PRECLINICAL PHARMACOKINETIC REPORT

Developmental Biology and Solid Tumor Program

P-PKSR Study 18423-83444

STUDY TITLE:

SUMMARY OF THE PHARMACOKINETICS (PK) OF DACTOLISIB (BEZ-235) IN MICE

SHORT TITLE:	**Dactolisib (BEZ-235) Full Project Summary**
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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.

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1.0 OBJECTIVES

- To detail the experiments performed to date regarding plasma, tumor, or dialysate pharmacokinetics (PK) of BEZ235 in mice
- To estimate the total plasma PK of BEZ235 in normal NOD-SCID mice and CD1 nude mice bearing MAST-3 neuroblastoma orthotopic xenografts
- To confirm a murine equivalent dosage (MED) for BEZ235, recapitulating the Day 1 plasma exposure as quantified by the area under the unbound plasma concentration-time curve (AUC_u) at the recommended Phase 2 dose (RP2D) for humans (1600 mg QD)

2.0 MATERIALS AND METHODS

Starting in August of 2011, a number of murine PK studies for oral BEZ235 were conducted over a 20-month period, with bioanalysis via different groups and methods. The in vivo test compound BEZ235 was originally sourced from the Stewart Lab (Department of Pharmaceutical Sciences) via Novartis as a mono-tosylate salt (MW 641.74). Following the microdialysis study, the Dyer Lab sourced free base BEZ235 (MW 469.54) from third party vendors for all further in vivo dosing. BEZ235 was generally administered as a suspension in 0.5% methylcellulose (400 cPs) and 0.5% Tween 80 at 50 mg/kg or 70 mg/kg (10 mL/kg) as an unfasted oral gavage. However, a combination suspension formulation with OSI906 (6 mg/kg) was also dosed, as was a sequential gavage with OSI906 solution, and sparse plasma PK evaluated for potential interactions.

Blood samples (1-3 samples per mouse) for BEZ235 were acquired through retro-orbital bleeds using a capillary glass pipette with sodium heparin (NaHep) or though terminal cardiac puncture (NaHep). Plasma was generated by immediately centrifuging blood at 10000g for 2 minutes. Plasma was placed in separate microcentrifuge tubes and stored on dry ice until transfer to -80°C for long-term storage. Tumor tissue was excised, rinsed with PBS, placed in microcentrifuge tubes upon dry ice, and treated in kind. Dialysate fractions were collected, stored at ambient temperature, and transferred to -80°C for long-term storage at the end of the microdialysis experiment. **Appendix 6.1** provides a summary of the BEZ235 murine PK studies conducted to date in tabular format.

2.1 Bioanalytical

2.1.1 Initial Assay – LC-MS/MS, C. Stewart Lab (Pharmaceutical Sciences)

The first bioanalytical assay, applied to the PK studies through Study 3, was inadequately developed and validated. Upon a retrospective inspection after bioanalysis of experimental plasma samples from Studies 1-3, it was determined that the applied assay was not optimal for quantitation of BEZ235 in plasma, tumor, or dialysate solutions. Briefly, calibrators and QC samples failed to demonstrate the adequate specificity, sensitivity, stability, and reproducibility requisite for application to preclinical PK studies. Sample clean up, chromatography, mass spectrometer condition selection, and choice of internal standard (BKM120) all contributed to the assay underperformance. **Appendix 6.2** contains an example plasma chromatogram and calibration curve suggesting method inadequacy.

2.1.2 Interim Assay – Tier 3 LC-MS/MS, P-PKSR

For PK Studies 3 through 7 (starting with tumor homogenate samples from Study 3), a qualified LC-MS/MS assay was implemented and applied to experimental specimens. The assay was not formally validated, and each experimental sample run consisted of a fresh calibration curve with fresh quality control samples for each matrix. Each experimental run passed with adequate precision and accuracy (<30% CV and bias) and had acceptable linear correlation coefficients ($R>0.99$, $1/x^2$ weighting). Plasma, tumor, and dialysate sample stability and specificity in blank CD1 nu/nu plasma matrix were not assessed at the time.

Briefly, plasma samples underwent a protein precipitation with a 1:4 volume of 100% MeOH, with the supernatant placed in the appropriate vessel on the LC autosampler. Tumors were homogenized with a 1:5 volume of DDI H2O, similarly subjected to protein precipitation, and placed in the LC autosampler. The dialysate samples were subjected to a liquid-liquid extraction procedure using TBME, dry down of organic phase, and reconstitution in mobile phase prior to placement in the LC autosampler. BAG956 was chosen for the internal standard (IS) as it has physiochemical properties and a chemical structure similar to BEZ235.

