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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 and St. Jude Children's Research Hospital, 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, 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.

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PRECLINICAL PHARMACOKINETIC REPORT

Developmental Biology and Solid Tumor Program (DBSTP)

P-PKSR Study 103490-1063454

STUDY TITLE:

INITIAL PLASMA PHARMACOKINETICS OF VX-970 IN FEMALE CD1 NU/NU MICE AFTER A SINGLE ORAL DOSE

SHORT TITLE:	**VX-970 Initial PK**	
TEST ARTICLE:	VX-970	
SECTION:	Nonclinical Pharmacokinetics (Non-GLP)	
PRINCIPAL INVESTIGATOR(S)	Stewart, Elizabeth	
SJCRH SRM2 O/R:	103490-1063454	Preclinical Pharmacokinetic Shared Resource
REFERENCE STUDY NUMBERS:	NA	NA
IN VIVO SCIENTIST(S)	Stewart, Elizabeth Ocarz, Monica Gordon, Brittney	
BIOANALYTICAL SCIENTIST:	Caufield, William	
REPORT AUTHOR(S):	Freeman, Burgess Caufield, William Wang, Lindsey Stewart, Elizabeth	
REPORT FORMAT:	Nonregulated R	
REPORT STATUS:	FINAL	
DATE:	2018-06-04	

FOR P-PKSR APPROVED USE AND DISTRIBUTION

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Signatures (Nonregulated Report)

Approved By:

Burgess B. Freeman III, PharmD
Director
Preclinical Pharmacokinetic Shared Resource
St. Jude Children's Research Hospital

Date

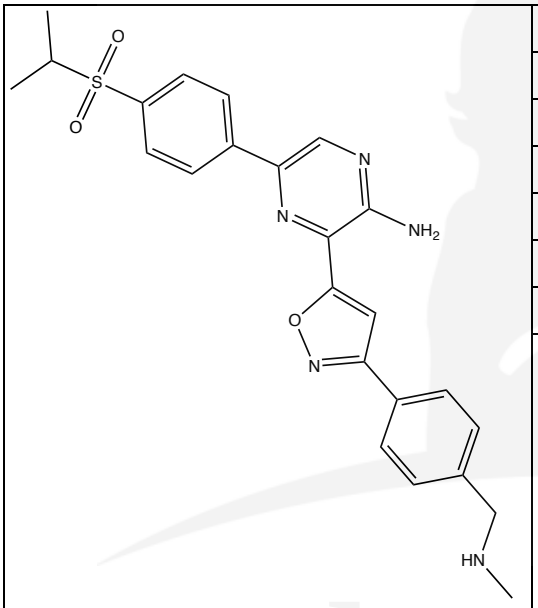
Table of Contents

1.0 INTRODUCTION

The ATR inhibitor VX-970 (VE-822, Vertex Pharmaceuticals to Merck KGaA, Darmstadt, Germany) is being investigated by the DBSTP (PI Dr. Elizabeth Stewart) for single agent and combination therapies in several pediatric solid tumors, including neuroblastoma (NBL). The goal of this initial study was to determine the plasma PK characteristics of VX-970 in a 10% TPGS / 90% UP Water formulation after a single 60 mg/kg dose in mice.

2.0 MATERIALS AND METHODS

2.1 Test Articles



Compound	VX-970
Molecular Weight	463.55
SJ REG #	SJ000855450-4
CAS #	1232416-25-9
Vendor	LC Laboratories
Lot #	L13289B001
Exp. Date	NA
Purity	95.14% - 100% (CBT-HTAC QC)

* QC documentation is included in Attached File 6.1.

2.2 Formulations

Formulation: VX-970 in 10% TPGS / 90% UP water, 6 mg/mL free base equivalent final nominal concentrations, 10 mL/kg gavage volume, 60 mg/kg dosage.

Item	Vendor	Lot #	Exp. Date
D-α-Tocopherol polyethylene glycol 1000 succinate (TPGS)	Sigma	BCBT2435	2018-03
DDI / UP H_2O	Millipore	NA	NA

The VX-970 formulation was prepared by Lindsey Wang on 2017-03-20 using a standardized procedure (see **Appendix 7.1**).Briefly, 12 mg of VX-970 was placed into a 2 mL volumetric flask, 0.2 mL of 40 ˚C pre-heated TPGS was added with agitation and vortexing, the total volume was brought up to 2 mL with 40 ˚C pre-heated UP water. The flask was indirectly sonicated in a water bath for 30 minutes. The dosing suspension was transferred into a dosing vial, and kept agitating on a magnetic stirrer using a micro stir bar at ambient temperature until use (see **§ 2.4 Dosing**).

