PRECLINICAL PHARMACOKINETIC REPORT

Developmental Biology and Solid Tumor Program

P-PKSR Study 134278-1406200

STUDY TITLE:

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

SHORT TITLE:	**Larotrectinib Screening Plasma Tumor PK (SPTPK)**
TEST ARTICLE:	Larotrectinib
SECTION:	Nonclinical Pharmacokinetics (Non-GLP)
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SJCRH SRM2 O/R:	134278-1406222 Preclinical Pharmacokinetic Shared Resource 124312-1298570
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FOR P-PKSR APPROVED USE AND DISTRIBUTION

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

The first larotrectinib PK study (SRM2 O/R 124312-1298570, SPPK) was a survival plasma PK evaluation using non-tumor bearing Athymic nude mice. Larotrectinib was suspended in 1% hydroxyethylcellulose (MW 720,000), 0.25% Tween 80, and ~0.05% simethicone at 3 mg/mL and administered as a 10 mL/kg oral gavage for a 30 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 larotrectinib PK study (SRM2 O/R 134278-1406200, SPTPK), the plasma and tumor PK were evaluated after a single oral dose of the larotrectinib 30 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, larotrectinib 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 larotrectinib (Abmole, Lot # NA, 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 LY3023414 (ADOOQ, Lot # L16126B001, purity 96.6%) in acetonitrile as an internal standard. A 1.5 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 1.58 and 1.40 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: larotrectinib 429.19 -> 342.00, and LY3023414 407.20 -> 319.10

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 larotrectinib 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 larotrectinib 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 larotrectinib 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 larotrectinib of 100 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 PK in our mice was in line with that reported for larotrectinib, with a 2 hr mean plasma concentration of 252 ug/L versus an extrapolated ~150 ug/L [3]. Larotrectinib showed a rapid distribution to tumor, with a Tmax at 1 hr, with tumor concentrations near unity with plasma. The plasma AUCtau of larotrectinib in children at the RP2D of 100 mg/m^2 PO BID was 2900 hr-ug/L [2], with an estimated AUCu of 540 hr-ug/L (Fu,p,h = 0.186). The mouse Fu,p value was similar at 0.226. The plasma AUCinf in mice was 2300 hr-ug/L, yielding a AUCu of 520 hr-ug/L. Therefore, a reasonable CRD would be 30-32.5 mg/kg PO BID, which is also the common preclinical regimen applied in mice [4].

3.0 REFERENCES

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4.0 TABLES, LISTINGS, AND FIGURES (TLFS)