To verify the accuracy and precision of experimental samples run with the initial assay, selected plasma samples from Study 1 (N=9 samples) were re-run along with the plasma samples from Study 4 (microdialysis) using the qualified P-PKSR assay and compared with the original results (**Appendix 6.3**). While there was a negative bias for results from the initial assay, the overall mean of -12% was within the accepted tolerance accuracy for a validated assay (i.e. ± 15%) and no individual sample bias exceeded 30%. One sample was below the limit of quantitation for both applied assays (1 ng/mL). Given these findings, plasma results from the initial assay were deemed acceptable for use in pharmacokinetic analyses.

2.1.3 Final Assay – Tier 2 LC-MS/MS, P-PKSR

The interim method was further developed and validated prior to analysis of experimental plasma and MAST-3 tumor homogenate samples from Study 8. A draft version of the validation report is on file with the P-PKSR, but has not been finalized, as tumor homogenate stability studies are ongoing.

Briefly, plasma samples (25 µL) underwent a protein precipitation with a 1:3 volume of MeOH-Formic acid (100:0.1 v/v), Tumors were homogenized with a 1:5 volume of 5 mM Ammonium Bicarbonate (pH 7.0), and similarly subjected to protein precipitation. The assays for plasma and tumor homogenate were sensitive and specific, with a lower limit of quantitation (LLOQ) of 1 ng/mL with greater than five times the blank matrix background response at time of analyte HPLC elution.

The plasma and tumor homogenate assays demonstrated adequate intra- and inter-run precision and accuracy with less than 15% CV and bias, respectively. The assays were linear from 1 to 500 ng/mL ($R>0.99$, $1/x^2$ weighting); samples above this range were precisely and accurately diluted with blank matrix. While analyte carryover was less than 20% of a blank matrix response, it was still appreciable at ~16%. Finally, all samples demonstrated stability through two freeze-thaw cycles, and plasma samples were stable for 174 days stored at -80°C. **Appendix 6.4** contains an example plasma calibrator chromatogram and calibration curve for comparison to the initial assay depicted in Appendix 6.2.

2.2 Pharmacokinetic Analyses

A linear one compartment, first order absorption model (ADVAN2 TRANS2) was fit to all plasma concentration-time data in NONMEM 7.2 using the importance sampling population estimation method. Inter-individual variability (IIV) in apparent oral clearance (CL/F), apparent volume of distribution (V1/F), and absorption rate (KA) was assumed to be log-normally distributed and the covariance matrix was constrained to diagonal elements. The residual, intra-individual error was described using an additive and proportional model. Adequacy of model fit was determined by visual predictive checks and graphical inspection of residuals, as well as the -2 log likelihood value. Population and post-hoc Bayesian individual estimates of primary parameters were returned, and secondary non-compartmental parameters (AUC, C_{max}, $T_{1/2}$, T_{max}) were derived for each individual using standard formulae [1].

2.3 Data and Statistical Analyses

For the purpose of PK analyses and data graphing, all bioanaytical data below the LLOQ were treated as missing.

The effects of covariates upon post-hoc estimates of CL/F, V1/F, and KA were each tested in a univariate, forward addition manner with linear mixed effects models using R software. Briefly, parameters were log-transformed, and models were fit using maximum likelihood and an unstructured covariance and correlation matrix. PK parameters were treated as fixed effects and individual mice as a random effect. Prior to testing of covariates, inter-study variability was also tested as a random effect along with individual mice in a nested fashion (i.e. individual mouse nested in study). The covariates tested are listed and described in **Table 2.3.1.**

Table 2.3.1: Listing and Description of Covariates Tested for Effects on Post-Hoc Primary PK Parameters

Covariate	Description
STDY	Study: The PK study correlating to the description in **Appendix 5.1.**
GROUP	Group: A combination of study and dosage condition, whether dosed by different formulation on in conjunction with OSI906.
FORM	Formulation: The formulation applied (MC, MC/Tween, MC/Tween combo).
DAY	Day: Indicates the day of dosing relative to dosage form compounding. Day 1 indicates dosage was formulated on same day as dosing, Day 5 indicates 4 days had elapsed from the formulation time.
COMBO	Combination: Indicates whether BEZ235 was dosed alone or in combination with OSI906.

For a covariate effect on to be considered significant, its addition must have improved the model fit as evaluated by the likelihood ratio test at an α=0.05 level. For significant covariates, post-hoc general linear hypothesis tests with the Tukey HSD multiple comparison adjustment were performed to evaluate pair-wise differences between covariate groups.

3.0 RESULTS AND DISCUSSION

Overall, the one-compartment linear model adequately fit the data as indicated by visual inspection of the goodness of fit (GOF) residual plots and the post-hoc population and individual predicted concentration-time profiles (**Attachment 7.1**). A population mean fit along with observed concentrations normalized to a BEZ235 free base dosage of 70 mg/kg is depicted in **Appendix 6.5**. These plots indicate a tendency of the model to slightly over-predict concentrations, particularly at earlier time points after dosing. **Table 3.0.1** lists the primary population PK parameter estimates from the fitted model.