2.3 Animals

Six (6) female CD1 nu/nu mice (Jax Laboratories), aged 12-16 weeks and weighing from 21.3-25.3 g, were used. Mice were permitted standard chow and purified water *ad libitium* during the study, and were housed under SJCRH IACUC-approved animal husbandry conditions.

2.4 Dosing

Animals were dosed with 60 mg/kg VX-970 free base equivalents (6.0 mg/mL in final formulation) via a 10 mL/kg oral gavage using a 20 gauge flexible plastic feeding tube (Instech FTP-20-38) attached to a 1 mL syringe once. Individual dosages were determined based upon the total body weight of each animal recorded on the day of dosing. The calculated volume gavaged in mL was rounded to the nearest hundredth decimal place. Animals were dosed starting on 2017-03-20T15:45-16:00 and ending on 2017 -03-22T08:15:00-08:25.

2.5 Plasma Sample Collection

A batch sampling study design was used, whereby each animal provided four (4) non-terminal blood samples by retro-orbital bleed and one terminal blood sample via cardiac puncture upon sacrifice with an IACUC-approved technique. **Table 2.1** below lists the scheduled sampling schema. No individual animals were sampled outside the acceptable window for a nominal scheduled time point, i.e. ± 16.7% of the nominal time relative to dosage. For more information, see **Appendix 7.1. and 7.2.**

Table 2.1 Sample Collection Schedule

Time after dose (hr)	0.167	0.25	0.5*	1	2	4	8	16	24
Animal IDs: Group 1		M1 M2 M3	M1 M2 M3	M1 M2 M3				M1 M2 M3	M1 M2 M3
Animal IDs: Group 2	M4 M5 M6				M4 M5 M6	M4 M5 M6	M4 M5 M6		M4 M5 M6

* Sample time deviation. 30 minute time point was actually 40 minutes (0.67 hr)

At each survival sampling time point, the mouse was anesthetized with isoflurane as per IACUC approved protocol. Then ~50 µL of whole blood was collected from the retro-orbital plexus using a Minivette capillary device (Sarstedt, cat no. 17.2113.150, lot 5281601) pre-coated with K3EDTA and transferred into a plastic microcentrifuge tube (1.5 mL, Fisher cat # 05-408-129 or equivalent). For terminal samples, mice were anesthetized with 0.6 mL of Avertin (tribromoethanol, 12.5 mg/mL) by intraperitoneal injection, and 0.5 – 1 mL of whole blood was collected from closed cardiac puncture using a 25 gauge needle attached to a 1 mL syringe. Cardiac blood was then transferred into a Microvette K3EDTA microcentrifuge tube (Sarstedt, cat no. 20.1341.102, lot 5750411M), and gently vortexed. All blood samples were immediately centrifuged at ambient temperature for 2 min at 10000 rpm to generate plasma. Each plasma supernatant was transferred into an appropriately labeled microcentrifuge tube, placed on dry ice for remainder study, and transferred to -80 ºC until analysis.

2.6 Bioanalytical Summary

Matrix calibrators and quality controls were spiked with analyte from stock solutions prepared in acetonitrile using VX-970 (MedChem Express, Lot 12295, Purity 99%). Matrix samples, 25 µL each, were protein precipitated with 100 µL of 100 ng/mL VE821 (Cayman Chemical Co., Lot 0475197-11, Purity

≥98%) in acetonitrile as an internal standard. A 2 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 Waters XBridge BEH C18 (2.5 µm, 75 mm x 2.1 mm) column maintained at 50 °C with gradient elution at a flow rate of 0.40 mL/min. The binary mobile phase consisted of water-acetonitrile-formic acid (90:10:0.1 v/v) in reservoir A and acetonitrile-formic acid (100:0.1 v/v) in reservoir B. The initial mobile phase was maintained at 40% B for 0.5 minutes and was followed by a linear increase to 100% B at 1.4 minutes. The column was then rinsed for two minutes at 100% B and then equilibrated at the initial conditions for two minutes for a total run time of 5.4 minutes. Under these conditions, the analyte and IS eluted at 0.80 and 1.49 minutes, respectively.

