PRECLINICAL PHARMACOKINETIC REPORT

Developmental Biology and Solid Tumor Program

P-PKSR Study 18393-83342

STUDY TITLE:

PLASMA, TUMOR, AND TUMOR EXTRACELLULAR FLUID PHARMACOKINETICS OF LINSITINIB (OSI906) IN MICE BEARING NEUROBLASTOMA (MAST 3) ORTHOTOPIC XENOGRAFTS

SHORT TITLE:	**Linsitinib (OSI906) Plasma Tumor ECF PK**
TEST ARTICLE:	Linsitinib (OSI906)
SECTION:	Nonclinical Pharmacokinetics (Non-GLP)
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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) Studies

Pharmacokinetic (PK) studies were performed following single oral doses of linsitinib in both non-tumor bearing NOD SCID mice and CD1 nu/nu mice bearing MAST 3 neuroblastoma orthotopic xenografts. Additional details regarding in vivo PK studies are presented in **Table 1.1.** Briefly, plasma samples were obtained at various times up to 24 hours after dosing, with 1 to 3 samples acquired per mouse via retro-orbital bleeds with heparinized pipettes. Tumor bearing mice were sacrificed at selected post-dose time points, with paired plasma and tumor samples. Tumors were harvested, extracted, and rinsed with PBS. Tumor extracellular fluid (ECF) was sampled for compound concentrations in separate groups of tumor bearing mice using microdialysis. Microdialysis probes (BASi; 1 mm membrane) were introduced into tumors through cannulae inserted during tumor cell implantation. The probes were allowed to equilibrate prior to dosing, and recovery was estimated for each probe using retrodialysis techniques. The dialysate solution consisted of Lactated Ringers equivalent with 10% hydroxypropyl-β-cyclodextrin to improve recovery of the hydrophobic compounds. Dialysate fractions were collected periodically for up to 14 hours after dosing. At the end of collection, plasma, tumor, and dialysate samples were immediately placed on dry ice and stored at -80°C until analysis.

Table 1.1 Summary of Linsitinib PK Studies in Mice

PK Study Name	Mouse Strain	Dose/Formulation	Matrix	Sample Times
Plasma #1	NOD SCID	25 mg/kg PO in 25 mM tartaric acid	Plasma	3 mice; 0.25, 2, 8 hr 3 mice; 0.5, 4, 12 hr 3 mice; 1, 6, 24 hr 3 mice; 0.75, 10, 24 hr 3 mice; 24 hr
Plasma #2	CD1 nu/nu	50 mg/kg PO in 25 mM tartaric acid	Plasma	4 mice; 0.083, 1, 14 hr
Plasma #3	CD1 nu/nu (MAST3)	10 mg/kg PO in 25 mM tartaric acid	Plasma	4 mice; 0.083, 1, 14 hr
Plasma #4	CD1 nu/nu (MAST3)	10 mg/kg PO in 25 mM tartaric acid	Plasma	4 mice; 0.083, 1, 9 hr
Tumor	CD1 nu/nu (MAST3)	10 mg/kg PO in 25 mM tartaric acid	Plasma, Tumor	15 mice; 0.083, 0.6, 3.5, 7.5, 18 hr
Microdialysis – ECF	CD1 nu/nu (MAST3)	10 mg/kg PO in 25 mM tartaric acid	Plasma, ECF	3 mice; 0.083, 1, 16 hr & every 1.5 hr for 14 hr

1.2 Bioanalysis

Compound concentrations in mouse plasma, tumor, and dialysate samples were assessed using a sensitive and specific LC-MS/MS assay for linsitinib [1] (**Attached File X.X**). The method used ketoconazole as the internal standard, and demonstrated a linear response over the range of 1.05 to 375 ng/mL (R≥0.9950). 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 1.05 ng/mL. Sample dilution integrity was confirmed. The intra-run precision and accuracy for plasma was ≤ 8.32% CV and 97.4% to 101%, respectively Samples were prepared as follows: tumor was homogenized after dilution with purified water using a Fast-Prep 24 bead homogenizer system following the methods of Liang [2]. Plasma and tumor homogenates were protein precipitated with methanol and injected onto the LC-MS/MS system. Dialysate samples underwent a liquid-liquid extraction procedure using MTBE, were dried under vacuum and heat, and reconstituted with mobile phase for injection.

