PRECLINICAL PHARMACOKINETIC REPORT

Developmental Biology and Solid Tumor Program (DBSTP)

P-PKSR Study 109060-1119338

STUDY TITLE:

SCREENING PLASMA, TUMOR, AND BRAIN PHARMACOKINETICS OF BINIMETINIB IN FEMALE CD1 NU/NU MICE BEARING MAST39 RHB ORTHOTOPIC XENOGRAFTS AFTER A SINGLE ORAL DOSE

SHORT TITLE:	**Binimetinib Screening PK RHB**
TEST ARTICLES:	Binimetinib
SECTION:	Nonclinical Pharmacokinetics (Non-GLP)
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SJCRH SRM2 O/R:	109060-1119338 Preclinical Pharmacokinetic Shared Resource
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REPORT FORMAT	Nonregulated Report
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DATE:	2018-06-04

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 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, 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.

Signatures (Nonregulated Report)

Approved By:

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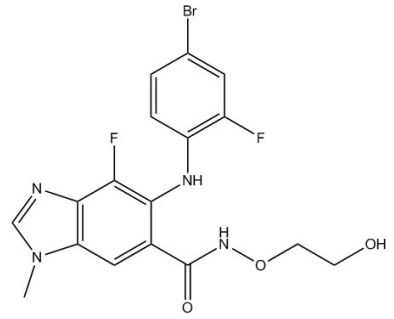
1.0 INTRODUCTION

The MEK inhibitor binimetinib is being investigated by the DBSTP (PI Dr. Elizabeth Stewart) for single agent and combination therapies in several pediatric solid tumors, including rhabdomyosarcoma (RHB). The goal of this study is to determine the plasma, tumor and brain PK characteristics of binimetinib after a single oral dose in mice.

2.0 MATERIALS AND METHODS

2.1 Test Articles



Compound	Binimetinib
Molecular Weight	441.23
SJ REG #	SJ000826811-5
CAS #	606143-89-9
Vendor	ADOOQ
Lot #	bnm-101
Exp. Date	NA
Purity	100% (CBT-HTAC QC) >98% (Vendor)

2.2 Formulations

Formulation: Binimetinib in 1% carboxymethylcellulose sodium (CMC Na, medium viscosity) / 0.5% Tween 80, 10 mL/kg gavage volume, 5 mg/kg dosage.

Item	Vendor	Lot #	Exp. Date
Carboxymethylcellulose sodium salt (medium viscosity)	Sigma	SLBN8656V	2020-07
Tween 80	Fisher	111721	2016-05
DDI / UP H_2O	Millipore	NA	NA

The binimetinib formulation was prepared by William Caufield on 2017-05-16 using a standardized procedure (see **Appendix 7.1**). Briefly, 2.5 mg of binimetinib was placed into a 5 mL volumetric flask followed by 1% carboxymethylcellulose sodium/ 0.5% Tween 80 up to the QS line. The flask was vortexed and then placed into an ultrasonic water bath for 30 minutes. The dosing suspension was visually checked for homogeneity (see **§ 2.4 Dosing**). NOTE: Some formulating materials were beyond the re-test / expiration dates; however, the probability of this deviation affecting the study findings is minimal, in the opinion of the P-PKSR scientists.

2.3 Animals

Fifteen (15) female CD1 nu/nu mice (Jax Laboratories), aged 12-16 weeks and weighing approximately 25 grams each, bearing MAST39 RHB xenograft tumors in the quadriceps area 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 once with 5 mg/kg binimetinib free base equivalents (0.5 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. Individual dosages were determined based upon the total body weight of each animal recorded on the day of dosing. The calculated gavage volume in mL was rounded to the nearest hundredth decimal place. Animals were dosed starting at Day 1 on 2017-05-16T11:49:00-13:28:00 and ending at Day 2 on 2017-05-17T08:00:00-08:50:00. For more information, see **Appendix 7.1**.