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

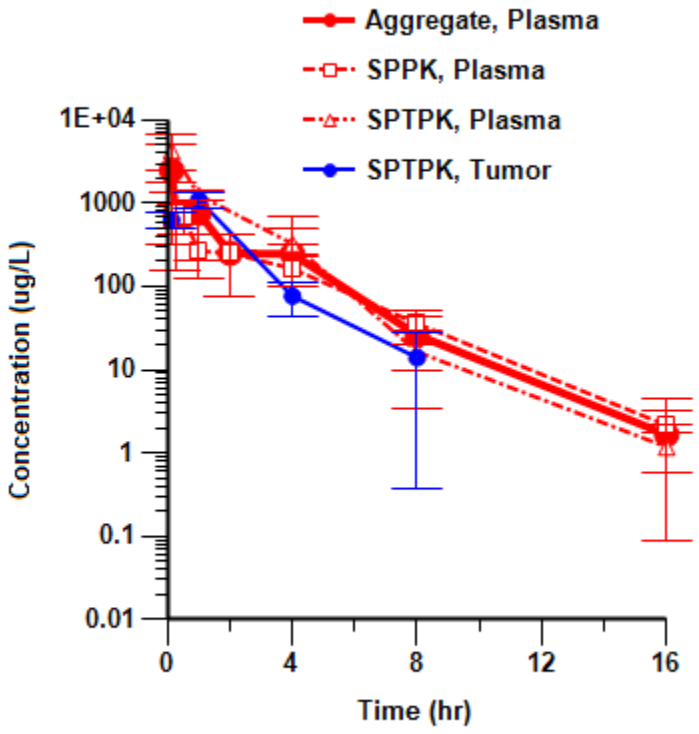

Table 4.1: NCA PK Parameter Estimates of Larotrectinib by Study and Group

		Analyte			
		Larotrectinib			
		Study			
		Aggregate	SPPK	SPTPK	
		Group	Group	Group	
		Plasma	Plasma	Plasma	Tumor
Parameter	Units	Estimate			
Cmax	ug/L	2480	753	4290	1100
Tmax	hr	0.125	0.250	0.125	1.00
AUClast	hr*ug/L	2300	1630	4960	2100
AUCinf	hr*ug/L	2300	1640	4960	2120
Kel	1/hr	0.406	0.360	0.448	0.613
T1/2	hr	1.71	1.93	1.55	1.13
CL/F	L/hr/kg	13.0	18.3	6.05	14.2
Vz/F	L/kg	32.2	50.9	13.5	23.1
Clast	ug/L	1.67	2.15	1.18	14.0

		Analyte			
		Larotrectinib			
		Study			
		Aggregate	SPPK	SPTPK	
		Group	Group	Group	
		Plasma	Plasma	Plasma	Tumor
Parameter	Units	Estimate			
Tlast	hr	16.0	16.0	16.0	8.00
Kp,tumor*	-	*	-	-	0.92

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

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

		Analyte			
		Larotrectinib			
		Study			
		Aggregate	SPPK	SPTPK	
		Group	Group	Group	
		Plasma	Plasma	Plasma	Tumor
Time (hr)		Concentration (ug/L)			
0.125	N	6	3	3	3
	Mean	2480	662	4290	628
	SD	2570	335	2560	137
	Min	442	442	2770	537
	Median	1910	496	2860	561
	Max	7250	1050	7250	786
	CV%	104	50.6	59.7	21.9
	Geometric Mean	1540	612	3860	619
	CV% Geometric Mean	155	49.5	59.0	21.1
0.250	N	3	3		
	Mean	753	753		
	SD	601	601		
	Min	67.8	67.8		
	Median	1000	1000		
	Max	1190	1190		
	CV%	79.8	79.8		
	Geometric Mean	432	432		
	CV% Geometric Mean	350	350		
0.500	N	3	3		
	Mean	686	686		
	SD	269	269		
	Min	375	375		
	Median	836	836		
	Max	847	847		
	CV%	39.3	39.3		
	Geometric Mean	643	643		
	CV% Geometric Mean	49.3	49.3		
1.000	N	6	3	3	3
	Mean	760	267	1250	1100
	SD	559	142	182	216
	Min	111	111	1040	947
	Median	717	303	1330	1010

Larotrectinib Screening Plasma Tumor PK (SPTPK)

		Analyte			
		Larotrectinib			
		Study			
		Aggregate	SPPK	SPTPK	
		Group	Group	Group	
		Plasma	Plasma	Plasma	Tumor
Time (hr)		Concentration (ug/L)			
	Max	1380	389	1380	1350
	CV%	73.6	53.1	14.5	19.6
	Geometric Mean	541	236	1240	1090
	CV% Geometric Mean	133	74.2	15.3	19.0
2.000	N	3	3		
	Mean	252	252		
	SD	175	175		
	Min	103	103		
	Median	206	206		
	Max	445	445		
	CV%	69.7	69.7		
	Geometric Mean	212	212		
	CV% Geometric Mean	84.0	84.0		
4.000	N	6	3	3	3
	Mean	245	164	326	76.8
	SD	248	63.3	360	32.5
	Min	104	114	104	39.5
	Median	138	142	133	91.8
	Max	742	235	742	99.0
	CV%	101	38.6	110	42.3
	Geometric Mean	184	156	217	71.1
	CV% Geometric Mean	85.2	38.3	147	54.6
8.000	N	6	3	3	3
	Mean	26.1	35.8	16.4	14.0
	SD	16.6	15.5	13.0	13.6
	Min	3.53	25.9	3.53	3.00
	Median	26.9	27.9	16.2	9.75
	Max	53.7	53.7	29.5	29.2
	CV%	63.7	43.2	79.1	97.3
	Geometric Mean	20.1	33.9	11.9	9.49
	CV% Geometric Mean	118	41.7	152	163
16.000	N	6	3	3	0
	Mean	1.67	2.15	1.18	
	SD	1.58	2.27	0.592	
	Min	0.500	0.500	0.500	
	Median	1.36	1.20	1.52	
	Max	4.74	4.74	1.53	
	CV%	94.6	106	50.0	
	Geometric Mean	1.22	1.42	1.05	
	CV% Geometric Mean	101	162	71.7	
24.000	N	0	0		
	Mean				
	SD				
	Min				
	Median				
	Max				

