate	38.00	LY3023414	1.00	Plasma	1205.20

LY3023414 Screening Plasma Tumor PK (SPTPK)

Study	Subject	Analyte	Time (hr)	Group	Concentration (ug/L)
Aggregate	39.00	LY3023414	1.00	Plasma	1160.80
Aggregate	40.00	LY3023414	4.00	Plasma	408.67
Aggregate	41.00	LY3023414	4.00	Plasma	346.92
Aggregate	42.00	LY3023414	4.00	Plasma	542.58
Aggregate	43.00	LY3023414	8.00	Plasma	465.62
Aggregate	44.00	LY3023414	8.00	Plasma	158.17
Aggregate	45.00	LY3023414	8.00	Plasma	1937.90
Aggregate	46.00	LY3023414	16.00	Plasma	2.82
Aggregate	47.00	LY3023414	16.00	Plasma	0.50
Aggregate	48.00	LY3023414	16.00	Plasma	3.16
SPPK	25.00	LY3023414	0.13	Plasma	83.10
SPPK	25.00	LY3023414	1.00	Plasma	85.21
SPPK	25.00	LY3023414	16.00	Plasma	76.94 84.89
SPPK	26.00	LY3023414	0.13	Plasma	195.78
SPPK	26.00	LY3023414	1.00	Plasma	143.72
SPPK	26.00	LY3023414	16.00	Plasma	37.71 44.32
SPPK	27.00	LY3023414	0.13	Plasma	83.40
SPPK	27.00	LY3023414	1.00	Plasma	146.81
SPPK	27.00	LY3023414	16.00	Plasma	0.50 0.50
SPPK	28.00	LY3023414	0.25	Plasma	3417.80
SPPK	28.00	LY3023414	2.00	Plasma	582.72
SPPK	28.00	LY3023414	24.00	Plasma	0.50 0.50
SPPK	29.00	LY3023414	0.25	Plasma	5380.80
SPPK	29.00	LY3023414	2.00	Plasma	565.70
SPPK	29.00	LY3023414	24.00	Plasma	0.50 0.50
SPPK	30.00	LY3023414	0.25	Plasma	877.16
SPPK	30.00	LY3023414	2.00	Plasma	474.40
SPPK	30.00	LY3023414	24.00	Plasma	1.49 2.22
SPPK	31.00	LY3023414	0.50	Plasma	2112.50
SPPK	31.00	LY3023414	4.00	Plasma	439.22
SPPK	31.00	LY3023414	8.00	Plasma	119.02 85.10
SPPK	32.00	LY3023414	0.50	Plasma	1817.50
SPPK	32.00	LY3023414	4.00	Plasma	271.03
SPPK	32.00	LY3023414	8.00	Plasma	113.94 118.06

Study	Subject	Analyte	Time (hr)	Group	Concentration (ug/L)
SPPK	33.00	LY3023414	0.50	Plasma	1516.40
SPPK	33.00	LY3023414	4.00	Plasma	213.61
SPPK	33.00	LY3023414	8.00	Plasma	93.90 88.52
SPTPK	34.00	LY3023414	0.13	Plasma	3557.40
SPTPK	34.00	LY3023414	0.13	Tumor	372.87
SPTPK	35.00	LY3023414	0.13	Plasma	4237.10
SPTPK	35.00	LY3023414	0.13	Tumor	31.24
SPTPK	36.00	LY3023414	0.13	Plasma	8762.00
SPTPK	36.00	LY3023414	0.13	Tumor	1082.30
SPTPK	37.00	LY3023414	1.00	Plasma	1414.70
SPTPK	37.00	LY3023414	1.00	Tumor	1089.80
SPTPK	38.00	LY3023414	1.00	Plasma	1205.20
SPTPK	38.00	LY3023414	1.00	Tumor	322.98
SPTPK	39.00	LY3023414	1.00	Plasma	1160.80
SPTPK	39.00	LY3023414	1.00	Tumor	801.07
SPTPK	40.00	LY3023414	4.00	Plasma	408.67
SPTPK	40.00	LY3023414	4.00	Tumor	236.77
SPTPK	41.00	LY3023414	4.00	Plasma	346.92
SPTPK	41.00	LY3023414	4.00	Tumor	259.45
SPTPK	42.00	LY3023414	4.00	Plasma	542.58
SPTPK	42.00	LY3023414	4.00	Tumor	351.66
SPTPK	43.00	LY3023414	8.00	Plasma	465.62
SPTPK	43.00	LY3023414	8.00	Tumor	84.16
SPTPK	44.00	LY3023414	8.00	Plasma	158.17
SPTPK	44.00	LY3023414	8.00	Tumor	106.21
SPTPK	45.00	LY3023414	8.00	Plasma	1937.90
SPTPK	45.00	LY3023414	8.00	Tumor	134.72
SPTPK	46.00	LY3023414	16.00	Plasma	2.82
SPTPK	46.00	LY3023414	16.00	Tumor	3.00
SPTPK	47.00	LY3023414	16.00	Plasma	0.50
SPTPK	47.00	LY3023414	16.00	Tumor	3.00
SPTPK	48.00	LY3023414	16.00	Plasma	3.16
SPTPK	48.00	LY3023414	16.00	Tumor	21.30

