PRECLINICAL PHARMACOKINETIC REPORT

Developmental Biology and Solid Tumor Program

P-PKSR Study 156578 - 1645501

STUDY TITLE:

PLASMA AND TUMOR PHARMACOKINETICS OF IRINOTECAN (IRN) AND SN-38 IN FEMALE ATHYMIC NUDE MICE BEARING ES-8 EWINGS SARCOMA ORTHOTOPIC XENOGRAFTS AFTER A SINGLE INTRAPERITONEAL DOSE OF IRINOTECAN HCL (STD IRN, USP)

SHORT TITLE:	**Std IRN IP (IRN, SN-38) Plasma and ES-8 Tumor PK**
TEST ARTICLE:	Irinotecan Hydrochloride, USP
SECTION:	Nonclinical Pharmacokinetics (Non-GLP)
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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) Studies

The plasma pharmacokinetic (PK) profile of total irinotecan (IRN) and its active metabolite SN-38 were evaluated in female Athymic nude mice (Charles River), approximately 12 weeks in age, in a mix of non-tumor bearing mice and mice bearing ES-8 Ewing Sarcoma orthotopic xenografts (OTXs) across three separate studies. Standard Irinotecan hydrochloride (Std IRN, irinotecan HCl, USP) was obtained from SJCRH Pharmacy and diluted with normal saline, to yield a dose of 3.125 mg/kg for intraperitoneal (IP) injection. In select mice across the studies, survival retro-orbital bleeds using Sarstedt 50 uL KEDTA POCT devices were obtained under isoflurane anesthesia, whereas terminal blood samples were obtained under IP Avertin (tribromoethanol) anesthesia. Blood samples were collected upon KEDTA, obtained at various times up to 8 hours post-dose, immediately processed to plasma, and stored on dry ice until transfer to -80°C where they remained until analysis. Following terminal bleeds, animals were perfused with PBS to flush blood from the vasculature. Tissues were then extracted, rinsed with PBS as necessary, and then placed in appropriately labeled microcentrifuge tubes on dry ice. Tissue samples were then transferred to a -80°C freezer as soon as possible.

1.2 Bioanalysis

Frozen tumor samples were weighed in tared 15 mL Lysing Matrix D (MP Biomedical, Santa Ana, CA) tubes 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 (KEDTA) and tumor homogenate samples were analyzed for total irinotecan (SJ000312345-15, MCE) and SN-38 (SJ000311679-8, TCI America) with a qualified LC MS/MS assay. Plasma calibrators and quality controls were spiked with solutions prepared in DMSO. Plasma samples, 25 µL each, were stabilized against carboxylesterase activity by the addition of 5 µL of 200 mM zinc sulfate and then protein precipitated with 100 µL of 10 ng/mL camptothecin (Cayman Chemical Co., Batch 0515272-12) in methanol as an internal standard. A 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 C18 (2.6 µm, 50 mm x 2.1 mm) column maintained at 50 °C with gradient elution at a flow rate of 0.6 mL/min. The binary mobile phase consisted of water-acetonitrile-200 mM ammonium acetate pH 6.0 (90:10:10 v/v) in reservoir A and acetonitrile-water-200 mM ammonium acetate pH 6.0 (90:10:10 v/v) in reservoir B. The initial mobile phase consisted of 15% B with a linear increase to 60% B in 2.0 min. The column was then rinsed for 1.0 min at 100% B and then equilibrated at the initial conditions for 2.0 min for a total run time of 5 min. Under these conditions, irinotecan, IS and SN-38 eluted at 1.22, 1.43 and 1.48 min, respectively.

Analyte and IS were detected with tandem mass spectrometry using a SCIEX 5500 QTRAP in the positive ESI mode and the following mass transitions were monitored: Irinotecan 587.30 → 167.30, camptothecin (349.10 → 305.20) and SN-38 (393.10 → 305.20). The method qualification and bioanalytical runs all passed acceptance criteria for non-GLP assay performance. A linear model (1/X^2 weighting) fit the SN-38 calibrators across the 1 to 500 ng/mL range, with a correlation coefficient (R) of ≥ 0.9980 and 0.9992 for plasma and tumor, respectively. A linear model (1/X^2 weighting) fit the irinotecan calibrators across the 1 to 500 ng/mL range, with a correlation coefficient (R) of ≥ 0.9978 and 0.9972 for plasma and tumor, respectively. 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 for both matrices, with a functional LLOQ of 6 ng/mL for tumor considering dilution. Sample dilution integrity was confirmed. The intra-run precision and accuracy for SN-38 in plasma was ≤ 11.6% CV and 93.2% to 107%, respectively. The intra-run precision and accuracy for irinotecan in plasma was ≤ 10.2% CV and 90.5% to 107%, respectively.