Analyte and IS were detected with tandem mass spectrometry using a SCIEX API 5500 Q-TRAP in the positive ESI mode and the following mass transitions were monitored: VX-970 464.18 -> 432.70, VE821 369.42 -> 169.100.

The method qualification and bioanalytical runs all passed P-PKSR's 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 ≥ 0.9975. 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. The intra-run precision and accuracy was < 7.93% CV and 97.3% to 113%, respectively.

For more information, please refer the bioanalytical method qualification and run report archived by the P-PKSR. NOTE: Bioanalytical validation, qualification, and/or run reports are marked "COMPANY CONFIDENTIAL," and are not for distribution outside SJCRH as per P-PKSR policy.

2.7 Data and Statistical Analyses

The bioanalytical concentration results were processed by run and matrix using Analyst 1.6.2 software (SCIEX, Framingham, MA) and outputted as standardized tab delimited text (.txt) files. These .txt files were subsequently processed using R software [1]. The concentrations for analytes were grouped by compound, matrix, day, and nominal sample time, and arithmetic means (Mean) and standard deviations (SD) were generated. If at any time point, ≥ 2/3rds of the results were below the assay LLOQ (BLOQ), then the entire time point was treated as missing. Otherwise, any data BLOQ were replaced with a value of ½ LLOQ, and the concentration Mean and SD values calculated.

2.8 Pharmacokinetic (PK) Analyses

The VX-970 concentration-time (Ct) data was subjected to noncompartmental pharmacokinetic analysis (NCA) using Phoenix WinNonlin 6.4 (Certara USA, Inc., Princeton, NJ). The extravascular model (Model 202) 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 at least 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) + Clast (predicted)/Ke. Other parameters estimated included 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).

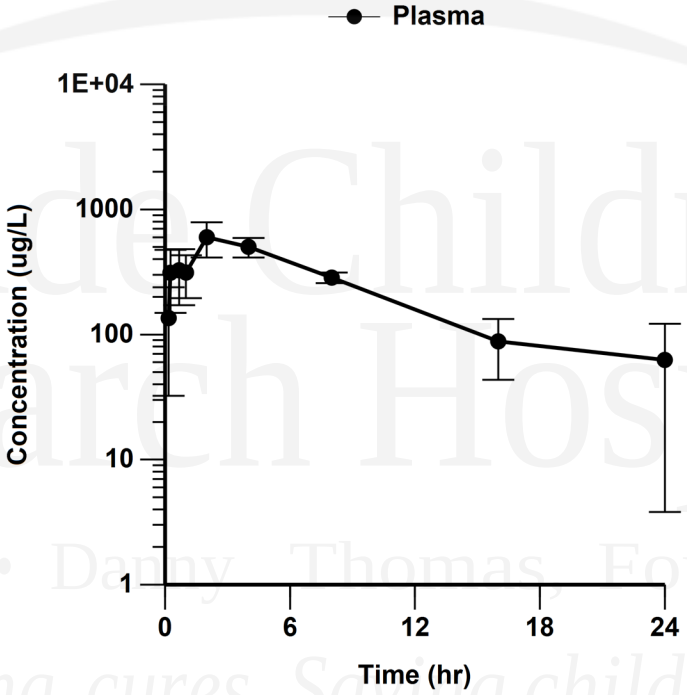
3.0 RESULTS AND DISCUSSION

VX-970 showed relatively slow absorption, with the Cmax observed at 2 hours. The inter-animal variability ranged from 9.8% to 93.9%, with comparably low %CV at 4 and 8 hrs, 17.7% and 9.8% respectively; most variability occurred at 24 hr. **Figure 3.1** presents the mean (SD) Ct profiles, while the corresponding NCA PK parameter estimates are reported in **Table 3.1**.

