PRECLINICAL PHARMACOKINETIC REPORT

Developmental Biology and Solid Tumor Program

P-PKSR Study 128911-1350632

STUDY TITLE:

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

SHORT TITLE:	**Erdafitinib Screening Plasma Tumor PK (SPTPK)**
TEST ARTICLE:	Erdafitinib
SECTION:	Nonclinical Pharmacokinetics (Non-GLP)
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SJCRH SRM2 O/R:	128911-1350632 Preclinical Pharmacokinetic Shared Resource 120294-1256547 117594-1216943
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REPORT FORMAT:	Study Summary
REPORT STATUS:	FINAL
DATE:	2020-04-14

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

Three separate PK studies of erdafitinib were conducted in female Athymic nude mice (Charles River Laboratories, Frederick, MD). However, study plans in the attached files erroneously documented CD1 nu mice, as in vivo scientists were in period of transitioning models across strains.

The first erdafitinib PK study (SRM2 O/R 117594-1216943, SPPK Solution) was a survival plasma PK evaluation using non-tumor bearing Athymic nude mice. Erdafitinib 12.5 mg/kg was first dissolved in a small amount of DMSO and formulated in 20% hydroxy-propyl beta cyclodextrin (HPBCD) at 1.25 mg/mL for a 10 mL/kg gavage volume. 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 erdafitinib PK study (RPT.120294-1256547, SPTPK Solution), the plasma and tumor PK were evaluated using 12.5 mg/kg erdafitinib 20% HPBCD solution formulation. 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.

The third erdafitinib PK study (SRM2 O/R 128911-1350632, SPPK Suspension) was a repeat of the first plasma-only study, using 12.5 mg/kg erdafitinib suspended in 1% hydroxyethylcellulose (MW 720,000), 0.25% Tween 80, and ~0.05% simethicone, 1.25 mg/kg for a 10 mL/kg gavage.

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, erdafitinib 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 erdafitinib (MCE, Lot # 17782, purity 97.6%) 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 50 ng/mL AZD4547 (LC-Labs, Lot # L11075B002) in acetonitrile as an internal standard. A 1 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 (2.6 µm C18 100Å, 50 x 2.1 mm) column maintained at 50 °C with gradient elution at a flow rate of 0.4 mL/min. The binary mobile phase consisted of water-acetonitrile (9:1 v/v) + 0.1% formic acid in reservoir A and methanol-formic acid (100:0.1 v/v)) in reservoir B. The initial mobile phase consisted of 35% 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 1.27 and 1.18 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: 447.25 -> 388.20 for erdafitinib and 464.27 -> 217.20 for AZD4547

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 0.9938. 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 ≤ 4.07% CV and 88.1% to 108%, respectively.

1.3 Pharmacokinetic (PK) Analysis

The resultant erdafitinib 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 erdafitinib 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 erdafitinib 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 human unbound plasma PK value at the Phase 1 single agent maximum tolerated dose of erdafitinib 10 mg PO [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. However, given the variability within and between studies, focus is being placed on the aggregate plasma results for inferences.

Plasma and tumor PK of erdafitinib was seemingly erratic in our studied mice, showing an average Ct CV of 87%. Plasma concentrations were lower than those previously reported in mice by approximately 2.3-fold [3]. Due to the low exposure and high variability, multiple formulations were studied (20% HPBCD solution and 1% HEC / 0.25% Tween80 suspension), which offered no improvements. All formulations were found to be stable within the usage period and adequate (within 15% of nominal concentration). The RED plasma protein binding assay resulted in Fu,p,m and Fu,p,h values of 0.0229 and 0.0195, respectively. The reported Fu,p,h in literature is 0.0031 [2], which is ~6-fold lower than our estimate. Erdafitinib penetrated into the tumor well, showing ~4.5-fold higher exposure than plasma. The mouse total plasma AUCinf (Aggregate) was 76.4 hr-ug/L, with the total plasma concentrations ranging from less than 1 to 125 ug/L over an 8-hour post-dose period.