Table 4.4: LY3023414 Ct Summary (Mean, SD, N) by Group

Variable	Units	Analyte	Study	Group	Time (hr)	Mean (ug/L)	SD (ug/L)	N
Concentration	ug/L	LY3023414	Aggregate	Plasma	0.13	2819.80	3456.17	6.00
Concentration	ug/L	LY3023414	Aggregate	Plasma	0.25	3225.25	2257.99	3.00
Concentration	ug/L	LY3023414	Aggregate	Plasma	0.50	1815.47	298.06	3.00
Concentration	ug/L	LY3023414	Aggregate	Plasma	1.00	692.74	627.93	6.00

Variable	Units	Analyte	Study	Group	Time (hr)	Mean (ug/L)	SD (ug/L)	N
Concentration	ug/L	LY3023414	Aggregate	Plasma	2.00	540.94	58.25	3.00
Concentration	ug/L	LY3023414	Aggregate	Plasma	4.00	370.34	119.04	6.00
Concentration	ug/L	LY3023414	Aggregate	Plasma	8.00	353.36	606.06	9.00
Concentration	ug/L	LY3023414	Aggregate	Plasma	16.00	27.93	34.48	9.00
Concentration	ug/L	LY3023414	Aggregate	Plasma	24.00	0.95	0.74	6.00
Concentration	ug/L	LY3023414	SPPK	Plasma	0.13	120.76	64.97	3.00
Concentration	ug/L	LY3023414	SPPK	Plasma	0.25	3225.25	2257.99	3.00
Concentration	ug/L	LY3023414	SPPK	Plasma	0.50	1815.47	298.06	3.00
Concentration	ug/L	LY3023414	SPPK	Plasma	1.00	125.25	34.71	3.00
Concentration	ug/L	LY3023414	SPPK	Plasma	2.00	540.94	58.25	3.00
Concentration	ug/L	LY3023414	SPPK	Plasma	4.00	307.95	117.25	3.00
Concentration	ug/L	LY3023414	SPPK	Plasma	8.00	103.09	15.59	6.00
Concentration	ug/L	LY3023414	SPPK	Plasma	16.00	40.81	36.11	6.00
Concentration	ug/L	LY3023414	SPPK	Plasma	24.00	0.95	0.74	6.00
Concentration	ug/L	LY3023414	SPTPK	Plasma	0.13	5518.83	2829.15	3.00
Concentration	ug/L	LY3023414	SPTPK	Plasma	1.00	1260.23	135.60	3.00
Concentration	ug/L	LY3023414	SPTPK	Plasma	4.00	432.72	100.02	3.00
Concentration	ug/L	LY3023414	SPTPK	Plasma	8.00	853.90	951.28	3.00
Concentration	ug/L	LY3023414	SPTPK	Plasma	16.00	2.16	1.45	3.00
Concentration	ug/L	LY3023414	SPTPK	Tumor	0.13	495.47	536.15	3.00
Concentration	ug/L	LY3023414	SPTPK	Tumor	1.00	737.95	387.29	3.00
Concentration	ug/L	LY3023414	SPTPK	Tumor	4.00	282.63	60.85	3.00
Concentration	ug/L	LY3023414	SPTPK	Tumor	8.00	108.36	25.35	3.00
Concentration	ug/L	LY3023414	SPTPK	Tumor	16.00	9.10	10.56	3.00

5.0 ATTACHED FILES

Attached File 5.1 LY3023414 Screening Plasma PK.docx – *Final in vivo study plan as executed (SRM2 O/R 124312-1298570, SPPK)*

Attached File 5.2 LY3023414 Screening Plasma and Tumor PK.docx – *Final in vivo study plan as executed (SRM2 O/R 134278-1406200, SPTPK)*

Attached File 5.3 LY3023414 PK_non tumor.docx – *Digital data collection form from SPPK in vivo study*

Attached File 5.4 LY3023414 PK tumor bearing study sheet 2.docx – *Digital data collection form from in vivo SPTPK study*

Attached File 5.5 LY3023414 Screening Plasma and Tumor PK TLFs.docx – *Tables, listings, and figures from SPTPK report in Word document for reformatting or manipulations*