Table 3.0.1: Primary Population PK Parameters for BEZ235 in Mice after Oral Administration

Parameter	Description	Units	Estimate	Relative Std. Error (%)
CL/F	Apparent Oral Clearance	L/hr/kg	12.7	21.7
V1/F	Apparent Oral Volume	L/kg	189	16.3
KA	Absorption Rate Constant	hr^{-1}	2.11	38.1
$\omega_{CL/F}$	CL/F Inter-Individual Variability	% CV	70.1	57.3
$\omega_{V1/F}$	V1/F Inter-Individual Variability	% CV	84.5	20.2
ω_{KA}	KA Inter-Individual Variability	% CV	145	43.9
σ_{add}	Residual Error - Additive	µg/L	13.5	74.3
σ_{prop}	Residual Error - Proportional	%	43.6	10.6

The primary population PK parameters CL/F and V1/F were well estimated, with relative standard errors (RSEs) of around 20%. KA was moderately well estimated with an RSE < 50%, likely secondary to a lack of adequate samples within and between individuals in the acute absorption phase. All other parameters were estimated with adequate precision for preclinical studies (i.e. RSEs < 100%).

The IIV in the primary PK parameters was high, with CL/F and V1/F exhibiting IIVs (as % CV) of 70.1% and 84.5%, respectively. The IIV in KA was exceedingly high at 145%. The intra-individual, residual error was moderate at 43.6% proportional error and an additive error of 13.5 ug/L, indicating the possible presence of model misspecification.

The apparent extent and rate of BEZ235 absorption appeared to be highly variable with the oral suspension formulations, supported by the high IIV in not only KA, but also the apparent oral clearance, volume, and the apparent T½ (range: 1.9 to 57 hours). An unidentifiable portion of variability in CL/F and V1/F can be attributed to the denominator value of bioavailability (F), which remains unknown in mice. Moreover, the post-hoc secondary non-compartmental PK parameters associated with absorption, T_{max} and C_{max}, varied more than fifteen- and ten-fold, respectively. This variable and prolonged absorption in preclinical species with this suspension formulation is not unexpected, given the low solubility, high lipophilicity, and apparent Pgp transport of BEZ235 [2].

As per the IB, rats administered oral BEZ235 mono-tosylate 10 mg/kg in 0.5% methylcellulose exhibited ~50% bioavailability, but T_{max} values ranged from 2 to 24 hours, indicating poor solubility and probable absorption in the distal GI tract. Single dose AUC values from rats dosed at 30 and 50 mg/kg were less than proportionally higher than the AUC at 10 mg/kg, indicating solubility limited absorption in that dosage range. In dogs, oral bioavailability ranged from 4% to 34%, and was highly variable between and within animals; long and varied T_{max} values up to 24 hours were also observed. Finally, all these issues are also observed in humans with the clinical formulation of BEZ235. Thus, the suspension formulation in mice recapitulates clinical absorption and PK characteristics resulting from tablets or capsules in humans, more so than elaborate, enabled formulations (i.e. NMP/PEG300 solutions).

The focus of the covariate analysis was upon CL/F, as this is the PK parameter that defines systemic exposure by plasma AUC (AUC = DOSE*F/CL). Differences between studies or inter-study variability in CL/F values were not significant upon testing with the nested mixed effect model or using STDY as a covariate (p=0.73 and 0.20, respectively). STDY, GROUP, FORM, and COMBO were not significant covariates upon CL/F at an α=0.05 level. A significant difference between Day 1 (freshly prepared formulations) versus Day 5 (formulations stored at 4°C for approximately 96 hours) was noted, with a P value of 0.029. Day 5 CL/F values from Study 6 were 33% higher than the comparative Day 1 post hoc mean value. This finding is likely a result of a physical instability in the formulation over the time period, and may be due to BEZ235 ripening, flocculation, or "dropping" out of suspension. Notably, BEZ235 single agent and OSI906 combination formulations were all found to be chemically stable over a 5 day time period in a separate study (**Attachment 7.2**).