1.3 Pharmacokinetic (PK) Analysis

Resultant concentration-time (Ct) data for the compound were analyzed using a non-linear mixed effects population approach as implemented in ADAPT 5 using the MLEM algorithm [3]. A variety of models, parameterized using either inter-compartmental rate constants or clearances, were tested and assessed

for goodness of fit using the -2 log likelihood value, visual predictive checks, plots of model individual and population predicted vs. observed data, and residual plots. A log-normal inter-individual parameter distribution was assumed, with only diagonal elements of parameter covariance matrices estimated. Additive residual error was fixed to the lower limit of quantitation (LLOQ) value of the corresponding compound assay, while proportional residual error was either estimated or fixed to the assay's observed precision. Beal's M3 method was used to handle data that were below the LLOQ [4].

Secondary PK parameters were derived from the population and post-hoc individual subject model parameter estimates using standard formulae [5] and included the following: Apparent oral plasma clearance (CL/F, calculated as K_e x V_c/F), area under the plasma concentration-time curve (AUC_p, calculated as Dose*F/CL), and the unbound plasma AUC ($AUC_{u,p}$, calculated as AUC_p*F_u). The murine plasma F_u ratio value for mice was obtained from the Investigator's Brochure (Edition 4, 07 April 2009, OSI Pharmaceuticals, Boulder, CO, USA). To assess compound distribution into the MAST 3 neuroblastoma orthotopic xenografts, a tumor or ECF to unbound plasma partition coefficient ($K_{P,tumor}$, $K_{P,ECF}$) was estimated as either a primary model parameter or was calculated as the tumor or ECF AUC:$AUC_{u,p}$ ratio. Additionally, Monte Carlo simulations (n=1000 individual mice) with the model parameter estimates were used to generate 90% prediction intervals (90% PIs) for each compound's parameters.

The resultant PK data and estimates were then used to synthesize clinically reasonable dosing regimens for mouse efficacy studies. A clinically relevant dose (CRD) was calculated as the oral dose of compound achieving the same calculated $AUC_{u,p}$ estimated at the single agent human recommended Phase 2 dose (RP2D) or the maximally tolerated dose (MTD) reported in the literature. Median plasma, tumor, and tumor ECF Ct profiles were also simulated for each compound using the dosing regimens applied in the preclinical mouse efficacy studies. Then, these median Ct profiles were graphically compared with 72-hour median effective concentration (EC_{50}) estimate for compound activity in CellTiter Glo (CTG) ATP assays as a surrogate for in vitro and in vivo cytotoxic pharmacodynamic effect for the MAST 3 line.

2.0 RESULTS

Multi-compartmental models were simultaneously fit to each matrix for linsitinib. The plasma data were adequately described using a linear one-compartment model with rapid first order oral absorption. Tumor and ECF models were driven by unbound plasma concentrations in a manner similar to a forcing function [6]. Total tumor concentrations were well described using an apparent perfusion-limited component, whereas a perfusion-limited model with non-linear and linear elimination best described linsitinib extracellular fluid (ECF) concentrations. This ECF model suggests either a diffusion limited penetration with slow equilibrium between plasma, ECF, and tumor tissues, or a higher affinity, saturable binding in tumor. **Figure 2.1** describes the final structural model and the parameter estimates and precision are presented in **Table 2.1**, along with parameter abbreviation descriptions.