Table 3.1 Noncompartmental PK Parameter Estimates

		Matrix
		Plasma
Parameter	**Units**	**Estimate**
Cmax	ug/L	600
Tmax	hr	2.00
AUClast	hr*ug/L	5300
AUCinf	hr*ug/L	5780
Kel	1/hr	0.107
T1/2	hr	6.47
CL/F	L/hr/kg	10.4
Vz/F	L/kg	96.8
Clast	ug/L	62.6
Tlast	hr	24.0

Figure 3.1 Mean (SD) Ct Profiles



No mouse plasma PK data for VX-970 are available in the literature to date, so comparison of our results to historical values is not possible. For our mouse PK study, we selected the most commonly reported oral mouse dose of VX-970 of 60 mg/kg, given for brief intermittent periods in combinations with DNA

damaging agents [2,3]. The tolerability of continuous VX-970 in mice is unknown, particularly at the 60 mg/kg level. The human clinical plasma PK of VX-970 after intravenous administration in a Phase 1 study has been reported in abstract form [4]. Increases in Cmax and AUC were approximately linear with dose with a terminal half-life of ~ 16 hr. VX-970 demonstrating a recommended Phase 2 dose of 210 mg/m2 (D2,9) along with 1000 mg/m2 (D1,8) of gemcitabine. By graphical analyses, the total human plasma AUC for VX-970 was estimated at 6200 hr-ug/L at 210 mg/m2. As plasma protein binding information for VX-970 is not available for mice and humans, a clinically equivalent dose (CED) for mice is herein derived using total plasma AUCs, and is estimated at 60 mg/kg orally. This provides an AUC value in mice within 10% of that observed in the aforementioned Phase 1 study.

4.0 CONCLUSIONS

- VX-970 displayed moderately slow absorption and acceptable plasma exposure after oral administration of 60 mg/kg in 10% TPGS / 90% UP H2O in female non-tumor bearing CD1 nu mice.
- VX-970 demonstrated a plasma Cmax of 600 ug/L, AUCinf of 5780 hr-ug/L, and a terminal T1/2 of 6.47 hr in our mice.
- There are no previously reported plasma PK data for VX-970 in the literature, and very little published PK for humans available.
- A reasonable CED for VX-970 is 60 mg/kg, based upon total plasma AUCs.

5.0 REFERENCES

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6.0 ATTACHED FILES

Attached File 6.1. A13289_VE822_20170323_HTAC_completed.zip

7.0 APPENDICES

Appendix 7.1 Murine Pharmacokinetics (PK) of VX-970.docx

Date: TBD

Title: Initial plasma PK of oral VX-970

Animals: Female CD1 nu mice. Aged approx. 12 weeks at study execution.

Dosages: 60 mg/kg VX-970 by oral gavage, single dose

Formulation: VX-970 free base equivalents in 10% Vit E TPGS / 90% UP Water

Design: A total of 6 mice will be dosed, with 3 mice providing blood at each time point. Five (5) blood samples will be collected from each mouse after dosing. Survival sampling (S) will be performed by retro-orbital, facial vein, saphenous vein, or tail vein bleed at the indicated time points. The final sample for each mouse will be terminal by cardiac puncture (T).

Group #s	Dose Level	Mouse #s	Mouse Ear Tag IDs	Sample Times (hr)
1	60 mg/kg	1-3		S: 0.25, 0.5, 1, 16 T: 24
2	60 mg/kg	4-6		S: 0.167, 2, 4, 8 T: 24

Summary:

Materials:

- At least 24 Minivette POCT K3EDTA capillary devices (50 uL, Sarstedt 17.2113.150) for survival blood collections.
- 6 appropriately labeled Microvette 500 K3EDTA microcentrifuge screw top tubes (500 uL, Sarstedt 20.1341.100) for terminal cardiac blood collection and spin down.
- One set of 24 standard 0.5 mL screw-top microcentrifuge tubes (Fisher Cat# 02-681-333 or equivalent), pre-labeled with VX-970 IniPK, mouse #, and nominal time point in hrs for survival plasma collection.
- One set of 6 standard 2.0 mL screw-top microcentrifuge tubes (Fisher Cat# 02-681-343 or equivalent), pre-labeled with VX-970 IniPK, mouse #, and nominal time point in hrs for terminal plasma collection.
- Vit E TPGS (MP > 36 °C), ultra-pure water, PBS for flushing mice
- ~15 mg of VX-970 free base equivalents
- Mouse gavage needle and 1 mL syringes for PO administration
- 25 gauge needles and TB/insulin syringes for cardiac punctures
- Centrifuge (10000g) w/ microcentrifuge rotor (4°C preferred, but room temp. will suffice)
- Container of wet ice
- Styrofoam cooler with labeled cardboard vial box and **dry** ice

Procedure:

1. The day before the study, sort mice into groups, 3 mice per cage with 2 cages and perform weighing. Tattoo tails for identification, or refer to mouse ear tag numbers. Label cages with

group number, mouse numbers, and nominal time points. Each tattooed stripe represents the number of mouse in the cage's sequence. For example, the mouse with 1 stripe in Cage/Group 2 would be mouse #4 and the mouse with 2 stripes would be mouse #5, and so forth. Weigh each mouse, record weight in grams on the Study Worksheet, and calculate planned doses in mL.