Given the lack of confidence in our erdafitinib plasma protein binding estimates, as well as the erratic PK and exposures in our mice, a CRD could not be recommended. The literature supported dose of 12.5 mg/kg PO BID was instead suggested for mice. Clinically in adults, the estimated total plasma AUC of erdafitinib at 10 mg PO was 38500 hr-ug/L, whereas the unbound AUC was 119 hr-ng/mL [2]. We theorize that erdafitinib's low aqueous solubility, interspecies differences in plasma protein binding, particularly to alpha-1-acid glycoprotein, and variable tissue or tumor lysosomal accumulation [3] may have confounded our studies.

3.0 REFERENCES

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3. Perera TPS, Jovcheva E, Mevellec L, Vialard J, Lange DD, Verhulst T, Paulussen C, Ven KVD, King P, Freyne E, Rees DC, Squires M, Saxty G, Page M, Murray CW, Gilissen R, Ward G, Thompson NT, Newell DR, Cheng N, Xie L, Yang J, Platero SJ, Karkera JD, Moy C, Angibaud P, Laquerre S, Lorenzi MV. Discovery and Pharmacological Characterization of JNJ-42756493 (Erdafitinib), a Functionally Selective Small-Molecule FGFR Family Inhibitor. Mol Cancer Ther. 2017 Jun 1;16(6):1010–20.

4.0 TABLES, LISTINGS, AND FIGURES (TLFS)

Figure 4.1: Mean (SD) Ct Profile of Erdafitinb by Study and Group

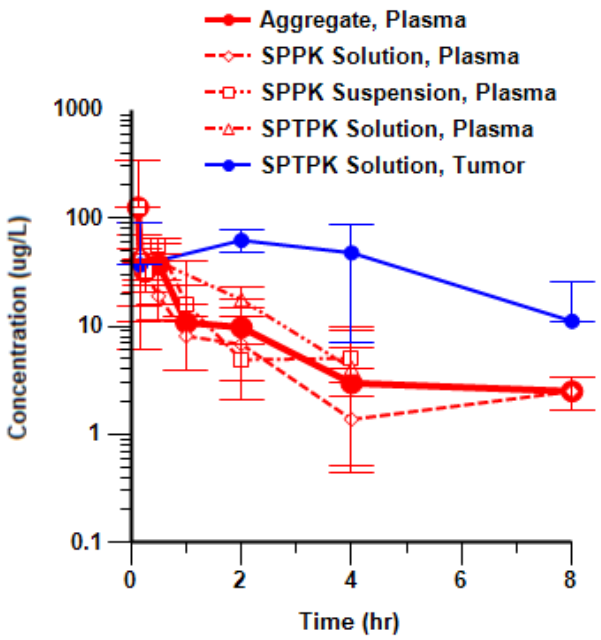

Table 4.1: NCA PK Parameter Estimates of Erdafitinib by Study and Group

		Analyte				
		Erdafitinib				
		Study				
		Aggregate	SPPK Solution	SPPK Suspension	SPTPK Solution	
		Group	Group	Group	Group	
		Plasma	Plasma	Plasma	Plasma	Tumor
Parameter	Units	Estimate				
Cmax	ug/L	125	33.3	125	47.3	62.1
Tmax	hr	0.125	0.167	0.125	0.167	2.00
AUClast	hr*ug/L	65.8	40.0	62.6	77.5	303
AUCinf	hr*ug/L	76.4	55.7	75.5	84.2	343
Kel	1/hr	0.201	0.122	0.330	0.640	0.298
T1/2	hr	3.45	5.69	2.10	1.08	2.33
CL/F	L/hr/kg	164	225	166	148	36.4
Vz/F	L/kg	815	1850	502	232	122
Clast	ug/L	2.50	2.50	5.05	4.09	11.1
Tlast	hr	8.00	8.00	4.00	4.00	8.00
Kp,tumor*		*				4.49