Figure 2.1 Linsitinib PK Model for Plasma, Tumor, and Tumor ECF in Mice

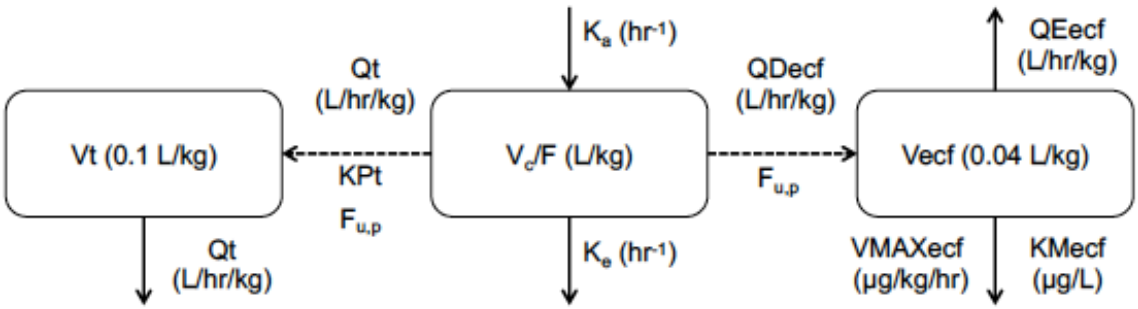

Table 2.1 Linsitinib PK Model Parameter Estimates

Matrix	Parameter	Units	Estimate	%RSE	IIV (%CV)	%RSE
Plasma	K_e	hr^{-1}	9.06E-02	15.2	38.3	22
	V_c/F	L/kg	3.89	11	50.1	29.8
	K_a	hr^{-1}	15.5	44.5	50.3	108
	$F_{u,p}$	-	0.066	FIXED		
	σ add	µg/L	1	FIXED		
	σ prop	%	23.5	19		
Tumor	Qt	L/hr/kg	0.44	63.1	50.4	360
	KPt	-	0.926	14.3	31.2	68.4
	Vt	L/kg	0.1	FIXED		
	σ add	µg/L	1	FIXED		
	σ prop	%	5.51	81.3		
ECF	VMAXecf	µg/kg/hr	18.1	271	54.4	518
	KMecf	µg/L	70.4	143	34.7	561
	QDecf	L/hr/kg	0.134	132	46.9	496
	QEecf	L/hr/kg	2.17E-03	236	32.9	586
	Vecf	L/kg	4.00E-02	FIXED		
	σ add	µg/L	0.5	FIXED		
	σ prop	%	25.4	17.6		

Abbreviations – %RSE, percent relative standard error; IIV, inter-individual variability; K_e, elimination rate constant; V_c/F, apparent oral volume of distribution of central compartment; K_a, oral absorption rate constant; $F_{u,p}$, fraction unbound in plasma; Qt, tumor apparent perfusional flow; KPt, tumor partition coefficient; Vt, tumor volume (assuming specific density of 1.0); VMAXecf, maximum velocity of elimination in extracellular fluid; KMecf, concentration of half-maximal velocity of elimination in extracellular fluid; QDecf, extracellular fluid apparent distributional flow; QEecf, extracellular fluid clearance; Vecf, estimated volume of the extracellular fluid; Qecf, extracellular fluid apparent perfusional flow; KPecf, extracellular fluid partition coefficient; σ add, additive residual error as a standard deviation; σ prop, proportional residual error as a percentage.

Linsitinib plasma PK parameters were well estimated as indicated by the small to modest %RSE values, all generally being < 50%. Inter-animal variability on Ka was not well estimated (108% RSE), due to insufficient numbers of mice and samples in rapid absorption phase. Tumor and ECF parameters were not as precise, most likely due to the limited data, inter-animal variability, and model misspecification. Despite this relative imprecision, the models demonstrated adequate goodness of fit upon visual inspection with some bias (data not shown). The joint model tended to overpredict total tumor homogenate values at later time points, and globally underpredicted ECF concentrations. Tumor ECF concentrations were higher than total tumor homogenate for the first ~10 hours, but then were similar after an apparent equilibrium had been reached. See **Section 4.0** for figures. However, the modeled partition coefficients compared well with noncompartmental methods. The PK parameters displayed appreciable inter-animal and residual variability, likely resulting from variances in gavage administration between studies, husbandry conditions (i.e. ad libitum food), and model misspecification. However, such PK variability can be anticipated in any longer-term preclinical efficacy or clinical studies.

Our plasma PK results were appreciably different from the limited published mouse PK for linsitinib. The median plasma AUC for linsitinib reported by Mulvihill et al. was 26741 hr-ng/mL at 25 mg/kg PO in CD1 nude mice [7], whereas our simulated median was 74220 hr-ng/mL (90% PI: 23421 – 215452). While the previously reported median resides within our 90% PI, there remains an almost 3-fold difference in the median values.

We derived a clinically relevant dose (CRD) for linsitinib based upon the Monte Carlo simulated $AUC_{u,p}$ values in mice and the observed clinical $AUC_{u,p}$ at the single agent MTD or RP2D from literature. At the

human RP2D for linsitinib of 150 mg PO BID, the daily unbound plasma AUC was estimated to be 1610 hr-ng/L [8,9]. The unbound fraction in plasma for humans (Fu,p,h) was reported as 0.033 [7]. Assuming linear PK across species and with dose, and the difference in plasma protein binding between species, a dosage of approximately 8.2 mg/kg PO QD in mice would be equivalent. Doses of linsitinib 6 mg/kg and 13 mg/kg PO QD were used in applicable efficacy studies, the daily administration being chosen for logistical convenience and for adherence to mouse regimens in literature [7]. Notably, linsitinib tumor and tumor ECF concentration predictions failed to meet the target in vitro EC_{50} values at the selected clinically relevant dose level of 6 mg/kg in mice (**Attached File 5.1**).