After dosing, the remaining formulation was stored at 4 ºC protected from light and submitted to the P-PKSR for assessment of compound concentration using the plasma bioanalytical method. The volume of the remaining formulation was not large enough to permit sampling at multiple strata. Briefly, after coming to ambient temperature and vortexing, triplicate 50 µL aliquots were taken from the middle of the dosing formulation vessel and transferred to a 5 mL volumetric flask. Each flask was filled to QS with acetonitrile, with this being further diluted with a 20-fold volume of compound-free mouse plasma.

2.5 Plasma and Tissue Sample Collection

A serial sacrifice study design was used, whereby each animal provided one sample at one time point upon termination 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**.

Table 2.1 Sample Collection Schedule

Time after dose (hr)	0.167	2	4	8	12
Animal IDs	M1	M4	M7	M10	M13
	M2	M5	M8	M11	M14
	M3	M6	M9	M12	M15
* Sample time deviation. None reported, 100% sampled at nominal scheduled times.					

At each sampling time point, the mouse was anesthetized with 0.6 mL of Avertin (tribromoethanol, 12.5 mg/mL) by intraperitoneal injection. Then 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.

After blood collection from each animal, the right ventricle was punctured and the animal was perfused with 10 mL of calcium- and magnesium-free PBS through the left ventricle. The orthotopic xenograft was excised, rinsed with PBS, weighed, and divided into aliquots. The portion submitted for compound bioanalysis was transferred into an appropriately labeled microcentrifuge tube or Falcon tube, placed on dry ice for remainder of 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 Binimetinib (ADOOQ, SJ000826811-5, Purity 100%). Matrix samples, 25 µL each, were protein precipitated with 100 µL of 100 ng/mL selumetinib sulfate (ABMOL, SJ000556682-9, Purity 100%) 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 Phenomenex Kinetex C18 (2.6 µm, 50 mm x 2.1 mm) column maintained at ambient temperature with gradient elution at a flow rate of 0.50 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 10% B for 0.5 minutes and was followed by a linear increase to 100% B at 2.75 minutes. The column was then rinsed for 1.25 minutes at 100% B and then equilibrated at the initial conditions for two minutes for a total run time of six minutes. Under these conditions, the analyte and IS eluted at 1.59 and 1.70 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: binimetinib 441.04 -> 165.10, selumetinib 457.00 -> 394.90.

The 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 ≥ 0.9999. 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 < 5.29% CV and 95.3% to 101%, 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 which were subsequently processed using R software [1]. The concentrations for analytes were grouped by compound, matrix (plasma, brain or tumor), 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 binimetinib arithmetic mean concentration-time (Ct) data for each matrix were 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). To evaluate the precision of the AUCinf estimate, the percent AUC extrapolated to infinity (AUC %Extrap) was also estimated. The apparent partition coefficient of compound from the plasma to tumor (Kp,tumor) was estimated as the ratio of the AUCinf, tumor to AUCinf plasma when available.

3.0 RESULTS AND DISCUSSION

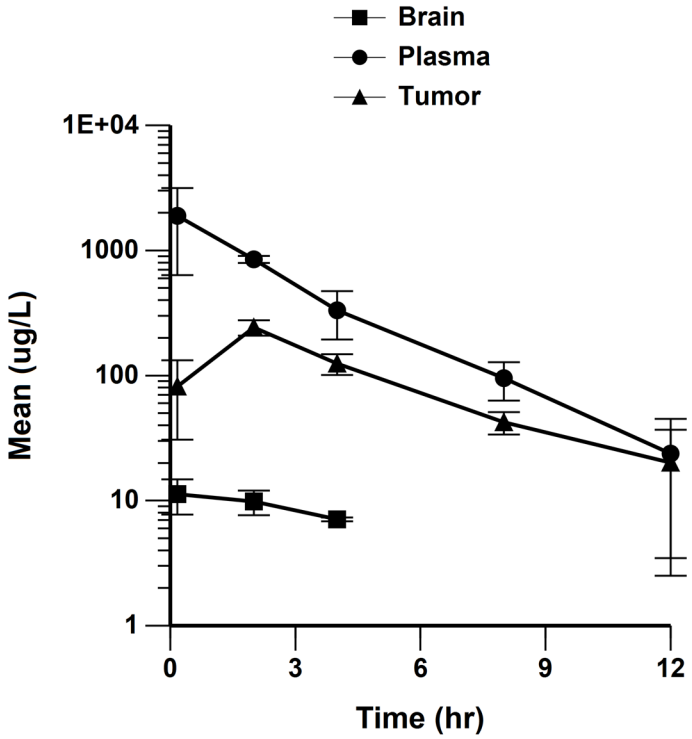
Binimetinib displayed moderate within-study PK variability with concentration coefficients of variation (CV) ranging from 6.3% to 89.5% for plasma, 14.1% to 82.8% for tumor, and 3.6% to 31.3% for brain. Most of the variability was noted at the 12 hour time point. The binimetinib plasma PK appeared to slightly differ