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

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

		Analyte				
		Erdafitinib				
		Study				
		Aggregate	SPPK Solution	SPPK Suspension	SPTPK Solution	
		Group	Group	Group	Group	
		Plasma	Plasma	Plasma	Plasma	Tumor
Time (hr)		Concentration (ug/L)				
0.125	N	3		3		
	Mean	125		125		
	SD	214		214		
	Min	1.65		1.65		
	Median	2.10		2.10		
	Max	372		372		
	CV%	171		171		
	Geometric Mean	10.9		10.9		
	CV% Geometric Mean	10800		10800		
0.167	N	6	3		3	3
	Mean	40.3	33.3		47.3	36.8
	SD	29.5	18.0		41.3	53.2
	Min	0.500	19.6		0.500	3.00
	Median	40.2	26.7		63.0	9.18
	Max	78.5	53.7		78.5	98.1
	CV%	73.2	54.1		87.2	145
	Geometric Mean	20.3	30.4		13.5	13.9
	CV% Geometric Mean	588	55.5		5930	478
0.250	N	6	3	3		
	Mean	31.9	31.5	32.3		
	SD	7.63	10.6	5.74		
	Min	23.8	23.8	27.0		
	Median	29.3	27.1	31.5		
	Max	43.6	43.6	38.4		
	CV%	23.9	33.6	17.8		
	Geometric Mean	31.2	30.4	31.9		
	CV% Geometric Mean	23.5	32.6	17.8		

Erdafitinib Screening Plasma Tumor PK (SPTPK)

		Analyte				
		Erdafitinib				
		Study				
		Aggregate	SPPK Solution	SPPK Suspension	SPTPK Solution	
		Group	Group	Group	Group	
		Plasma	Plasma	Plasma	Plasma	Tumor
Time (hr)		Concentration (ug/L)				
0.500	N	6	3	3		
	Mean	37.1	19.0	55.2		
	SD	21.1	7.67	8.57		
	Min	11.6	11.6	47.9		
	Median	37.4	18.4	53.1		
	Max	64.6	26.9	64.6		
	CV%	57.0	40.4	15.5		
	Geometric Mean	31.3	17.9	54.8		
	CV% Geometric Mean	75.8	44.0	15.3		
1.000	N	9	6	3		
	Mean	10.8	8.09	16.1		
	SD	13.2	4.25	24.1		
	Min	1.92	2.66	1.92		
	Median	6.06	6.98	2.50		
	Max	44.0	13.3	44.0		
	CV%	122	52.5	149		
	Geometric Mean	6.68	7.07	5.96		
	CV% Geometric Mean	130	66.0	441		
2.000	N	9	3	3	3	3
	Mean	9.75	6.80	4.90	17.6	62.1
	SD	7.66	7.91	1.81	5.39	14.8
	Min	1.51	1.51	2.88	11.3	45.9
	Median	6.37	3.00	5.44	20.4	65.6
	Max	20.9	15.9	6.37	20.9	74.9
	CV%	78.6	116	36.9	30.7	23.8
	Geometric Mean	6.89	4.16	4.64	16.9	60.9
	CV% Geometric Mean	121	183	43.9	35.7	25.7
4.000	N	12	6	3	3	3
	Mean	2.97	1.37	5.05	4.09	47.7

Erdafitinib Screening Plasma Tumor PK (SPTPK)