3.0 REFERENCES

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4.0 TABLES, LISTINGS, AND FIGURES (TLF

Figure 4.1: Mean Population Predicted Plasma Ct Profile of Linsitinib Dose Normalized to 10 mg/kg PO in Mice

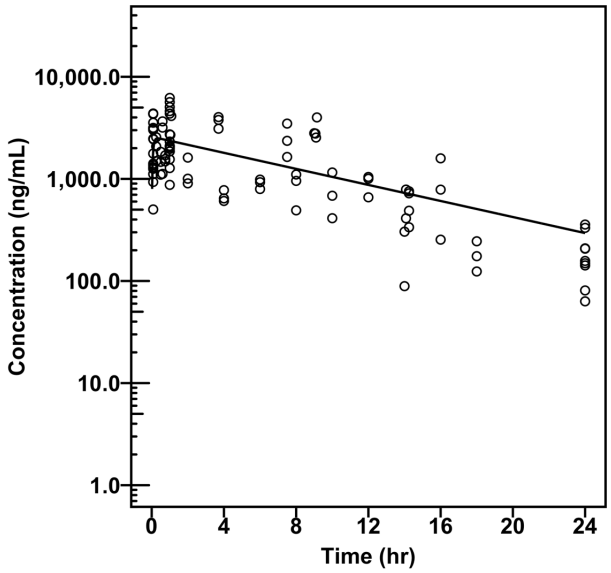

Figure 4.2: Mean Population Predicted Tumor Homogenate Ct Profile of Linsitinib Dose Normalized to 10 mg/kg PO in Mice

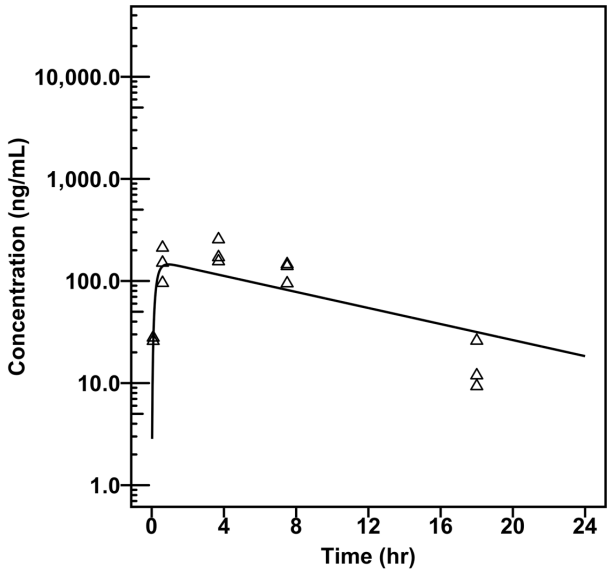

Figure 4.3: Mean Population Predicted Tumor ECF Ct Profile of Linsitinib Dose Normalized to 10 mg/kg PO in Mice

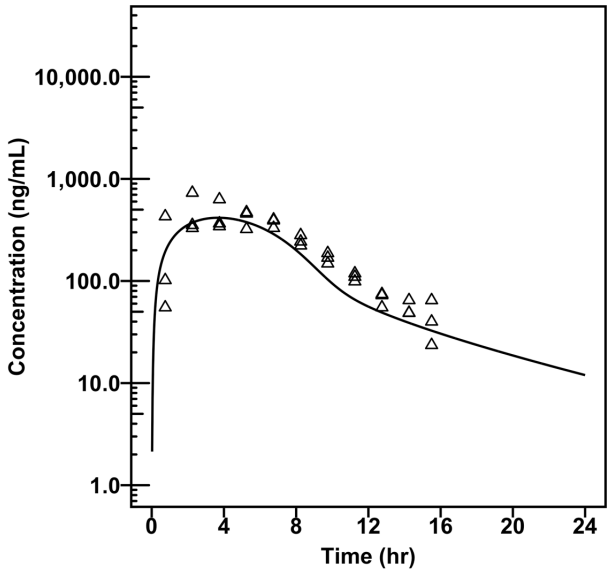

Table 4.1: Listing of Observed Plasma, Tumor Homogenate, and Tumor Ct Data for Linsitinib PK Modeling