For the tumor homogenate matrix, the intra-run precision and accuracy for SN-38 was ≤ 8.94% CV and 92.3% to 105%, respectively. The intra-run precision and accuracy for irinotecan in tumor homogenate was ≤ 11.5% CV and 93.1% to 104%, respectively.

1.3 Pharmacokinetic (PK) Analysis

The IRN and SN-38 concentration-time (Ct) data were grouped by matrix and nominal 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. Ct summary statistics including the arithmetic mean and standard deviation were then generated. The mean (+SD) Ct profiles were then plotted by analyte and matrix, and presented as figures.

Mean Ct values were subjected to noncompartmental analysis (NCA) using Phoenix WinNonlin 8.1 (Certara USA, Inc., Princeton, NJ). The extravascular model was applied, and area under the Ct curve (AUC) values were estimated using the "linear up log down" method. The terminal phase was defined as all presented mean Ct points past 0.5 hours until the end of the profile, and the elimination rate constant (Kel) was estimated using an unweighted log-linear regression of the terminal phase. The terminal elimination half-life (T1/2) was estimated as 0.693/Kel, and the AUC from time 0 to infinity (AUCinf) was estimated as the AUC to the last time point (AUClast) + Clast (predicted)/Kel. Other 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 clearance (CL/F = Dose/AUCinf), and apparent terminal volume of distribution (Vz/F). The apparent plasma-to-tumor partition coefficient (Kp,inf) was estimated as the ratio of the AUCinf in tissue to AUCinf plasma, whereas Kp,last was similarly estimated using AUClast values.

2.0 RESULTS

After Std IRN 3.125 mg/kg IP, resultant IRN and SN-38 Ct data demonstrated extreme variability between and within mice, with coefficients of variation of up to 179%. The source of this variability is unclear, but it may be a result of compound sinking into large, vascular, and heterogenous orthotopic tumors. Variability could have also been due to continuing plasma esterase activity in collected samples before freezing.

The absorption rate of Std IRN was rapid, with the Tmax occurring at 15 minutes post-dose. After Cmax, plasma concentrations of IRN an SN-38 diminished in a nearly mono-exponential manner. A possible distribution phase may exist, but it is not discernable with the high variability in Ct data. The apparent plasma terminal half-life of was 2.60 hours for IRN and 2.22 hours for SN-38. The apparent plasma clearance (CL/F) of IRN was high at 67.3 mL/min/kg, or approximately 74.8% of murine hepatic blood flow. The apparent plasma terminal volume of distribution (Vz/F) for IRN was also high at 15.2 L/kg. The apparent plasma clearance (CL/F) of SN-38 was high at 163 mL/min/kg, well in excess of murine hepatic blood flow. The apparent plasma terminal volume of distribution (Vz/F) for SN-38 was also high at 31.4 L/kg. All terminal phase derived parameters should be interpreted with caution, given the high variability in Ct data and the poor terminal phase regression R^2 values in this study. The bioavailability of Std IRN by the IP route in mice is unknown in the current study, but it is assumed to be high.

The PK profile of SN-38, the active metabolite of the prodrug IRN, in the current study is appreciably different from our previous findings in mice. As published in Stewart et al. 2014 [1], the plasma Cmax and AUC of SN-38 after a 1.25 mg/kg IP Std IRN dose was 8.79 ng/mL and 23.1 hr-ng/mL, respectively, in CD1 nu mice. When adjusted proportionally for dose, SN-38 plasma exposures in this current study were 4- to 7-fold higher than expected.

Given the high variability in Ct data, the poor terminal phase regressions, and the much higher than expected average exposures, a reliable clinically relevant dosage for Std IRN could not be derived from this data. In general, the results from this current PK study should be considered with caution. Previous

studies have found the 1.25 mg/kg IP dosage to equate to 10-20 mg/m^2 in children by plasma SN-38 AUC.