An evaluation of covariate effects upon V1/F and KA was also undertaken. There was a significant difference in V1/F between Studies 1-4 and 5-8, with Studies 5-8 using the free base 70 mg/kg dosage having about two-fold higher V1/F values. The KA values for Study 5 were significantly smaller than all other studies, likely due to the rising concentrations in the terminal phase, resulting in an extreme absorption "flip-flop" phenomenon. These findings for V1/F and KA are likely due to absorption differences between the soluble tosylate salt suspension at 50 mg/kg and the free base suspension at 70 mg/kg – a prolonged and variable absorption phase evident for the latter likely resulted in longer apparent half-lives governed by absorption. Finally, a significantly higher V1/F was also noted for the combinations, whether BEZ235 and OSI906 were dosed together in suspension or as two separate oral gavages at 5 mL/kg each. This indicates that the combination may have physical compatibility issues in vivo, diminishing the rate but not extent of BEZ235 absorption. Despite these findings, total exposure by AUC was not significantly different amongst these groups, as this is governed solely by CL/F (*vide supra*).

Finally, a murine or species equivalent dosage (MED or SED) for BEZ235 was derived. The MED is defined as the mouse dosage achieving the Day 1 unbound plasma AUC achieved in humans at the BEZ235 RP2D of 1600 mg QD. The table below describes the derivation of this key parameter by linear proportionality.

Table 3.0.1: Derivation of a Murine Equivalent Dosage (MED) for BEZ235

Species	Dosage	D1 AUC (hr-ng/mL)	D1 AUC_u (hr-ng/mL)	Murine Equivalent Dosage (MED)
Human	1600 mg QD	3730 [3]	74.6	47.5 mg/kg
Mouse	70 mg/kg	5110	110	

Note: Fraction unbound in plasma ($F_{u,p}$) is 0.02 for both humans and mice [2]

BEZ235 demonstrates high inter-individual PK variability in mice and humans, and the murine Population PK model tends to slightly over-predict concentrations at early time points, and thus slightly over-predict AUC. With this in mind, dosages in mice ranging from 50 to 70 mg/kg of BEZ235 free base in 0.5% MC/Tween suspension provide clinically appreciable unbound plasma exposures, and are recommended for in vivo efficacy studies in murine xenograft models. Of note, the 70 mg/kg dosage will achieve or exceed the mean human unbound AUC in ~86% of mice, yielding the highest chance of success if the xenograft models are sensitive.

4.0 CONCLUSIONS

- While the initial assay from the Stewart Lab was not optimal, the data were within specifications for use in pharmacokinetic (PK) modeling.
- The interim, qualified BEZ235 assay by the P-PKSR performed adequately, and produced data within specification for PK modeling.
- A sensitive, specific, and validated LC-MS/MS method for BEZ235 in mouse plasma and tumor homogenate has been developed and applied to experimental samples from Study 8.
- The mouse plasma BEZ235 concentrations were best described with a one-compartment, linear model with first order absorption.
- There is an exceedingly high inter-individual PK variability (70%-145%) in mice receiving BEZ235 suspension by gavage.
- The strict Murine Equivalent Dosage is 47.5 mg/kg BEZ235 free base in 0.5% MC/Tween suspension; however, dosages up to 70 mg/kg provide unbound plasma AUCs in a clinically relevant range.
- There may be a physical interaction when BEZ235 and OSI906 are co-administered that reduces the rate but not the extent of BEZ235 absorption.

5.0 REFERENCES

[1] M. Gibaldi and D. Perrier, Eds., *Pharmacokinetics, Second Edition*, 2nd ed. CRC Press, 1982.
[2] "BEZ235 Investigator's Brochure, Edition 4.0." Novartis AG, 13-May-2010.
[3] J. D. Peyton, J. Rodon Ahnert, H. Burris, C. Britten, L. C. Chen, J. Tabernero, V. Duval, N. Rouyrre, A. P. Silva, C. Quadt, and J. Baselga, "A dose-escalation study with the novel formulation of the oral pan-class I PI3K inhibitor BEZ235, solid dispersion system (SDS) sachet, in patients with advanced solid tumors.," *Asco Meet. Abstr.*, vol. 29, no. 15_suppl, p. 3066, Jun. 2011.

6.0 APPENDICES

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Appendix 6.1: Table of Oral BEZ235 Pharmacokinetic Studies