from the previous study, with 34% lower Cmax and AUCinf, and a much shorter T1/2 compared to that observed previously (see RPT.104223-1070687). However, upon visual examination, much of the difference could be attributed to the different sampling scheme – with the last time point being 12 hours for current study vs. 24 hours for previous. The assessed binimetinib concentration in the remaining dosing suspension from the current study was 104.13% of the nominal expected concentration, while it was 98.73% in previous study. Slower distribution of binimetinib was observed in tumor compared to both plasma and brain in current study, Tmax,tumor at 2 hour, while both Tmax,plasma and Tmax,brain at 0.167 hr. A Kp,tumor of 0.249 was estimated. Low brain exposure was observed, with brain samples BLOQ after 4 hours, with a Kp,brain of 0.0207. The current findings do not change the previously recommended clinically relevant dose (CRD) of 3 mg/kg PO BID for mice. **Table 3.1** and **Figure 3.1** present the NCA PK parameter estimates and the Mean (SD) Ct profiles, respectively.

Table 3.1 Noncompartmental PK Parameter Estimates

		Matrix		
		Brain	**Plasma**	**Tumor**
Parameter	**Units**	**Estimate**		
Cmax	ug/L	11.3	1890	242
Tmax	hr	0.167	0.167	2.00
AUClast	hr*ug/L	37.0	4610	1080
AUCinf	hr*ug/L	97.0	4690	1170
AUC_%Extrap	%	61.8	1.57	7.15
Kel	1/hr	0.121	0.330	0.228
T1/2	hr	5.71	2.10	3.04
CL/F	L/hr/kg	51.6	1.07	4.29
Vz/F	L/kg	425	3.23	18.8
Clast	ug/L	7.08	23.8	20.1
Tlast	hr	4.00	12.0	12.0
Kp,tumor	-	-	-	0.249
Kp,brain	-	0.0207	-	-

Figure 3.1 Mean (SD) Ct Profiles



4.0 CONCLUSIONS

- The plasma PK of binimetinib was sufficiently similar to the plasma only study in nontumor bearing female CD1 nus.
- Distribution of binimetinib to the orthotopic RHB tumor was relatively slow (Tmax = 2hr), and the extent of distribution was low-to-moderate (Kp,tumor = 0.249).
- Brain penetration of binimetinib was low, with a Kp,brain ~ 0.02.
- The recommended CED for binimetinib remains 3 mg/kg PO BID in mice.

5.0 REFERENCES

1. R Core Team. R: A language and environment for statistical computing. [Internet]. Vienna, Austria: R Foundation for Statistical Computing; 2016. Available from: https://www.R-project.org/

6.0 ATTACHED / RELATED FILES

RPT.104223-1070687 Binimetinib Initial PK.pdf – Initial Plasma Pharmacokinetics of Binimetinib in Female CD1 nu/nu Mice after a Single Oral Dose.