		Analyte			
		Larotrectinib			
		Study			
		Aggregate	SPPK	SPTPK	
		Group	Group	Group	
		Plasma	Plasma	Plasma	Tumor
Time (hr)		Concentration (ug/L)			
	CV%				
	Geometric Mean				
	CV% Geometric Mean				

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

Study	Subject	Analyte	Time (hr)	Group	Concentration (ug/L)
Aggregate	49.00	Larotrectinib	0.13	Plasma	495.72
Aggregate	49.00	Larotrectinib	1.00	Plasma	302.75
Aggregate	49.00	Larotrectinib	16.00	Plasma	1.20
Aggregate	50.00	Larotrectinib	0.13	Plasma	1047.70
Aggregate	50.00	Larotrectinib	1.00	Plasma	388.56
Aggregate	50.00	Larotrectinib	16.00	Plasma	4.74
Aggregate	51.00	Larotrectinib	0.13	Plasma	442.43
Aggregate	51.00	Larotrectinib	1.00	Plasma	111.17
Aggregate	51.00	Larotrectinib	16.00	Plasma	0.50
Aggregate	52.00	Larotrectinib	0.25	Plasma	1191.80
Aggregate	52.00	Larotrectinib	2.00	Plasma	206.40
Aggregate	52.00	Larotrectinib	24.00	Plasma	
Aggregate	53.00	Larotrectinib	0.25	Plasma	999.67
Aggregate	53.00	Larotrectinib	2.00	Plasma	103.29
Aggregate	53.00	Larotrectinib	24.00	Plasma	
Aggregate	54.00	Larotrectinib	0.25	Plasma	67.80
Aggregate	54.00	Larotrectinib	2.00	Plasma	444.96
Aggregate	54.00	Larotrectinib	24.00	Plasma	
Aggregate	55.00	Larotrectinib	0.50	Plasma	847.36
Aggregate	55.00	Larotrectinib	4.00	Plasma	114.13
Aggregate	55.00	Larotrectinib	8.00	Plasma	25.90
Aggregate	56.00	Larotrectinib	0.50	Plasma	375.16
Aggregate	56.00	Larotrectinib	4.00	Plasma	142.45
Aggregate	56.00	Larotrectinib	8.00	Plasma	53.69
Aggregate	57.00	Larotrectinib	0.50	Plasma	835.78
Aggregate	57.00	Larotrectinib	4.00	Plasma	235.07
Aggregate	57.00	Larotrectinib	8.00	Plasma	27.95
Aggregate	58.00	Larotrectinib	0.13	Plasma	7251.20
Aggregate	59.00	Larotrectinib	0.13	Plasma	2771.20
Aggregate	60.00	Larotrectinib	0.13	Plasma	2857.90
Aggregate	61.00	Larotrectinib	1.00	Plasma	1044.90
Aggregate	62.00	Larotrectinib	1.00	Plasma	1333.30
Aggregate	63.00	Larotrectinib	1.00	Plasma	1381.50
Aggregate	64.00	Larotrectinib	4.00	Plasma	741.69
Aggregate	65.00	Larotrectinib	4.00	Plasma	103.61
Aggregate	66.00	Larotrectinib	4.00	Plasma	133.33

Larotrectinib Screening Plasma Tumor PK (SPTPK)