		Analyte				
		Erdafitinib				
		Study				
		Aggregate	SPPK Solution	SPPK Suspension	SPTPK Solution	
		Group	Group	Group	Group	
		Plasma	Plasma	Plasma	Plasma	Tumor
Time (hr)		Concentration (ug/L)				
	SD	3.43	0.872	4.61	5.06	40.5
	Min	0.500	0.500	2.15	0.500	11.1
	Median	1.83	1.33	2.64	1.90	40.6
	Max	10.4	2.82	10.4	9.89	91.3
	CV%	115	63.4	91.2	124	85.0
	Geometric Mean	1.81	1.14	3.89	2.11	34.5
	CV% Geometric Mean	136	79.1	104	289	144
8.000	N	6	6	0	0	3
	Mean	2.50	2.50			11.1
	SD	0.805	0.805			14.1
	Min	1.45	1.45			3.00
	Median	2.62	2.62			3.00
	Max	3.27	3.27			27.3
	CV%	32.2	32.2			126
	Geometric Mean	2.38	2.38			6.27
	CV% Geometric Mean	35.9	35.9			202
16.000	N	0		0	0	0
	Mean					
	SD					
	Min					
	Median					
	Max					
	CV%					
	Geometric Mean					
	CV% Geometric Mean					
24.000	N	0		0		
	Mean					
	SD					
	Min					

		Analyte				
		Erdafitinib				
		Study				
		Aggregate	SPPK Solution	SPPK Suspension	SPTPK Solution	
		Group	Group	Group	Group	
		Plasma	Plasma	Plasma	Plasma	Tumor
Time (hr)		Concentration (ug/L)				
	Median					
	Max					
	CV%					
	Geometric Mean					
	CV% Geometric Mean					

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

Study	Subject	Analyte	Group	Time (hr)	Concentration (ug/L)
Aggregate	121a	Erdafitinib	Plasma	0.25	43.56
Aggregate	121a	Erdafitinib	Plasma	0.50	26.94
Aggregate	121a	Erdafitinib	Plasma	1.00	12.98
Aggregate	121a	Erdafitinib	Plasma	4.00	1.43
Aggregate	121a	Erdafitinib	Plasma	8.00	3.27
Aggregate	122a	Erdafitinib	Plasma	0.25	23.82
Aggregate	122a	Erdafitinib	Plasma	0.50	11.63
Aggregate	122a	Erdafitinib	Plasma	1.00	6.06
Aggregate	122a	Erdafitinib	Plasma	4.00	0.50
Aggregate	122a	Erdafitinib	Plasma	8.00	1.45
Aggregate	123a	Erdafitinib	Plasma	0.25	27.08
Aggregate	123a	Erdafitinib	Plasma	0.50	18.41
Aggregate	123a	Erdafitinib	Plasma	1.00	7.90
Aggregate	123a	Erdafitinib	Plasma	4.00	1.76
Aggregate	123a	Erdafitinib	Plasma	8.00	3.27
Aggregate	124a	Erdafitinib	Plasma	0.17	19.56
Aggregate	124a	Erdafitinib	Plasma	1.00	2.66
Aggregate	124a	Erdafitinib	Plasma	2.00	1.51
Aggregate	124a	Erdafitinib	Plasma	4.00	0.50
Aggregate	124a	Erdafitinib	Plasma	8.00	1.75
Aggregate	125a	Erdafitinib	Plasma	0.17	26.67
Aggregate	125a	Erdafitinib	Plasma	1.00	5.68
Aggregate	125a	Erdafitinib	Plasma	2.00	3.00
Aggregate	125a	Erdafitinib	Plasma	4.00	1.23
Aggregate	125a	Erdafitinib	Plasma	8.00	2.20

Erdafitinib Screening Plasma Tumor PK (SPTPK)