Tumor penetration of IRN and SN-38 was moderate with Kp,inf values of 1.13 and 1.69 respectively. Tumor concentrations of both analytes were on par to slightly higher than plasma. The calculated average concentration (Cavg = AUCinf / 24hrs) of SN-38 in the tumor over a daily dosing interval was 15.1 ng/mL with the 3.125 mg/kg IP dosage.

3.0 REFERENCES

1. Stewart E, Goshorn R, Bradley C, Griffiths LM, Benavente C, Twarog NR, Miller GM, Caufield W, Freeman BB, Bahrami A, Pappo A, Wu J, Loh A, Karlström Å, Calabrese C, Gordon B, Tsurkan L, Hatfield MJ, Potter PM, Snyder SE, Thiagarajan S, Shirinifard A, Sablauer A, Shelat AA, Dyer MA. Targeting the DNA Repair Pathway in Ewing Sarcoma. Cell Rep. 2014 Nov 6;9(3):829–40.

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4.0 TABLES, LISTINGS, AND FIGURES (TLFS)

Figure 4.1: Mean (SD) Ct Profiles by Analyte and Group

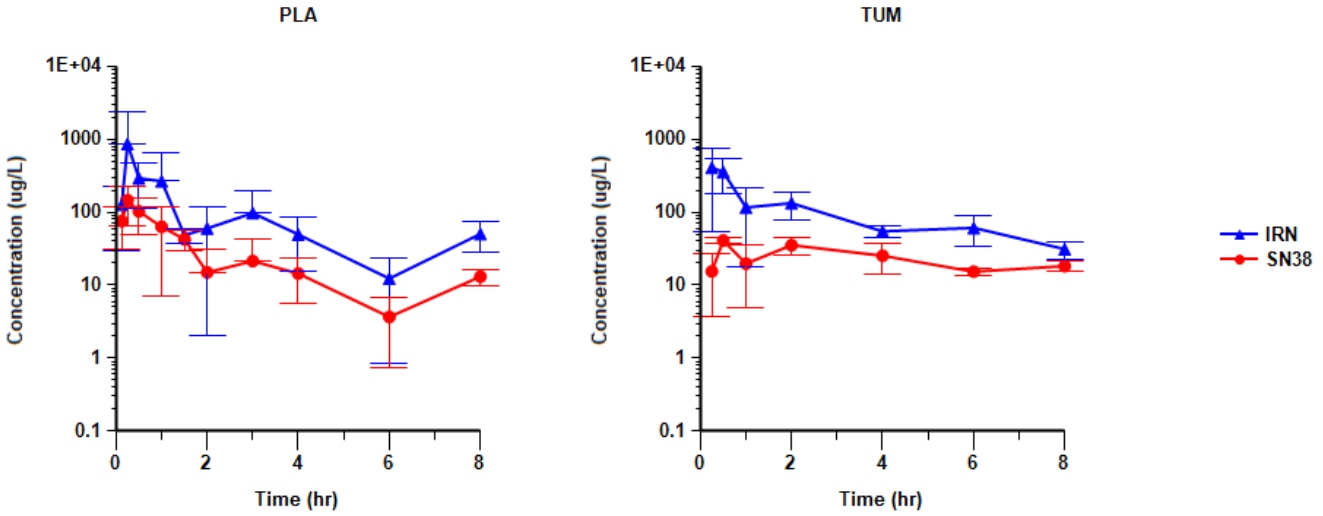

Table 4.1: NCA Parameter Estimates by Analyte and Group

		Group			
		PLA		TUM	
		Analyte		Analyte	
		IRN	SN38	IRN	SN38
Parameter	Units	Estimate			
Cmax	ug/L	859	146	408	40.9
Tmax	hr	0.250	0.250	0.250	0.500
AUClast	hr*ug/L	697	197	759	184
AUCinf	hr*ug/L	773	214	873	362
Kel	1/hr	0.266	0.312	0.257	0.0912
T1/2	hr	2.60	2.22	2.70	7.60
CL/F	L/hr/kg	4.04	9.78	3.58	5.78
Vz/F	L/kg	15.2	31.4	13.9	63.3
Clast	ug/L	50.4	13.1	31.2	18.2
Tlast	hr	8.00	8.00	8.00	8.00