2. The day before or the morning of the study, formulate VX-970 in vehicle as a solution for oral gavage (6 mg/mL, 0.25 mL for a 25 g mouse = 60 mg/kg)
    a. Add 12 mg of VX-970 free base equivalents to a tared 2 mL volumetric flask
    b. Gently heat TPGS to 40°C to melt the waxy substance into a thick liquid
    c. To the flask, add 0.2 mL of the warmed TPGS and agitate with pipette to wet the powder.
    d. Slowly QS with ambient temperature UP water, with agitation, to 2 mL total under gentle heat
    e. Vortex and/or sonicate for up to 30 min to ensure a homogenous solution. Immediately prior to administration, vortex and check for visual homogeneity.
        i. Gentle heating might be required to get it to re-dissolve in formulation.
    f. Keep at ambient temperature or higher; do not refrigerate or freeze!

3. Execute in vivo study according to the Study Worksheet
    a. NOTE: All actual times for dosing and samples should be referenced to the same study clock.
    b. Dose mice by PO gavage; record the actual dose volume administered in mL and the actual times of administration.
    c. At each time point, collect the blood sample by the indicated means and record the actual sample time (from the start of the collection), and make notes of any issues.
        i. S: Survival bleed – Anesthetize the mouse per IACUC protocol. Using a Microvette POCT, proceed to collect 50 uL of whole blood from the designated sampling site with the device. Gently agitate to mix the anticoagulant. Place blood into appropriate pre-labeled tube. All samples should be processed to plasma ASAP, but if necessary, put on wet ice until centrifugation.
        ii. T: Terminal cardiac puncture – Anesthetize the mouse per IACUC protocol. Proceed to collect 500 uL of whole blood from aorta. Place blood into appropriate pre-labeled Microvette K3EDTA tube and gently agitate. All samples should be processed to plasma ASAP, but if necessary, put on wet ice until centrifugation.
    d. Centrifuge the whole blood samples at 10000g for 2 min. to generate plasma.
    e. Remove plasma supernatant, place in appropriate pre-labeled tube from Set #2; place in vial box in cooler on dry ice and transfer to -80°C as soon as possible.
    f. Please submit remaining formulation in the original dosing vial stored at ambient temperature for stability assessment.

Appendix 7.2 VX-970 PK non tumor raw.PDF

VX-970 PK Study: 60 mg/kg oral gavage, [6mg/ml]

Mouse #	Mouse weight (g)	Mouse Dose (ml)	Dose Time (3/20/17)	Bleed Time 15 min (3/20/17)	Bleed Time 30 min* (3/20/17)	Bleed Time 1 hour (3/20/17)	Bleed Time 16 hr (3/21/17)	Harvest Time 24 hr (3/21/17)
1	21.9	0.22	3:45p ✓	4:00p ✓	4:25p ✓ (40 min)	4:45p ✓	7:45a ✓	3:45p ✓
2	22.7	0.23	3:50p ✓	4:05p ✓	4:30p ✓ (40 min)	4:50p ✓	7:50a ✓	3:50p ✓
3	22	0.22	3:55p ✓	4:10p ✓	4:35p ✓ (40 min)	4:55p ✓	7:55a ✓	3:55p ✓

*Tube states 30 min timepoint, actual time point is 40 min

Mouse #	Mouse weight (g)	Mouse Dose (ml)	Dose Time (3/21/17)	Bleed Time 10 min (3/21/17)	Bleed Time 2 hr (3/21/17)	Bleed Time 4 hour (3/21/17)	Bleed Time 8 hr (3/21/17)	Harvest Time 24 hr (3/22/17)
4	25.3	0.25	8:15a ✓	8:25a ✓	10:15a ✓	12:15p ✓	4:15p ✓	8:15a ✓
5	23.6	0.24	8:20a ✓	8:30a ✓	10:20a ✓	12:20p ✓	4:20p ✓	8:20a ✓
6	21.3	0.21	8:25a ✓	8:35a ✓	10:25a ✓	12:25p ✓	4:25p ✓	8:25a ✓