Study	Subject	Analyte	Group	Time (hr)	Concentration (ug/L)
Aggregate	126a	Erdafitinib	Plasma	0.17	53.75
Aggregate	126a	Erdafitinib	Plasma	1.00	13.27
Aggregate	126a	Erdafitinib	Plasma	2.00	15.90
Aggregate	126a	Erdafitinib	Plasma	4.00	2.82
Aggregate	126a	Erdafitinib	Plasma	8.00	3.05
Aggregate	127a	Erdafitinib	Plasma	0.17	0.50
Aggregate	128a	Erdafitinib	Plasma	0.17	62.96
Aggregate	129a	Erdafitinib	Plasma	0.17	78.46
Aggregate	130a	Erdafitinib	Plasma	2.00	20.44
Aggregate	131a	Erdafitinib	Plasma	2.00	11.34
Aggregate	132a	Erdafitinib	Plasma	2.00	20.90
Aggregate	133a	Erdafitinib	Plasma	4.00	9.89
Aggregate	134a	Erdafitinib	Plasma	4.00	0.50
Aggregate	135a	Erdafitinib	Plasma	4.00	1.90
Aggregate	136a	Erdafitinib	Plasma	8.00	
Aggregate	137a	Erdafitinib	Plasma	8.00	
Aggregate	138a	Erdafitinib	Plasma	8.00	
Aggregate	139a	Erdafitinib	Plasma	16.00	
Aggregate	140a	Erdafitinib	Plasma	16.00	
Aggregate	141a	Erdafitinib	Plasma	16.00	
Aggregate	142a	Erdafitinib	Plasma	0.13	2.10
Aggregate	142a	Erdafitinib	Plasma	1.00	1.92
Aggregate	142a	Erdafitinib	Plasma	16.00	
Aggregate	143a	Erdafitinib	Plasma	0.13	1.65
Aggregate	143a	Erdafitinib	Plasma	1.00	2.50
Aggregate	143a	Erdafitinib	Plasma	16.00	
Aggregate	144a	Erdafitinib	Plasma	0.13	371.67
Aggregate	144a	Erdafitinib	Plasma	1.00	44.03
Aggregate	144a	Erdafitinib	Plasma	16.00	
Aggregate	145a	Erdafitinib	Plasma	0.25	26.96
Aggregate	145a	Erdafitinib	Plasma	2.00	6.37
Aggregate	145a	Erdafitinib	Plasma	24.00	
Aggregate	146a	Erdafitinib	Plasma	0.25	38.36
Aggregate	146a	Erdafitinib	Plasma	2.00	2.88
Aggregate	146a	Erdafitinib	Plasma	24.00	
Aggregate	147a	Erdafitinib	Plasma	0.25	31.47
Aggregate	147a	Erdafitinib	Plasma	2.00	5.44
Aggregate	147a	Erdafitinib	Plasma	24.00	
Aggregate	148a	Erdafitinib	Plasma	0.50	47.89
Aggregate	148a	Erdafitinib	Plasma	4.00	2.15
Aggregate	148a	Erdafitinib	Plasma	8.00	

Erdafitinib Screening Plasma Tumor PK (SPTPK)