IndividID	Time	Plasma (ng/mL)	Tumor Homogenate (ng/mL)	Tumor ECF (ng/mL)	Study	Dosage (mg/kg)
m1001	0.083	1300	25.9		Tumor	10
m1002	0.083	4320	27.9		Tumor	10
m1003	0.6	3180	151		Tumor	10
m1004	0.6	1120	95.7		Tumor	10
m1005	0.6	3660	212		Tumor	10
m1006	3.7	4030	256		Tumor	10
m1007	3.7	3780	156		Tumor	10
m1008	3.7	3100	171		Tumor	10
m1009	7.5	3480	94.8		Tumor	10
m1010	7.5	2360	140		Tumor	10
m1011	7.5	1640	146		Tumor	10
m1012	18	175	26		Tumor	10
m1013	18	124	11.9		Tumor	10
m1014	18	245	9.33		Tumor	10
m1101	0.083	1410			Plasma #3	10
m1101	1	2100			Plasma #3	10

Linsitinib (OSI906) Plasma Tumor ECF PK

IndividID	Time	Plasma (ng/mL)	Tumor Homogenate (ng/mL)	Tumor ECF (ng/mL)	Study	Dosage (mg/kg)
m1101	14.083	786			Plasma #3	10
m1102	0.1	2440			Plasma #3	10
m1102	1.03333	2700			Plasma #3	10
m1102	14.083	411			Plasma #3	10
m1103	0.083	3550			Plasma #3	10
m1103	1	4360			Plasma #3	10
m1103	14	304			Plasma #3	10
m1104	0.083	3120			Plasma #3	10
m1104	1	2320			Plasma #3	10
m1104	14	89			Plasma #3	10
m1105	0.083	5580			Plasma #2	50
m1105	1	7770			Plasma #2	50
m1105	14.25	3780			Plasma #2	50
m1106	0.083	2510			Plasma #2	50
m1106	1	4370			Plasma #2	50
m1106	14.25	1680			Plasma #2	50
m1107	0.083	6280			Plasma #2	50
m1107	1	9300			Plasma #2	50
m1107	14.25	3610			Plasma #2	50
m1108	0.083	15100			Plasma #2	50
m1108	1	10500			Plasma #2	50
m1108	14.25	2440			Plasma #2	50
m1201	0.083	3160			Plasma #4	10
m1201	1.08333	4130			Plasma #4	10
m1201	9	2800			Plasma #4	10
m1202	0.083	1360			Plasma #4	10
m1202	1	5050			Plasma #4	10
m1202	9.15	4000			Plasma #4	10
m1203	0.083	4360			Plasma #4	10
m1203	1	5650			Plasma #4	10
m1203	9.06667	2780			Plasma #4	10
m1204	0.083	4370			Plasma #4	10
m1204	1	6210			Plasma #4	10
m1204	9.1	2540			Plasma #4	10
m1301	0.083	2470			Microdialysis - ECF	10