7.0 APPENDICES

Appendix 7.1 Binimetinib Prelim PK.docx

Murine Pharmacokinetics (PK) of Binimetinib

Client Investigators: Dr. E. Stewart

Date: Week of May 15, 2017

Title: Preliminary plasma, RHB tumor, and brain PK of oral binimetinib

Animals: Female CD1 nu mice bearing MAST39 NB xenografts, Aged approx. 12 weeks at study execution.

Dosages: 5 mg/kg binimetinib by oral gavage, single dose

Formulation: Binimetinib free base equivalents in 1% carboxymethylcellulose sodium (CMC Na, medium viscosity) / 0.5% Tween 80

Design: A total of 15 mice will be dosed, each mouse will be sacrificed at the relative time point

Group	Mouse #s	Mouse Ear Tag IDs	Sample Times
1	1-3		0.167 hr
2	4-6		2 hr
3	7-9		4 hr
4	10-12		8 hr
5	13-15		12 hr

Time	0.167 hr	2 hr	4 hr	8 hr	12 hr
Groups	1	2	3	4	5
Mouse #s	1-3	4-6	7-9	10-12	13-15
Planned Sample Time	Day 1 8:10 AM	Day 1 10:00 AM	Day 1 2:00 PM	Day 2 8:00 AM	Day 2 8:00 AM

Summary:

Materials:

- For whole blood from cardiac puncture, a set of 15 Microvette 500 K3EDTA (Sarstedt 20.1341.100) 500 uL microcentrifuge tubes, pre-labeled with Binimetinib, group #, mouse #, and nominal time point in hrs.
- For plasma, a set of 15 screw-top microcentrifuge tubes, pre-labeled with Binimetinib, group #, mouse #, and nominal time point in hrs
- For RHB tumors, a set of 15 screw-top microcentrifuge tubes prelabled with Binimetinib, group #, mouse #, and nominal time point in hrs
  - Falcon style tubes are acceptable if tumor mass is anticipated to exceed the capacity of microcentrifuge tubes
- Carboxymethylcellulose sodium (CMC Na), Tween 80, ultra pure (UP) water
- ~5 mg of binimetinib 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 5 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

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Appendix 7.1 Binimetinib Prelim PK.docx (continued)

Murine Pharmacokinetics (PK) of Binimetinib

Client Investigators: Dr. E. Stewart

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. Prior to the study, formulate the 1% CMC Na / 0.5% Tween 80 solution vehicle
    a. Preparation Notes for CMC Na:
        i. The product is soluble in water (20 mg/mL). The key to dissolving CMC Na is to add the solid carefully to the water so that it is well dispersed (well-wetted).
        ii. Adding water to the dry solid produces a "clump" of solid that is very difficult to dissolve; the solid must be added to the water.
        iii. Adding the solid slowly in portions, with gentle vortexing and physical agitation, may be necessary.
        iv. Stir gently or shake intermittently; do not stir constantly with a magnetic stirring bar. High heat (>40 °C) is not needed, and may actually slow down the solubilization process.
    b. Preformulate the 1% CMC Na / 0.5% Tween 80 vehicle
        i. Slowly add 500 mg of CMC Na to ~35 mL or ambient temperature UP water, agitate gently and vortex until it appears mostly dissolved
        ii. Add 250 microliters (µL) of ambient temperature Tween 80, agitate gently and disperse briefly (watch for foaming)
        iii. QS to 50 mL with UP water, vortex or sonicate as necessary (with gentle heat if necessary, ~37 °C) to form a homogenous solution
        iv. Store at ambient temperature, caution on microbial stability (1-2wks max)

3. The day before or the morning of the study, formulate binimetinib in vehicle as a solution for oral gavage (0.5 mg/mL, 0.25 mL for a 25 g mouse = 5 mg/kg)
    a. In a 5 mL volumetric flask, to 2.5 mg of the binimetinib free base equivalents, slowly QS to volume using the 1% CMC Na / 0.5% Tween 80 vehicle at ambient temperature. Pipette and gently shake/stir the interim suspension of binimetinib.
    b. Vortex and/or sonicate for up to 30 min to ensure a homogenous suspension. Immediately prior to administration, vortex and check for visual homogeneity.