Study	Subject	Analyte	Time (hr)	Group	Concentration (ug/L)
Aggregate	67.00	Larotrectinib	8.00	Plasma	29.48
Aggregate	68.00	Larotrectinib	8.00	Plasma	3.53
Aggregate	69.00	Larotrectinib	8.00	Plasma	16.23
Aggregate	70.00	Larotrectinib	16.00	Plasma	0.50
Aggregate	71.00	Larotrectinib	16.00	Plasma	1.52
Aggregate	72.00	Larotrectinib	16.00	Plasma	1.53
SPPK	49.00	Larotrectinib	0.13	Plasma	495.72
SPPK	49.00	Larotrectinib	1.00	Plasma	302.75
SPPK	49.00	Larotrectinib	16.00	Plasma	1.20
SPPK	50.00	Larotrectinib	0.13	Plasma	1047.70
SPPK	50.00	Larotrectinib	1.00	Plasma	388.56
SPPK	50.00	Larotrectinib	16.00	Plasma	4.74
SPPK	51.00	Larotrectinib	0.13	Plasma	442.43
SPPK	51.00	Larotrectinib	1.00	Plasma	111.17
SPPK	51.00	Larotrectinib	16.00	Plasma	0.50
SPPK	52.00	Larotrectinib	0.25	Plasma	1191.80
SPPK	52.00	Larotrectinib	2.00	Plasma	206.40
SPPK	52.00	Larotrectinib	24.00	Plasma	
SPPK	53.00	Larotrectinib	0.25	Plasma	999.67
SPPK	53.00	Larotrectinib	2.00	Plasma	103.29
SPPK	53.00	Larotrectinib	24.00	Plasma	
SPPK	54.00	Larotrectinib	0.25	Plasma	67.80
SPPK	54.00	Larotrectinib	2.00	Plasma	444.96
SPPK	54.00	Larotrectinib	24.00	Plasma	
SPPK	55.00	Larotrectinib	0.50	Plasma	847.36
SPPK	55.00	Larotrectinib	4.00	Plasma	114.13
SPPK	55.00	Larotrectinib	8.00	Plasma	25.90
SPPK	56.00	Larotrectinib	0.50	Plasma	375.16
SPPK	56.00	Larotrectinib	4.00	Plasma	142.45
SPPK	56.00	Larotrectinib	8.00	Plasma	53.69
SPPK	57.00	Larotrectinib	0.50	Plasma	835.78
SPPK	57.00	Larotrectinib	4.00	Plasma	235.07
SPPK	57.00	Larotrectinib	8.00	Plasma	27.95
SPTPK	58.00	Larotrectinib	0.13	Plasma	7251.20
SPTPK	58.00	Larotrectinib	0.13	Tumor	785.99
SPTPK	59.00	Larotrectinib	0.13	Plasma	2771.20
SPTPK	59.00	Larotrectinib	0.13	Tumor	560.86
SPTPK	60.00	Larotrectinib	0.13	Plasma	2857.90
SPTPK	60.00	Larotrectinib	0.13	Tumor	537.33
SPTPK	61.00	Larotrectinib	1.00	Plasma	1044.90
SPTPK	61.00	Larotrectinib	1.00	Tumor	1012.20
SPTPK	62.00	Larotrectinib	1.00	Plasma	1333.30
SPTPK	62.00	Larotrectinib	1.00	Tumor	947.42
SPTPK	63.00	Larotrectinib	1.00	Plasma	1381.50
SPTPK	63.00	Larotrectinib	1.00	Tumor	1350.00
SPTPK	64.00	Larotrectinib	4.00	Plasma	741.69
SPTPK	64.00	Larotrectinib	4.00	Tumor	39.47
SPTPK	65.00	Larotrectinib	4.00	Plasma	103.61
SPTPK	65.00	Larotrectinib	4.00	Tumor	99.01
SPTPK	66.00	Larotrectinib	4.00	Plasma	133.33