		Group			
		PLA		TUM	
		Analyte		Analyte	
		IRN	SN38	IRN	SN38
Parameter	Units	Estimate			
Kp,last	-	-	-	1.09	0.934
Kp,inf	-	-	-	1.13	1.69

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

		Analyte			
		IRN		SN38	
		Group		Group	
		PLA	TUM	PLA	TUM
Time (hr)		Concentration (ug/L)			
0.125	N	3		3	
	Mean	127		75.4	
	SD	97.5		45.0	
	Min	28.5		24.2	
	Median	130		93.5	
	Max	223		109	
	CV%	76.6		59.7	
	Geometric Mean	93.8		62.7	
	CV% Geometric Mean	146		99.0	
0.250	N	6	3	6	3
	Mean	859	408	146	15.4
	SD	1540	354	80.8	11.7
	Min	4.76	3.00	2.00	3.00
	Median	266	563	162	17.1

Std IRN IP (IRN, SN-38) Plasma and ES-8 Tumor PK

		Analyte			
		IRN		SN38	
		Group		Group	
		PLA	TUM	PLA	TUM
Time (hr)		Concentration (ug/L)			
	Max	3980	658	223	26.1
	CV%	179	86.7	55.3	75.6
	Geometric Mean	222	104	81.2	11.0
	CV% Geometric Mean	1050	11100	523	165
0.500	N	12	3	12	3
	Mean	292	356	103	40.9
	SD	180	178	53.7	3.40
	Min	0.500	155	1.65	37.3
	Median	289	421	112	41.3
	Max	605	493	166	44.1
	CV%	61.6	49.9	52.3	8.31
	Geometric Mean	127	318	63.4	40.8
	CV% Geometric Mean	1330	69.3	293	8.41
1.000	N	6	3	6	3
	Mean	267	116	62.9	19.7
	SD	380	98.3	55.6	15.0
	Min	1.49	3.00	0.500	3.00
	Median	132	164	47.4	24.4
	Max	1010	181	141	31.9
	CV%	142	84.7	88.5	75.9
	Geometric Mean	70.5	44.7	27.0	13.3
	CV% Geometric Mean	1530	1540	859	208
1.500	N	3		3	

Std IRN IP (IRN, SN-38) Plasma and ES-8 Tumor PK

		Analyte			
		IRN		SN38	
		Group		Group	
		PLA	TUM	PLA	TUM
Time (hr)		Concentration (ug/L)			
	Mean	48.4		42.5	
	SD	11.1		13.0	
	Min	36.9		27.6	
	Median	49.3		48.8	
	Max	59.0		51.1	
	CV%	23.0		30.5	
	Geometric Mean	47.5		41.0	
	CV% Geometric Mean	24.1		35.4	
2.000	N	6	3	6	3
	Mean	60.0	133	14.9	35.3
	SD	58.0	54.0	15.4	9.15
	Min	0.500	73.6	0.500	25.4
	Median	59.9	147	12.5	37.0
	Max	146	179	42.6	43.5
	CV%	96.7	40.5	103	25.9
	Geometric Mean	14.7	125	6.91	34.5
	CV% Geometric Mean	3430	49.3	397	28.1
3.000	N	3		3	
	Mean	97.3		21.4	
	SD	102		22.1	
	Min	10.5		2.37	
	Median	72.3		16.1	
	Max	209		45.6	

Std IRN IP (IRN, SN-38) Plasma and ES-8 Tumor PK

		Analyte			
		IRN		SN38	
		Group		Group	
		PLA	TUM	PLA	TUM
Time (hr)		Concentration (ug/L)			
	CV%	104		103	
	Geometric Mean	54.2		12.0	
	CV% Geometric Mean	299		291	
4.000	N	6	3	6	3
	Mean	49.5	54.6	14.4	25.3
	SD	34.0	9.07	8.88	11.5
	Min	11.3	47.5	2.86	12.9
	Median	45.4	51.4	17.2	27.4
	Max	100	64.8	24.0	35.6
	CV%	68.6	16.6	61.5	45.3
	Geometric Mean	38.5	54.1	11.0	23.3
	CV% Geometric Mean	101	16.2	114	56.4
6.000	N	6	3	6	3
	Mean	12.3	61.0	3.66	15.3
	SD	11.5	27.1	2.94	1.90
	Min	0.500	44.9	0.500	13.5
	Median	12.8	45.8	3.92	15.1
	Max	30.4	92.4	8.07	17.3
	CV%	93.2	44.5	80.2	12.4
	Geometric Mean	5.16	57.5	2.30	15.2
	CV% Geometric Mean	545	42.9	186	12.4
8.000	N	3	3	3	3
	Mean	50.4	31.2	13.1	18.2