STDY	Study ID	Strain	Dosage	Matrix	Design	Group	Form	Day	Combo
1	Plasma #1	NOD SCID	50 mg/kg PO in 0.5% MC (400 cPs)	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	0	1	1	0
2	Plasma #2	NOD SCID	50 mg/kg PO in 0.5% MC (400 cPs) & 0.5% Tween 80	Plasma	6 mice; 0.083, 1, 5.2 hr 6 mice; 1, 1.4, 22.5 hr	1	2	1	0
3	Tumor	CD1 nu/nu (MAST3)	50 mg/kg PO in 0.5% MC (400 cPs) & 0.5% Tween 80	Plasma, Tumor	15 mice; 0.083, 0.75, 3.5, 7.5, 18 hr	1	2	1	0
4	Microdialysis – ECF	CD1 nu/nu (MAST3)	50 mg/kg PO in 0.5% MC (400 cPs) & 0.5% Tween 80	Plasma, ECF	3 mice; 0.117, 7.5, 10 hr & every 1 hr for 10 hr	1	2	1	0
5	Plasma #3, combo D1	CD1 nu/nu	70 mg/kg PO in 0.5% MC (400 cPs) & 0.5% Tween 80	Plasma	3 mice; 1, 3.5, 7 hr	2	2	1	0
			& 6 mg/kg OSI906 in 0.5% MC (400 cPs) & 0.5% Tween 80		3 mice; 1, 3.5, 7 hr	3	3	1	1
6	Plasma #3, combo D5	CD1 nu/nu	70 mg/kg PO in 0.5% MC (400 cPs) & 0.5% Tween 80	Plasma	3 mice; 1, 3.5, 7 hr	4	2	5	0
			& 6 mg/kg OSI906 in 0.5% MC (400 cPs) & 0.5% Tween 80		3 mice; 1, 3.5, 7 hr	5	3	5	1
7	Plasma #4 combos	CD1 nu/nu	50 mg/kg PO in 0.5% MC (400 cPs) & 0.5% Tween 80	Plasma	2 mice; 3.5 hr	5	2	1	0
			70 mg/kg PO in 0.5% MC (400 cPs) & 0.5% Tween 80	Plasma	2 mice; 3.5 hr	5	2	1	0
			6 mg/kg OSI as solution, then 70 mg/kg BEZ suspension as above	Plasma	2 mice; 3.5 hr	6	2	1	2
			6/70 mg/kg OSI/BEZ combo suspension	Plasma	2 mice; 3.5 hr	7	3	1	1
8	Tumor #2	CD1 nu/nu (MAST3)	50 mg/kg PO in 0.5% MC (400 cPs) & 0.5% Tween 80	Plasma, Tumor	15 mice; 0.083, 0.67, 3.17, 5, 15 hr	8	2	1	0

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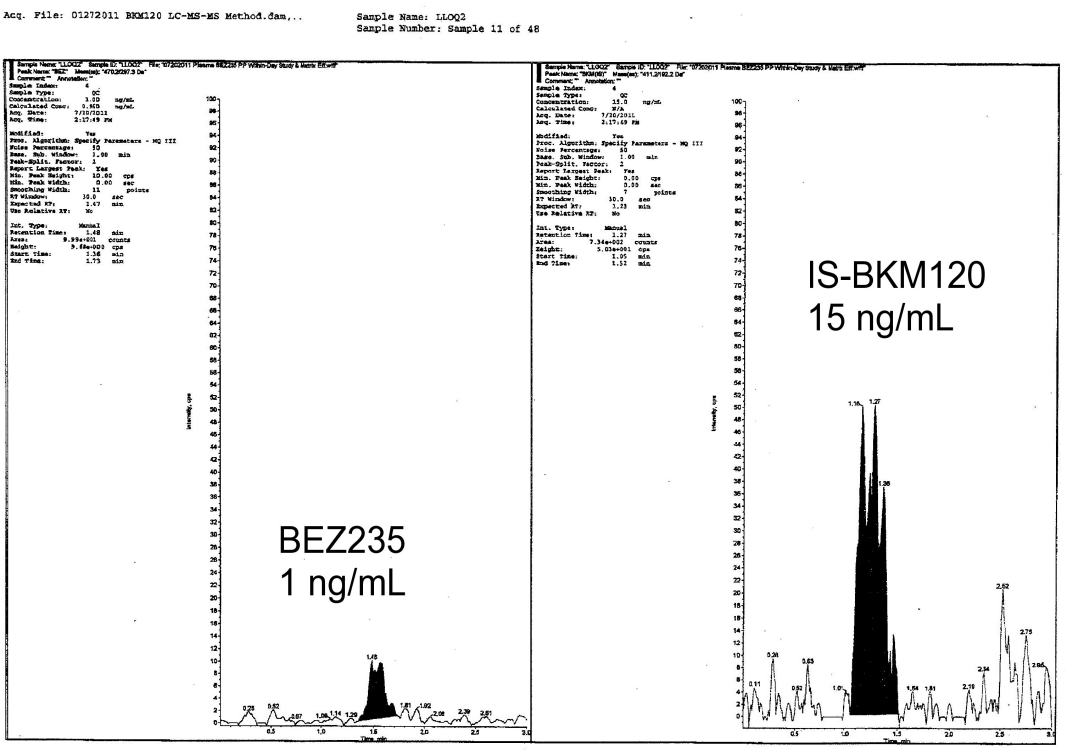
Appendix 6.2: Example BEZ235 Chromatogram at the LLOQ (1 ng/mL) and BEZ235 Calibration Curve in Plasma from INITIAL Assay