Study	Subject	Analyte	Time (hr)	Group	Concentration (ug/L)
SPTPK	66.00	Larotrectinib	4.00	Tumor	91.81
SPTPK	67.00	Larotrectinib	8.00	Plasma	29.48
SPTPK	67.00	Larotrectinib	8.00	Tumor	29.20
SPTPK	68.00	Larotrectinib	8.00	Plasma	3.53
SPTPK	68.00	Larotrectinib	8.00	Tumor	3.00
SPTPK	69.00	Larotrectinib	8.00	Plasma	16.23
SPTPK	69.00	Larotrectinib	8.00	Tumor	9.75
SPTPK	70.00	Larotrectinib	16.00	Plasma	0.50
SPTPK	70.00	Larotrectinib	16.00	Tumor	
SPTPK	71.00	Larotrectinib	16.00	Plasma	1.52
SPTPK	71.00	Larotrectinib	16.00	Tumor	
SPTPK	72.00	Larotrectinib	16.00	Plasma	1.53
SPTPK	72.00	Larotrectinib	16.00	Tumor	

Table 4.4: Larotrectinib 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	Larotrectinib	Aggregate	Plasma	0.13	2477.69	2574.20	6.00
Concentration	ug/L	Larotrectinib	Aggregate	Plasma	0.25	753.09	601.21	3.00
Concentration	ug/L	Larotrectinib	Aggregate	Plasma	0.50	686.10	269.34	3.00
Concentration	ug/L	Larotrectinib	Aggregate	Plasma	1.00	760.36	559.31	6.00
Concentration	ug/L	Larotrectinib	Aggregate	Plasma	2.00	251.55	175.25	3.00
Concentration	ug/L	Larotrectinib	Aggregate	Plasma	4.00	245.05	247.75	6.00
Concentration	ug/L	Larotrectinib	Aggregate	Plasma	8.00	26.13	16.63	6.00
Concentration	ug/L	Larotrectinib	Aggregate	Plasma	16.00	1.67	1.58	6.00
Concentration	ug/L	Larotrectinib	Aggregate	Plasma	24.00			0.00
Concentration	ug/L	Larotrectinib	SPPK	Plasma	0.13	661.95	335.13	3.00
Concentration	ug/L	Larotrectinib	SPPK	Plasma	0.25	753.09	601.21	3.00
Concentration	ug/L	Larotrectinib	SPPK	Plasma	0.50	686.10	269.34	3.00
Concentration	ug/L	Larotrectinib	SPPK	Plasma	1.00	267.49	142.02	3.00
Concentration	ug/L	Larotrectinib	SPPK	Plasma	2.00	251.55	175.25	3.00
Concentration	ug/L	Larotrectinib	SPPK	Plasma	4.00	163.88	63.25	3.00
Concentration	ug/L	Larotrectinib	SPPK	Plasma	8.00	35.84	15.49	3.00
Concentration	ug/L	Larotrectinib	SPPK	Plasma	16.00	2.15	2.27	3.00
Concentration	ug/L	Larotrectinib	SPPK	Plasma	24.00			0.00
Concentration	ug/L	Larotrectinib	SPTPK	Plasma	0.13	4293.43	2561.87	3.00
Concentration	ug/L	Larotrectinib	SPTPK	Plasma	1.00	1253.23	182.02	3.00
Concentration	ug/L	Larotrectinib	SPTPK	Plasma	4.00	326.21	360.12	3.00
Concentration	ug/L	Larotrectinib	SPTPK	Plasma	8.00	16.41	12.98	3.00
Concentration	ug/L	Larotrectinib	SPTPK	Plasma	16.00	1.18	0.59	3.00
Concentration	ug/L	Larotrectinib	SPTPK	Tumor	0.13	628.06	137.28	3.00
Concentration	ug/L	Larotrectinib	SPTPK	Tumor	1.00	1103.21	216.17	3.00
Concentration	ug/L	Larotrectinib	SPTPK	Tumor	4.00	76.76	32.49	3.00
Concentration	ug/L	Larotrectinib	SPTPK	Tumor	8.00	13.98	13.60	3.00
Concentration	ug/L	Larotrectinib	SPTPK	Tumor	16.00			0.00

5.0 ATTACHED FILES

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

Attached File 5.2 Larotrectinib Screening Plasma and Tumor PK v2.docx – *Final in vivo study plan as executed (SRM2 O/R 134278-1406200, SPTPK)*

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

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

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