Study	Subject	Analyte	Group	Time (hr)	Concentration (ug/L)
Aggregate	149a	Erdafitinib	Plasma	0.50	64.65
Aggregate	149a	Erdafitinib	Plasma	4.00	2.64
Aggregate	149a	Erdafitinib	Plasma	8.00	
Aggregate	150a	Erdafitinib	Plasma	0.50	53.14
Aggregate	150a	Erdafitinib	Plasma	4.00	10.36
Aggregate	150a	Erdafitinib	Plasma	8.00	
SPPK Solution	121.00	Erdafitinib	Plasma	0.25	43.56
SPPK Solution	121.00	Erdafitinib	Plasma	0.50	26.94
SPPK Solution	121.00	Erdafitinib	Plasma	1.00	12.98
SPPK Solution	121.00	Erdafitinib	Plasma	4.00	1.43
SPPK Solution	121.00	Erdafitinib	Plasma	8.00	3.27
SPPK Solution	122.00	Erdafitinib	Plasma	0.25	23.82
SPPK Solution	122.00	Erdafitinib	Plasma	0.50	11.63
SPPK Solution	122.00	Erdafitinib	Plasma	1.00	6.06
SPPK Solution	122.00	Erdafitinib	Plasma	4.00	0.50
SPPK Solution	122.00	Erdafitinib	Plasma	8.00	1.45
SPPK Solution	123.00	Erdafitinib	Plasma	0.25	27.08
SPPK Solution	123.00	Erdafitinib	Plasma	0.50	18.41
SPPK Solution	123.00	Erdafitinib	Plasma	1.00	7.90
SPPK Solution	123.00	Erdafitinib	Plasma	4.00	1.76
SPPK Solution	123.00	Erdafitinib	Plasma	8.00	3.27
SPPK Solution	124.00	Erdafitinib	Plasma	0.17	19.56
SPPK Solution	124.00	Erdafitinib	Plasma	1.00	2.66
SPPK Solution	124.00	Erdafitinib	Plasma	2.00	1.51
SPPK Solution	124.00	Erdafitinib	Plasma	4.00	0.50
SPPK Solution	124.00	Erdafitinib	Plasma	8.00	1.75
SPPK Solution	125.00	Erdafitinib	Plasma	0.17	26.67
SPPK Solution	125.00	Erdafitinib	Plasma	1.00	5.68
SPPK Solution	125.00	Erdafitinib	Plasma	2.00	3.00
SPPK Solution	125.00	Erdafitinib	Plasma	4.00	1.23
SPPK Solution	125.00	Erdafitinib	Plasma	8.00	2.20
SPPK Solution	126.00	Erdafitinib	Plasma	0.17	53.75
SPPK Solution	126.00	Erdafitinib	Plasma	1.00	13.27
SPPK Solution	126.00	Erdafitinib	Plasma	2.00	15.90
SPPK Solution	126.00	Erdafitinib	Plasma	4.00	2.82
SPPK Solution	126.00	Erdafitinib	Plasma	8.00	3.05
SPPK Suspension	142.00	Erdafitinib	Plasma	0.13	2.10
SPPK Suspension	142.00	Erdafitinib	Plasma	1.00	1.92
SPPK Suspension	142.00	Erdafitinib	Plasma	16.00	
SPPK Suspension	143.00	Erdafitinib	Plasma	0.13	1.65
SPPK Suspension	143.00	Erdafitinib	Plasma	1.00	2.50
SPPK Suspension	143.00	Erdafitinib	Plasma	16.00	

Erdafitinib Screening Plasma Tumor PK (SPTPK)

Study	Subject	Analyte	Group	Time (hr)	Concentration (ug/L)
SPPK Suspension	144.00	Erdafitinib	Plasma	0.13	371.67
SPPK Suspension	144.00	Erdafitinib	Plasma	1.00	44.03
SPPK Suspension	144.00	Erdafitinib	Plasma	16.00	
SPPK Suspension	145.00	Erdafitinib	Plasma	0.25	26.96
SPPK Suspension	145.00	Erdafitinib	Plasma	2.00	6.37
SPPK Suspension	145.00	Erdafitinib	Plasma	24.00	
SPPK Suspension	146.00	Erdafitinib	Plasma	0.25	38.36
SPPK Suspension	146.00	Erdafitinib	Plasma	2.00	2.88
SPPK Suspension	146.00	Erdafitinib	Plasma	24.00	
SPPK Suspension	147.00	Erdafitinib	Plasma	0.25	31.47
SPPK Suspension	147.00	Erdafitinib	Plasma	2.00	5.44
SPPK Suspension	147.00	Erdafitinib	Plasma	24.00	
SPPK Suspension	148.00	Erdafitinib	Plasma	0.50	47.89
SPPK Suspension	148.00	Erdafitinib	Plasma	4.00	2.15
SPPK Suspension	148.00	Erdafitinib	Plasma	8.00	
SPPK Suspension	149.00	Erdafitinib	Plasma	0.50	64.65
SPPK Suspension	149.00	Erdafitinib	Plasma	4.00	2.64
SPPK Suspension	149.00	Erdafitinib	Plasma	8.00	
SPPK Suspension	150.00	Erdafitinib	Plasma	0.50	53.14
SPPK Suspension	150.00	Erdafitinib	Plasma	4.00	10.36
SPPK Suspension	150.00	Erdafitinib	Plasma	8.00	
SPTPK Solution	127.00	Erdafitinib	Plasma	0.17	0.50
SPTPK Solution	127.00	Erdafitinib	Tumor	0.17	3.00
SPTPK Solution	128.00	Erdafitinib	Plasma	0.17	62.96
SPTPK Solution	128.00	Erdafitinib	Tumor	0.17	9.18
SPTPK Solution	129.00	Erdafitinib	Plasma	0.17	78.46
SPTPK Solution	129.00	Erdafitinib	Tumor	0.17	98.08
SPTPK Solution	130.00	Erdafitinib	Plasma	2.00	20.44
SPTPK Solution	130.00	Erdafitinib	Tumor	2.00	65.57
SPTPK Solution	131.00	Erdafitinib	Plasma	2.00	11.34
SPTPK Solution	131.00	Erdafitinib	Tumor	2.00	45.89
SPTPK Solution	132.00	Erdafitinib	Plasma	2.00	20.90
SPTPK Solution	132.00	Erdafitinib	Tumor	2.00	74.90
SPTPK Solution	133.00	Erdafitinib	Plasma	4.00	9.89
SPTPK Solution	133.00	Erdafitinib	Tumor	4.00	91.26
SPTPK Solution	134.00	Erdafitinib	Plasma	4.00	0.50
SPTPK Solution	134.00	Erdafitinib	Tumor	4.00	11.12
SPTPK Solution	135.00	Erdafitinib	Plasma	4.00	1.90
SPTPK Solution	135.00	Erdafitinib	Tumor	4.00	40.61
SPTPK Solution	136.00	Erdafitinib	Plasma	8.00	
SPTPK Solution	136.00	Erdafitinib	Tumor	8.00	3.00