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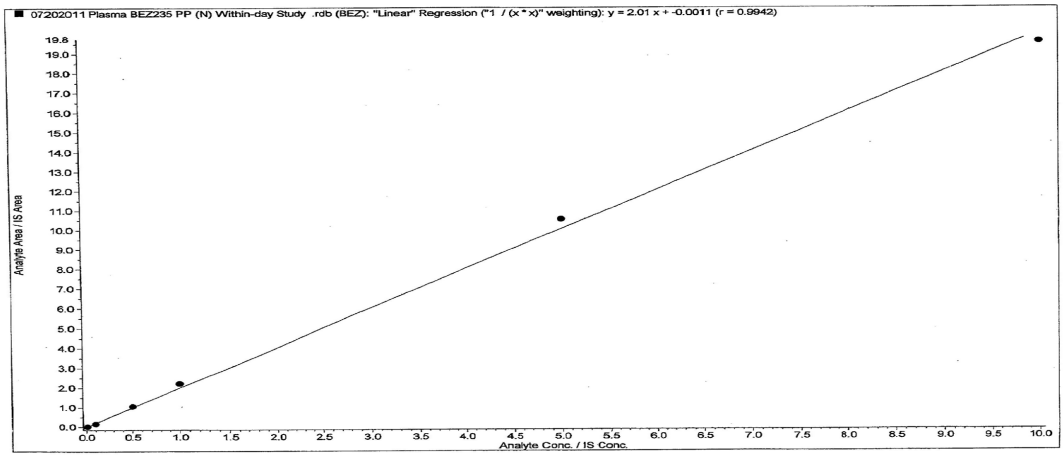
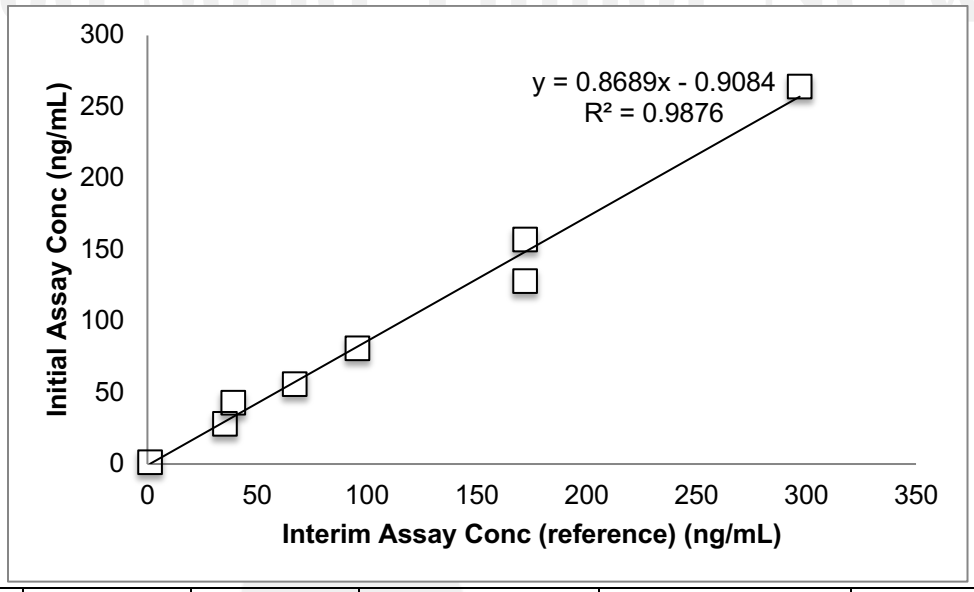


Appendix 6.3: Assessment of Reproducibility of Initial Assay Plasma Results with the P-PKSR Interim Assay



Study	Mouse ID	Sample Time (hr)	Interim Assay Concentration (ng/mL)	Initial Assay Concentration (ng/mL)	Difference (%)
1	2151	8	95.7	80.7	-15.67
1	2152	8	67.3	56	-16.79
1	2154	12	172	157	-8.72
1	2155	12	297	264	-11.11
1	2157	24	1.22	1.17	-4.10
1	2158	24	172	128	-25.58
1	2153	8	39.3	42.6	8.40
Initial Assay Mean Bias (%)					**-11.87**