		Analyte			
		IRN		SN38	
		Group		Group	
		PLA	TUM	PLA	TUM
Time (hr)		Concentration (ug/L)			
	SD	22.7	8.31	3.37	2.73
	Min	24.1	21.6	11.1	15.7
	Median	62.9	35.4	11.3	17.9
	Max	64.1	36.5	17.0	21.1
	CV%	45.1	26.7	25.7	15.0
	Geometric Mean	46.0	30.3	12.8	18.1
	CV% Geometric Mean	60.5	30.1	24.7	15.0

Table 4.3: Ct Summary (Mean, SD, N) by Analyte and Group

Analyte	Group	Time (hr)	Mean (ug/L)	SD (ug/L)	N
IRN	PLA	0.125	127	97.5	3
IRN	PLA	0.250	859	1540	6
IRN	PLA	0.500	292	180	12
IRN	PLA	1.00	267	380	6
IRN	PLA	1.50	48.4	11.1	3
IRN	PLA	2.00	60.0	58.0	6
IRN	PLA	3.00	97.3	102	3
IRN	PLA	4.00	49.5	34.0	6
IRN	PLA	6.00	12.3	11.5	6
IRN	PLA	8.00	50.4	22.7	3
IRN	TUM	0.250	408	354	3
IRN	TUM	0.500	356	178	3

Analyte	Group	Time (hr)	Mean (ug/L)	SD (ug/L)	N
IRN	TUM	1.00	116	98.3	3
IRN	TUM	2.00	133	54.0	3
IRN	TUM	4.00	54.6	9.07	3
IRN	TUM	6.00	61.0	27.1	3
IRN	TUM	8.00	31.2	8.31	3
SN38	PLA	0.125	75.4	45.0	3
SN38	PLA	0.250	146	80.8	6
SN38	PLA	0.500	103	53.7	12
SN38	PLA	1.00	62.9	55.6	6
SN38	PLA	1.50	42.5	13.0	3
SN38	PLA	2.00	14.9	15.4	6
SN38	PLA	3.00	21.4	22.1	3
SN38	PLA	4.00	14.4	8.88	6
SN38	PLA	6.00	3.66	2.94	6
SN38	PLA	8.00	13.1	3.37	3
SN38	TUM	0.250	15.4	11.7	3
SN38	TUM	0.500	40.9	3.40	3
SN38	TUM	1.00	19.7	15.0	3
SN38	TUM	2.00	35.3	9.15	3
SN38	TUM	4.00	25.3	11.5	3
SN38	TUM	6.00	15.3	1.90	3
SN38	TUM	8.00	18.2	2.73	3

Table 4.4: Ct Data Listings by Subject, Analyte, Group, and Time

Subject	Analyte	Group	Time (hr)	Concentration (ug/L)
S1_M1	IRN	PLA	0.125	223.38

Std IRN IP (IRN, SN-38) Plasma and ES-8 Tumor PK

Subject	Analyte	Group	Time (hr)	Concentration (ug/L)
S1_M1	IRN	PLA	1.00	143.07
S1_M1	IRN	PLA	3.00	72.34
S1_M1	SN38	PLA	0.125	108.66
S1_M1	SN38	PLA	1.00	117.25
S1_M1	SN38	PLA	3.00	16.13
S1_M2	IRN	PLA	0.125	129.61
S1_M2	IRN	PLA	1.00	120.53
S1_M2	IRN	PLA	3.00	209.05
S1_M2	SN38	PLA	0.125	93.47
S1_M2	SN38	PLA	1.00	140.80
S1_M2	SN38	PLA	3.00	45.59
S1_M3	IRN	PLA	0.125	28.52
S1_M3	IRN	PLA	1.00	15.18
S1_M3	IRN	PLA	3.00	10.51
S1_M3	SN38	PLA	0.125	24.22
S1_M3	SN38	PLA	1.00	23.72
S1_M3	SN38	PLA	3.00	2.37
S1_M4	IRN	PLA	0.250	265.60
S1_M4	IRN	PLA	1.50	36.87
S1_M4	IRN	PLA	4.00	46.02
S1_M4	SN38	PLA	0.250	124.89
S1_M4	SN38	PLA	1.50	27.57
S1_M4	SN38	PLA	4.00	18.85
S1_M5	IRN	PLA	0.250	266.07
S1_M5	IRN	PLA	1.50	49.31
S1_M5	IRN	PLA	4.00	11.35