Study	Subject	Analyte	Group	Time (hr)	Concentration (ug/L)
SPTPK Solution	137.00	Erdafitinib	Plasma	8.00	
SPTPK Solution	137.00	Erdafitinib	Tumor	8.00	3.00
SPTPK Solution	138.00	Erdafitinib	Plasma	8.00	
SPTPK Solution	138.00	Erdafitinib	Tumor	8.00	27.35
SPTPK Solution	139.00	Erdafitinib	Plasma	16.00	
SPTPK Solution	139.00	Erdafitinib	Tumor	16.00	
SPTPK Solution	140.00	Erdafitinib	Plasma	16.00	
SPTPK Solution	140.00	Erdafitinib	Tumor	16.00	
SPTPK Solution	141.00	Erdafitinib	Plasma	16.00	
SPTPK Solution	141.00	Erdafitinib	Tumor	16.00	

Table 4.4: Erdafitinb 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	Erdafitinib	Aggregate	Plasma	0.13	125.14	213.50	3.00
Concentration	ug/L	Erdafitinib	Aggregate	Plasma	0.17	40.32	29.50	6.00
Concentration	ug/L	Erdafitinib	Aggregate	Plasma	0.25	31.87	7.63	6.00
Concentration	ug/L	Erdafitinib	Aggregate	Plasma	0.50	37.11	21.14	6.00
Concentration	ug/L	Erdafitinib	Aggregate	Plasma	1.00	10.78	13.16	9.00
Concentration	ug/L	Erdafitinib	Aggregate	Plasma	2.00	9.75	7.66	9.00
Concentration	ug/L	Erdafitinib	Aggregate	Plasma	4.00	2.97	3.43	12.00
Concentration	ug/L	Erdafitinib	Aggregate	Plasma	8.00	2.50	0.80	6.00
Concentration	ug/L	Erdafitinib	Aggregate	Plasma	16.00			0.00
Concentration	ug/L	Erdafitinib	Aggregate	Plasma	24.00			0.00
Concentration	ug/L	Erdafitinib	SPPK Solution	Plasma	0.17	33.33	18.04	3.00
Concentration	ug/L	Erdafitinib	SPPK Solution	Plasma	0.25	31.48	10.58	3.00
Concentration	ug/L	Erdafitinib	SPPK Solution	Plasma	0.50	18.99	7.67	3.00
Concentration	ug/L	Erdafitinib	SPPK Solution	Plasma	1.00	8.09	4.25	6.00
Concentration	ug/L	Erdafitinib	SPPK Solution	Plasma	2.00	6.80	7.91	3.00
Concentration	ug/L	Erdafitinib	SPPK Solution	Plasma	4.00	1.37	0.87	6.00
Concentration	ug/L	Erdafitinib	SPPK Solution	Plasma	8.00	2.50	0.80	6.00
Concentration	ug/L	Erdafitinib	SPPK Suspension	Plasma	0.13	125.14	213.50	3.00
Concentration	ug/L	Erdafitinib	SPPK Suspension	Plasma	0.25	32.26	5.74	3.00
Concentration	ug/L	Erdafitinib	SPPK Suspension	Plasma	0.50	55.22	8.57	3.00
Concentration	ug/L	Erdafitinib	SPPK Suspension	Plasma	1.00	16.15	24.14	3.00
Concentration	ug/L	Erdafitinib	SPPK Suspension	Plasma	2.00	4.90	1.81	3.00
Concentration	ug/L	Erdafitinib	SPPK Suspension	Plasma	4.00	5.05	4.61	3.00
Concentration	ug/L	Erdafitinib	SPPK Suspension	Plasma	8.00			0.00
Concentration	ug/L	Erdafitinib	SPPK Suspension	Plasma	16.00			0.00