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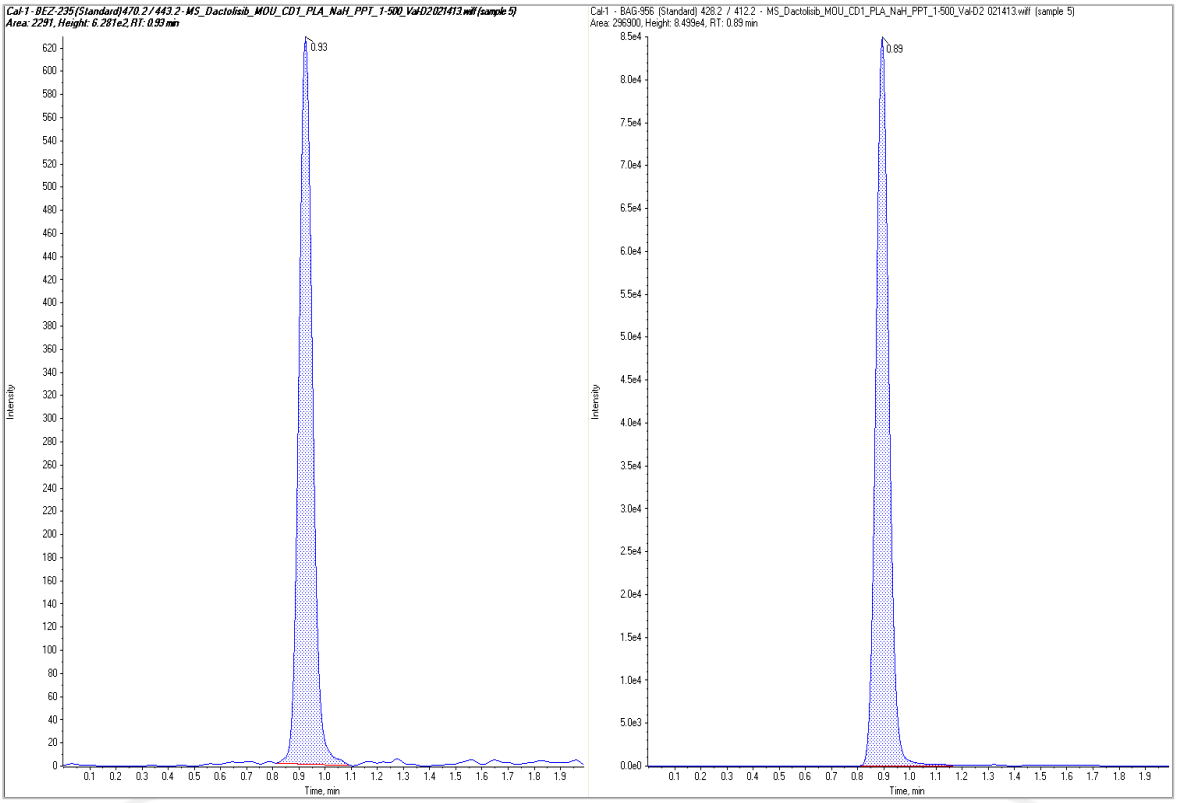
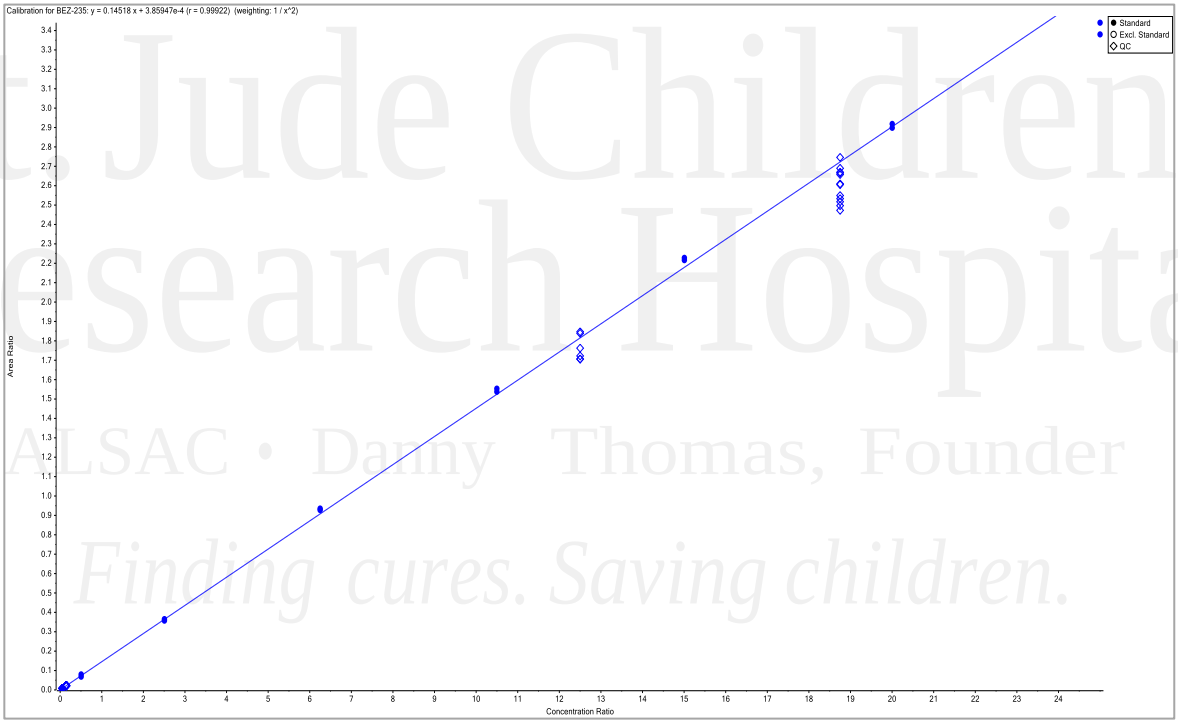
Appendix 6.4: Example BEZ235 Plasma Calibrator Chromatogram at the LLOQ (1 ng/mL) and BEZ235 Calibration Curve in Plasma from FINAL Assay