4. 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 terminal 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. T: Terminal cardiac puncture – Anesthetize the mouse per IACUC protocol. Proceed to collect 500 µL 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. Perfuse animal with PBS or equivalent to flush blood from vasculature.
    g. Extract RHB tumor and rinse with PBS, place in microcentrifuge tube or equivalent in cooler on dry ice and transfer to -80°C as soon as possible.
    h. Extract Brain and rinse with PBS, place in microcentrifuge tube or equivalent in cooler on dry ice and transfer to -80°C as soon as possible.
    i. Please submit remaining formulation in the original dosing vial stored at ambient temperature for stability assessment.

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Appendix 7.2 Binimetinibs_A7172.pdf

Binimetinib PK: 5/16 - 5/17/17 - Beth Stewart, Monica Ocarz, Brittney Gordon, Victoria Honnell, Kaley Blankenship

Animals: Female CD1 nu mice bearing MAST39 RMS xenografts. Aged approx. 12 weeks at study execution.

Dosages: 5 mg/kg binimetinib by oral gavage, single dose

Formulation: Binimetinib free base equivalents in 1% carboxymethylcellulose sodium (CMC Na, medium viscosity) / 0.5% Tween 80, made by Bill Caufield 5/16/17, stored room temp

Mouse #	Weight (g)	Dose (ml)	Time dose	Time Harvest	Time Point	Total Tumor (g)	Tumor wt in tube (g)
1	28.1	0.28	1:15	1:25	10 min	3.49	1.22
2	31.2	0.31	1:22	1:32	10 min	3.47	1.14
3	28.9	0.29	1:28	1:38	10 min	4.58	1.13
4	30.6	0.31	12:00	2:00	2hr	4.12	1.30
5	28.7	0.29	12:05	2:05	2hr	5.15	1.32
6	30.0	0.30	12:10	2:10	2hr	3.60	1.23
7	27.2	0.27	11:49	3:49	4hr	2.31	1.07
8	31.1	0.31	11:54	3:54	4hr	3.16	1.09
9	25.8	0.26	11:59	3:59	4hr	4.21	1.43
10	30.3	0.30	8:00	4:00	8hr	6.67	1.33
11	27.6	0.28	8:05	4:05	8hr	5.12	1.02
12	25.0	0.25	8:10	4:10	8hr	3.67	1.43
13	30.4	0.30	8:40	8:40	12hr	3.30	1.02
14	27.2	0.27	8:45	8:45	12hr	3.22	0.99
15	27.2	0.27	8:50	8:50	12hr	3.50	1.26

Mouse anesthetized with avertin. Blood removed by cardiac puncture and placed in 500 microliter EDTA microvette tube, spun, and plasma placed immediately on dry ice. Mouse perfused with 10 mL PBS-/-. Tumor from leg muscle removed, and brain removed and all placed on dry ice. Samples placed in the top of -80 freezer (Freeman) on 5/17/17