Std IRN IP (IRN, SN-38) Plasma and ES-8 Tumor PK

Subject	Analyte	Group	Time (hr)	Concentration (ug/L)
S1_M5	SN38	PLA	0.250	132.18
S1_M5	SN38	PLA	1.50	48.77
S1_M5	SN38	PLA	4.00	4.25
S1_M6	IRN	PLA	0.250	210.38
S1_M6	IRN	PLA	1.50	59.03
S1_M6	IRN	PLA	4.00	76.91
S1_M6	SN38	PLA	0.250	222.84
S1_M6	SN38	PLA	1.50	51.10
S1_M6	SN38	PLA	4.00	21.07
S1_M7	IRN	PLA	0.500	2.32
S1_M7	IRN	PLA	2.00	0.50
S1_M7	IRN	PLA	6.00	0.50
S1_M7	SN38	PLA	0.500	4.52
S1_M7	SN38	PLA	2.00	1.64
S1_M7	SN38	PLA	6.00	0.50
S1_M8	IRN	PLA	0.500	0.50
S1_M8	IRN	PLA	2.00	0.50
S1_M8	IRN	PLA	6.00	0.50
S1_M8	SN38	PLA	0.500	1.65
S1_M8	SN38	PLA	2.00	0.50
S1_M8	SN38	PLA	6.00	0.50
S1_M9	IRN	PLA	0.500	254.26
S1_M9	IRN	PLA	2.00	34.58
S1_M9	IRN	PLA	6.00	8.84
S1_M9	SN38	PLA	0.500	149.51
S1_M9	SN38	PLA	2.00	42.58

Std IRN IP (IRN, SN-38) Plasma and ES-8 Tumor PK

Subject	Analyte	Group	Time (hr)	Concentration (ug/L)
S1_M9	SN38	PLA	6.00	3.02
S3_M1	IRN	PLA	0.250	425.83
S3_M1	IRN	TUM	0.250	563.32
S3_M1	SN38	PLA	0.250	191.01
S3_M1	SN38	TUM	0.250	26.15
S3_M2	IRN	PLA	0.250	3983.30
S3_M2	IRN	TUM	0.250	657.82
S3_M2	SN38	PLA	0.250	203.53
S3_M2	SN38	TUM	0.250	17.14
S3_M3	IRN	PLA	0.250	4.76
S3_M3	IRN	TUM	0.250	3.00
S3_M3	SN38	PLA	0.250	2.00
S3_M3	SN38	TUM	0.250	3.00
S3_M4	IRN	PLA	0.500	462.80
S3_M4	IRN	TUM	0.500	420.99
S3_M4	SN38	PLA	0.500	166.15
S3_M4	SN38	TUM	0.500	37.31
S3_M5	IRN	PLA	0.500	493.38
S3_M5	IRN	TUM	0.500	493.03
S3_M5	SN38	PLA	0.500	150.17
S3_M5	SN38	TUM	0.500	44.07
S3_M6	IRN	PLA	0.500	604.76
S3_M6	IRN	TUM	0.500	155.25
S3_M6	SN38	PLA	0.500	70.77
S3_M6	SN38	TUM	0.500	41.32
S3_M7	IRN	PLA	1.00	1.49