Variable	Units	Analyte	Study	Group	Time (hr)	Mean (ug/L)	SD (ug/L)	N
Concentration	ug/L	Erdafitinib	SPPK Suspension	Plasma	24.00			0.00
Concentration	ug/L	Erdafitinib	SPTPK Solution	Plasma	0.17	47.31	41.27	3.00
Concentration	ug/L	Erdafitinib	SPTPK Solution	Plasma	2.00	17.56	5.39	3.00
Concentration	ug/L	Erdafitinib	SPTPK Solution	Plasma	4.00	4.09	5.06	3.00
Concentration	ug/L	Erdafitinib	SPTPK Solution	Plasma	8.00			0.00
Concentration	ug/L	Erdafitinib	SPTPK Solution	Plasma	16.00			0.00
Concentration	ug/L	Erdafitinib	SPTPK Solution	Tumor	0.17	36.76	53.20	3.00
Concentration	ug/L	Erdafitinib	SPTPK Solution	Tumor	2.00	62.12	14.81	3.00
Concentration	ug/L	Erdafitinib	SPTPK Solution	Tumor	4.00	47.67	40.53	3.00
Concentration	ug/L	Erdafitinib	SPTPK Solution	Tumor	8.00	11.12	14.06	3.00
Concentration	ug/L	Erdafitinib	SPTPK Solution	Tumor	16.00			0.00

5.0 ATTACHED FILES

Attached File 5.1 Erdafitinib Screening PK PLA.docx – *Final in vivo study plan as executed (SRM2 OR 117594-1216943, SPPK Solution)*

Attached File 5.2 Erdafitinib Screening PLA TUM PK PLA.docx – *Final in vivo study plan as executed (SRM2 OR 120294-1256547, SPTPK Solution)*

Attached File 5.3 Erdafitinib Screening Plasma PK.docx – *Final in vivo study plan as executed (SRM2 OR 128911-1350632, SPPK Suspension)*

Attached File 5.4 Erdafitinib PK tumor bearing study sheet 2.docx – *Digital data collection form for in vivo study (SRM2 OR 120294-1256547, SPTPK Solution)*

Attached File 5.5 Erdafitinib PK_non tumor_3-8-18.docx – *Digital data collection form for in vivo study (SRM2 OR 128911-1350632, SPPK Suspension)*

Attached File 5.6 Erdafitinib Screening Plasma Tumor PK TLFs.docx – *Tables, listings, and figures in Word format for reformatting or manipulations*

Attached File 5.7 RPT.120294-1256547 Erdafitinib Screening PK RHB MAST 39 (20% HPBCD).pdf – *Original report for SPTPK Solution study.*