3/20/17 – 3/22/17
Beth Stewart
Brittney Gordon
Monica Ocarz
Kaley Blankenship
Victoria Honnell

** Drug formulated by Lindsey Wang on 3/20/17, stored on spinner, room temp.

CD-1 nude females

Appendix 7.3 Listing of Ct Data

Component_Name	Matrix	Subject	Time (hr)	Concentration (ug/L)
VX-970	Plasma	M1	0.25	127.15
VX-970	Plasma	M1	0.67	164.42
VX-970	Plasma	M1	1.00	177.98
VX-970	Plasma	M1	16.00	40.04
VX-970	Plasma	M1	24.00	8.03
VX-970	Plasma	M2	0.25	435.58
VX-970	Plasma	M2	0.67	342.56
VX-970	Plasma	M2	1.00	391.85
VX-970	Plasma	M2	16.00	128.34
VX-970	Plasma	M2	24.00	47.36
VX-970	Plasma	M3	0.25	373.16
VX-970	Plasma	M3	0.67	472.68
VX-970	Plasma	M3	1.00	369.05
VX-970	Plasma	M3	16.00	96.14
VX-970	Plasma	M3	24.00	24.81
VX-970	Plasma	M4	0.17	254.44
VX-970	Plasma	M4	2.00	761.09
VX-970	Plasma	M4	4.00	566.69
VX-970	Plasma	M4	8.00	291.23
VX-970	Plasma	M4	24.00	174.71
VX-970	Plasma	M5	0.17	76.72
VX-970	Plasma	M5	2.00	393.61
VX-970	Plasma	M5	4.00	400.93
VX-970	Plasma	M5	8.00	254.94
VX-970	Plasma	M5	24.00	53.75
VX-970	Plasma	M6	0.17	75.16
VX-970	Plasma	M6	2.00	645.84
VX-970	Plasma	M6	4.00	540.66
VX-970	Plasma	M6	8.00	309.60
VX-970	Plasma	M6	24.00	67.20

Appendix 7.4 Extended Summary Statistics of Ct Data

		Matrix
		Plasma
Time (hr)		Concentration (ug/L)
0.167	N	3
	Mean	135.437
	SD	103.063
	Min	75.16
	Median	76.72
	Max	254.44
	CV%	76.1
	Geometric Mean	113.625
	CV% Geometric Mean	79.26
0.250	N	3
	Mean	311.963
	SD	163.068
	Min	127.15
	Median	373.16
	Max	435.58
	CV%	52.3
	Geometric Mean	274.427
	CV% Geometric Mean	75.37
0.670	N	3
	Mean	326.553
	SD	154.752
	Min	164.42
	Median	342.56
	Max	472.68
	CV%	47.4
	Geometric Mean	298.598
	CV% Geometric Mean	58.34
1.00	N	3
	Mean	312.960
	SD	117.451
	Min	177.98
	Median	369.05

VX-970 Initial PK

		Matrix
		Plasma
Time (hr)		Concentration (ug/L)
	Max	391.85
	CV%	37.5
	Geometric Mean	295.251
	CV% Geometric Mean	46.15
2.00	N	3
	Mean	600.180
	SD	187.947
	Min	393.61
	Median	645.84
	Max	761.09
	CV%	31.3
	Geometric Mean	578.374
	CV% Geometric Mean	35.36
4.00	N	3
	Mean	502.760
	SD	89.143
	Min	400.93
	Median	540.66
	Max	566.69
	CV%	17.7
	Geometric Mean	497.103
	CV% Geometric Mean	18.93
8.00	N	3
	Mean	285.257
	SD	27.815
	Min	254.94
	Median	291.23
	Max	309.60
	CV%	9.8
	Geometric Mean	284.332
	CV% Geometric Mean	9.96
16.0	N	3
	Mean	88.171
	SD	44.688

VX-970 Initial PK

		Matrix
		Plasma
Time (hr)		Concentration (ug/L)
	Min	40.04
	Median	96.14
	Max	128.34
	CV%	50.7
	Geometric Mean	79.050
	CV% Geometric Mean	66.70
24.0	N	6
	Mean	62.643
	SD	58.832
	Min	8.03
	Median	50.56
	Max	174.71
	CV%	93.9
	Geometric Mean	42.572
	CV% Geometric Mean	138.23