Std IRN IP (IRN, SN-38) Plasma and ES-8 Tumor PK

Subject	Analyte	Group	Time (hr)	Concentration (ug/L)
S3_M7	IRN	TUM	1.00	3.00
S3_M7	SN38	PLA	1.00	0.50
S3_M7	SN38	TUM	1.00	3.00
S3_M8	IRN	PLA	1.00	1007.10
S3_M8	IRN	TUM	1.00	181.45
S3_M8	SN38	PLA	1.00	64.03
S3_M8	SN38	TUM	1.00	31.86
S3_M9	IRN	PLA	1.00	312.45
S3_M9	IRN	TUM	1.00	163.63
S3_M9	SN38	PLA	1.00	30.83
S3_M9	SN38	TUM	1.00	24.35
S3_M10	IRN	PLA	2.00	85.24
S3_M10	IRN	TUM	2.00	146.94
S3_M10	SN38	PLA	2.00	12.71
S3_M10	SN38	TUM	2.00	43.49
S3_M11	IRN	PLA	2.00	145.69
S3_M11	IRN	TUM	2.00	73.64
S3_M11	SN38	PLA	2.00	19.94
S3_M11	SN38	TUM	2.00	25.44
S3_M12	IRN	PLA	2.00	93.58
S3_M12	IRN	TUM	2.00	178.90
S3_M12	SN38	PLA	2.00	12.27
S3_M12	SN38	TUM	2.00	37.02
S3_M13	IRN	PLA	4.00	100.02
S3_M13	IRN	TUM	4.00	47.54
S3_M13	SN38	PLA	4.00	24.01

Std IRN IP (IRN, SN-38) Plasma and ES-8 Tumor PK

Subject	Analyte	Group	Time (hr)	Concentration (ug/L)
S3_M13	SN38	TUM	4.00	35.55
S3_M14	IRN	PLA	4.00	18.14
S3_M14	IRN	TUM	4.00	64.83
S3_M14	SN38	PLA	4.00	2.86
S3_M14	SN38	TUM	4.00	12.92
S3_M15	IRN	PLA	4.00	44.75
S3_M15	IRN	TUM	4.00	51.40
S3_M15	SN38	PLA	4.00	15.65
S3_M15	SN38	TUM	4.00	27.44
S5_M1	IRN	PLA	0.500	239.75
S5_M1	IRN	PLA	6.00	16.68
S5_M1	IRN	TUM	6.00	44.93
S5_M1	SN38	PLA	0.500	93.33
S5_M1	SN38	PLA	6.00	5.08
S5_M1	SN38	TUM	6.00	17.29
S5_M2	IRN	PLA	0.500	311.49
S5_M2	IRN	PLA	6.00	30.38
S5_M2	IRN	TUM	6.00	92.36
S5_M2	SN38	PLA	0.500	112.52
S5_M2	SN38	PLA	6.00	4.82
S5_M2	SN38	TUM	6.00	15.08
S5_M3	IRN	PLA	0.500	266.90
S5_M3	IRN	PLA	6.00	16.93
S5_M3	IRN	TUM	6.00	45.76
S5_M3	SN38	PLA	0.500	112.27
S5_M3	SN38	PLA	6.00	8.07

Subject	Analyte	Group	Time (hr)	Concentration (ug/L)
S5_M3	SN38	TUM	6.00	13.50
S5_M4	IRN	PLA	0.500	341.36
S5_M4	IRN	PLA	8.00	64.07
S5_M4	IRN	TUM	8.00	21.60
S5_M4	SN38	PLA	0.500	111.77
S5_M4	SN38	PLA	8.00	17.00
S5_M4	SN38	TUM	8.00	17.93
S5_M5	IRN	PLA	0.500	332.24
S5_M5	IRN	PLA	8.00	24.14
S5_M5	IRN	TUM	8.00	35.37
S5_M5	SN38	PLA	0.500	111.33
S5_M5	SN38	PLA	8.00	11.06
S5_M5	SN38	TUM	8.00	15.67
S5_M6	IRN	PLA	0.500	192.31
S5_M6	IRN	PLA	8.00	62.91
S5_M6	IRN	TUM	8.00	36.52
S5_M6	SN38	PLA	0.500	146.17
S5_M6	SN38	PLA	8.00	11.27
S5_M6	SN38	TUM	8.00	21.10

5.0 ATTACHED FILES

Attached File 5.1 Std IRN Study DCFs.zip – *Digital collection forms for nal-IRI in vivo PK studies*
Attached File 5.2 Std IRN IP (IRN, SN-38) Plasma and ES-8 Tumor PK TLFs.docx – *Report TLFs as a Word document for manipulation, plotting, and further presentation*