Appendix 7.3 Listing of Ct Data

Component_Name	Matrix	Subject	Time (hr)	Concentration (ug/L)
Binimetinib	Brain	M1	0.17	7.25
Binimetinib	Brain	M2	0.17	13.87
Binimetinib	Brain	M3	0.17	12.65
Binimetinib	Brain	M4	2.00	10.15
Binimetinib	Brain	M5	2.00	11.85
Binimetinib	Brain	M6	2.00	7.49
Binimetinib	Brain	M7	4.00	7.23
Binimetinib	Brain	M8	4.00	6.79
Binimetinib	Brain	M9	4.00	7.23
Binimetinib	Brain	M10	8.00	
Binimetinib	Brain	M11	8.00	
Binimetinib	Brain	M12	8.00	
Binimetinib	Brain	M13	12.00	
Binimetinib	Brain	M14	12.00	
Binimetinib	Brain	M15	12.00	
Binimetinib	Plasma	M1	0.17	703.77
Binimetinib	Plasma	M2	0.17	1765.80
Binimetinib	Plasma	M3	0.17	3210.00
Binimetinib	Plasma	M4	2.00	909.84
Binimetinib	Plasma	M5	2.00	834.80
Binimetinib	Plasma	M6	2.00	805.17
Binimetinib	Plasma	M7	4.00	196.04
Binimetinib	Plasma	M8	4.00	328.14
Binimetinib	Plasma	M9	4.00	473.53
Binimetinib	Plasma	M10	8.00	104.48
Binimetinib	Plasma	M11	8.00	59.46
Binimetinib	Plasma	M12	8.00	121.97
Binimetinib	Plasma	M13	12.00	48.21
Binimetinib	Plasma	M14	12.00	9.71
Binimetinib	Plasma	M15	12.00	13.35
Binimetinib	Tumor	M1	0.17	25.71
Binimetinib	Tumor	M2	0.17	94.05
Binimetinib	Tumor	M3	0.17	125.33
Binimetinib	Tumor	M4	2.00	219.57

Component_Name	Matrix	Subject	Time (hr)	Concentration (ug/L)
Binimetinib	Tumor	M5	2.00	281.83
Binimetinib	Tumor	M6	2.00	225.98
Binimetinib	Tumor	M7	4.00	99.51
Binimetinib	Tumor	M8	4.00	146.85
Binimetinib	Tumor	M9	4.00	127.38
Binimetinib	Tumor	M10	8.00	46.40
Binimetinib	Tumor	M11	8.00	32.45
Binimetinib	Tumor	M12	8.00	48.12
Binimetinib	Tumor	M13	12.00	39.31
Binimetinib	Tumor	M14	12.00	10.49
Binimetinib	Tumor	M15	12.00	10.50

Appendix 7.4 Extended Summary Statistics of Ct Data

		Matrix		
		Tumor	Plasma	Brain
Time (hr)		Concentration (ug/L)		
0.167	N	3	3	3
	Mean	81.697	1893.190	11.257
	SD	50.944	1257.962	3.523
	Min	25.71	703.77	7.25
	Median	94.05	1765.80	12.65
	Max	125.33	3210.00	13.87
	CV%	62.4	66.4	31.3
	Geometric Mean	67.172	1585.961	10.835
	CV% Geometric Mean	101.90	89.10	36.22
2.00	N	3	3	3
	Mean	242.460	849.937	9.829
	SD	34.246	53.952	2.200
	Min	219.57	805.17	7.49
	Median	225.98	834.80	10.15
	Max	281.83	909.84	11.85
	CV%	14.1	6.3	22.4
	Geometric Mean	240.922	848.812	9.657
	CV% Geometric Mean	13.72	6.28	23.69
4.00	N	3	3	3
	Mean	124.580	332.570	7.085
	SD	23.794	138.798	0.252
	Min	99.51	196.04	6.79
	Median	127.38	328.14	7.23
	Max	146.85	473.53	7.23
	CV%	19.1	41.7	3.6
	Geometric Mean	123.012	312.308	7.082
	CV% Geometric Mean	19.88	46.57	3.60
8.00	N	3	3	0
	Mean	42.321	95.302	
	SD	8.595	32.252	
	Min	32.45	59.46	
	Median	46.40	104.48	
	Max	48.12	121.97	

		Matrix		
		Tumor	**Plasma**	**Brain**
Time (hr)		**Concentration (ug/L)**		
	CV%	20.3	33.8	
	Geometric Mean	41.687	91.165	
	CV% Geometric Mean	22.04	39.21	
12.0	N	3	3	0
	Mean	20.099	23.754	
	SD	16.635	21.254	
	Min	10.49	9.71	
	Median	10.50	13.35	
	Max	39.31	48.21	
	CV%	82.8	89.5	
	Geometric Mean	16.298	18.418	
	CV% Geometric Mean	88.79	102.65	