BEZ235 **IS-BAG956**





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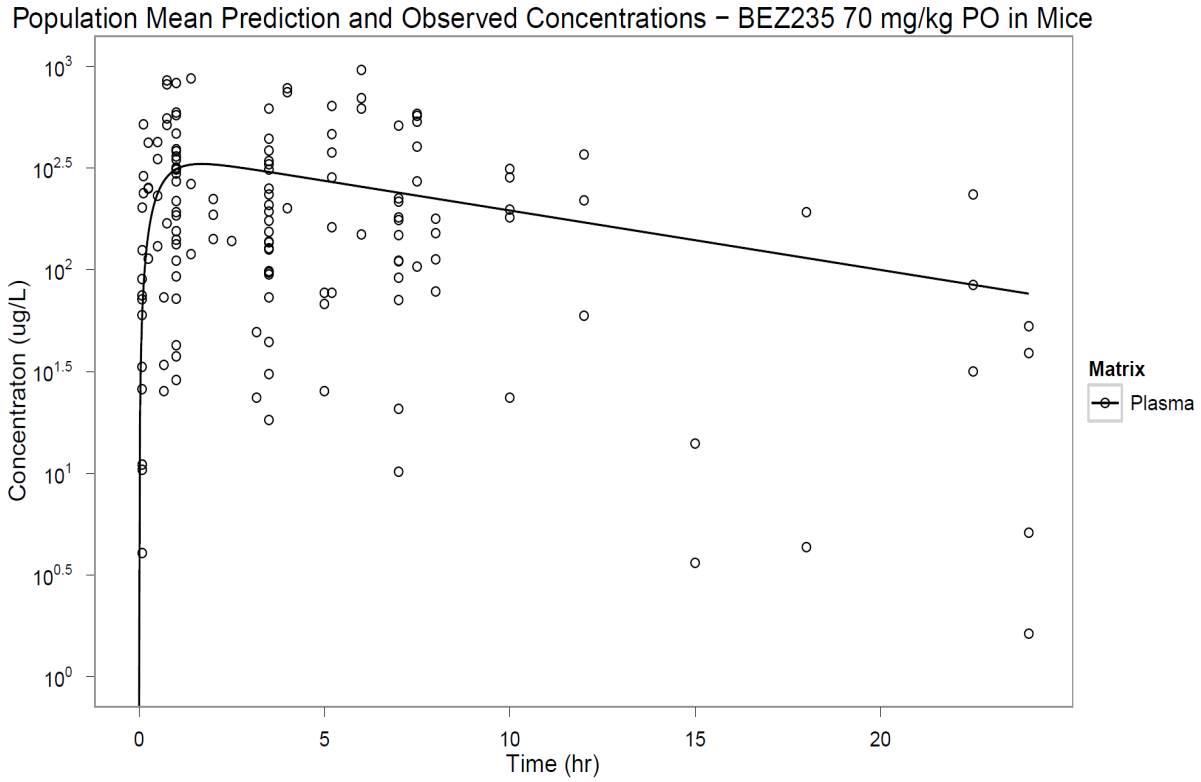
Appendix 6.5: Population Model Mean Prediction vs. Individual Observed Concentrations Normalized to BEZ235 Free Base 70 mg/kg PO in Mice



7.0 ATTACHEMENTS

7.1 Population Model Goodness-of-Fit and IPRED, PRED, and OBS BEZ235 Plasma Concentrations (bez_gof.pdf)

7.2 OSI-BKM-BEZ Formulation Chemical Stability Report 10-10-12.zip

7.3 Dactolisib (BEZ-235) Mouse Plasma Concentration-Time Data in Nonmem Format (BEZ235.csv) – *Note: The dosage variable (AMT) is in ug/kg units, TIME is in hours, and the concentration variable (DV) in ng/mL or ug/L. The CMT variable represents the compartment of the observation: 1 represents dosing in the gut and 2 represents plasma.*

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