Linsitinib (OSI906) Plasma Tumor ECF PK

IndividID	Time	Plasma (ng/mL)	Tumor Homogenate (ng/mL)	Tumor ECF (ng/mL)	Study	Dosage (mg/kg)
m1301	0.75			55.12	Microdialysis - ECF	10
m1301	1	4610			Microdialysis - ECF	10
m1301	2.25			353.06	Microdialysis - ECF	10
m1301	3.75			343.67	Microdialysis - ECF	10
m1301	5.25			457.29	Microdialysis - ECF	10
m1301	6.75			391.56	Microdialysis - ECF	10
m1301	8.25			222.54	Microdialysis - ECF	10
m1301	9.75			148.36	Microdialysis - ECF	10
m1301	11.25			109.86	Microdialysis - ECF	10
m1301	12.75			74.37	Microdialysis - ECF	10
m1301	14.25			64.88	Microdialysis - ECF	10
m1301	15.5			64.79	Microdialysis - ECF	10
m1301	16	1590			Microdialysis - ECF	10
m1302	0.083	933			Microdialysis - ECF	10
m1302	0.75			101.96	Microdialysis - ECF	10
m1302	1	2040			Microdialysis - ECF	10
m1302	2.25			330.14	Microdialysis - ECF	10
m1302	3.75			366.07	Microdialysis - ECF	10
m1302	5.25			470.94	Microdialysis - ECF	10
m1302	6.75			400.05	Microdialysis - ECF	10
m1302	8.25			243.47	Microdialysis - ECF	10
m1302	9.75			168.95	Microdialysis - ECF	10
m1302	11.25			99.04	Microdialysis - ECF	10
m1302	12.75			55.15	Microdialysis - ECF	10
m1302	14.25			48.84	Microdialysis - ECF	10
m1302	15.5			23.59	Microdialysis - ECF	10
m1302	16	254			Microdialysis - ECF	10
m1303	0.083	1770			Microdialysis - ECF	10
m1303	0.75			429.82	Microdialysis - ECF	10
m1303	1	2730			Microdialysis - ECF	10
m1303	2.25			731.09	Microdialysis - ECF	10
m1303	3.75			630.67	Microdialysis - ECF	10
m1303	5.25			322.69	Microdialysis - ECF	10
m1303	6.75			330.73	Microdialysis - ECF	10
m1303	8.25			281.19	Microdialysis - ECF	10

Linsitinib (OSI906) Plasma Tumor ECF PK

IndividID	Time	Plasma (ng/mL)	Tumor Homogenate (ng/mL)	Tumor ECF (ng/mL)	Study	Dosage (mg/kg)
m1303	9.75			187.46	Microdialysis - ECF	10
m1303	11.25			118.77	Microdialysis - ECF	10
m1303	12.75			72.57	Microdialysis - ECF	10
m1303	14.25			48.61	Microdialysis - ECF	10
m1303	15.5			40.04	Microdialysis - ECF	10
m1303	16	785			Microdialysis - ECF	10
m901	0.25	6400			Plasma #1	25
m901	2	4040			Plasma #1	25
m901	8	2760			Plasma #1	25
m902	0.25	5200			Plasma #1	25
m902	2	2510			Plasma #1	25
m902	8	2390			Plasma #1	25
m903	0.25	3730			Plasma #1	25
m903	2	2260			Plasma #1	25
m903	8	1230			Plasma #1	25
m904	0.5	4600			Plasma #1	25
m904	4	1940			Plasma #1	25
m904	12	2610			Plasma #1	25
m905	0.5	2750			Plasma #1	25
m905	4	1520			Plasma #1	25
m905	12	1650			Plasma #1	25
m906	0.5	3670			Plasma #1	25
m906	4	1610			Plasma #1	25
m906	12	2510			Plasma #1	25
m907	1	4920			Plasma #1	25
m907	6	2320			Plasma #1	25
m907	24	373			Plasma #1	25
m908	1	3190			Plasma #1	25
m908	6	1990			Plasma #1	25
m908	24	393			Plasma #1	25
m909	1	4650			Plasma #1	25
m909	6	2460			Plasma #1	25
m909	24	355			Plasma #1	25
m910	0.75	3710			Plasma #1	25
m910	10	1030			Plasma #1	25

IndividID	Time	Plasma (ng/mL)	Tumor Homogenate (ng/mL)	Tumor ECF (ng/mL)	Study	Dosage (mg/kg)
m910	24	158			Plasma #1	25
m911	0.75	3910			Plasma #1	25
m911	10	1710			Plasma #1	25
m911	24	518			Plasma #1	25
m912	0.75	4250			Plasma #1	25
m912	10	2890			Plasma #1	25
m912	24	893			Plasma #1	25
m913	24	522			Plasma #1	25
m914	24	829			Plasma #1	25
m915	24	202			Plasma #1	25

5.0 ATTACHED FILES

Attached File 5.1 linsitinib_ct_sim.pdf – *Day 15 population mean predicted Ct profiles in plasma, tumor, and tumor ECF for linsitinib (OSI906) 6 mg/kg PO QD in mice.*

Attached File 5.2 Linsitinib OSI906 CtData Listing.xlsx – *Table 4.1 in Excel file format. Listing of observed linsitinib concentrations in plasma, tumor homogenate, and tumor ECF used for modeling*

Attached File 5.3 Linsitinib (OSI906) Plasma Tumor ECF PK ADAPT5 Files.zip – *ADAPT5 modeling files and results used for analysis and reporting*