POPULATION PHARMACOKINETIC–PHARMACODYNAMIC MODELING OF EFAPROXIRAL IN CANCER PATIENTS RECEIVING RADIATION THERAPY

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Abstract

AIMS: Efaproxiral (EFP, RSR13), a synthetic allosteric modifier of hemoglobin (Hb), reduces O2-binding affinity in blood (p50) and is investigated as a radiation therapy sensitizer. The goal of this work was to describe the pharmacokinetics (PK) and pharmacodynamics (PD) of EFP in cancer (CA) patients. METHODS: Pooled data from 6 phase I –III trials included: 451 patients, 2582 plasma and 2881 RBC concentrations, and 2483 p50 values. Covariates were age, weight, height, sex, concomitant medications, CA type, Hb, albumin, creatinine clearance, body surface area (BSA) and dose. Data were analyzed using NONMEM. RESULTS: A linear, 2-compartment model with RBC:plasma proportionality constant and a linear RBC-p50 model described the PK-PD relationship. Parameters were consistent with previously reported values (%SE): CL=1.88 L/hr (8%), V1=10.5 L (2%), Q=2.58 L/hr (12%), V2=18.1 L (10%), SLPRBC=0.982 (1%), INTp50=26.9 mmHg (~0%), SLPp50=0.0193 mmHg/(µg/mL) (5%). The inclusion of covariates resulted in improvements in goodness of fit and decreases in the estimated inter-individual variances. The final model adequately described the central tendency and population variability for the observed data. CONCLUSIONS: Differences in PK-PD response due to CA type were small, may have been study-related and were probably not clinically relevant. EFP exposure increased with age, but the clinical relevance of this effect was unknown. BSA was the most important predictor of EFP disposition.

PARTIAL SUPPORT: Allos Therapeutics Inc.

CONFLICT OF INTEREST: Marc R. Gastonguay is a paid consultant for Allos Therapeutics, Inc. and other pharma/biotech companies. Jürgen Venitz is a paid consultant for Allos Therapeutics Inc.

Introduction

- Efaproxiral (EFP), a synthetic allosteric modifier of Hb, reduces O_2-binding affinity in blood (p50, partial pressure of oxygen to achieve 50% saturation) and is investigated as a radiation therapy sensitizer.
- The objectives of the population (POP) pharmacokinetic (PK) - pharmacodynamic (PD) analysis were:
  - to describe the PK of EFP, including its distribution to red blood cells (RBC);
  - to describe the PK-PD relationship for EFP using p50 as an endpoint,
  - to quantify POP PK and PD parameters for this system, including typical values and random inter-individual and residual variabilities,
  - to identify any individual-specific covariate factors (e.g. demographics, disease state, etc.) that are predictive of the unexplained random variability

Data

- EFP exposure and response data were pooled across six Phase I – Phase III clinical trials doses ranging from 75-100 mg/kg given 2-3 times per week
- A total of 451 subjects (224 males and 227 females) contributed data to the population PK-PD analysis. Distributions of covariate, demographic factors are presented in Table 1, with correlations between continuous covariates presented in Table 2.
- Covariates included: age, weight, height, sex, concomitant medications, baseline hemoglobin (BHb), baseline albumin (BALB), baseline creatinine (BSCr), baseline creatinine clearance (CLCr) (also CLCr truncated at a max of 150ml/min), body surface area (BSA), maximum administered dose (MDOS) and primary cancer type (CATP; 1=lung, 2=breast, 3=cranial glioblastoma multiforme, 4=other).
- The database contained a total of 7,946 observations: 2582 plasma EFP concentrations, 2881 RBC EFP concentrations, 2483 p50 values (from phase I and II studies only)

Table 1: Summary of Covariates

Continuous Covariates

	Age (yrs)	Weight (kg)	Height (cm)	Baseline Hemoglobin (mg/dL)	Baseline Albumin (mg/dL)	Baseline Creatinine (mg/dL)	Ideal Body Weight (kg)	Body Surface Area (m^2)	Baseline Creatinine Clearance (mL/min)	Truncated Creatinine Clearance (mL/min)
Minimum	28	38.6	135	8.7	2.2	0.1	29.4	1.31	28.8	28.8
Maximum	87	129	193	17.8	5	1.6	86.8	2.5	973	150
Mean	56.9	72.8	169	13.1	3.64	0.745	62.7	1.83	113	107
Median	57	72.3	169	13.2	3.6	0.7	61.6	1.82	106	106

All Subjects (N = 451)

Categorical Covariates

	Sex		**Cancer Type**				**Race**					
	Male	Female	Lung	Breast	CGM	Other	Caucasian	Black	Native American	Asian	Hispanic	Other[b]
Number[a]	224	227	229	78	72	72	407	26	1	3	9	5
Percentage	49.7	50.3	50.8	17.3	16	16	90.2	5.8	0.2	0.7	2	1.1

[a] Total number of subjects (N = 451)

[b] Two individuals with "Race Unknown" were imputed as "Other"

Table 2: Continuous Covariate Correlations

	Age (yrs)	Weight (kg)	Height (cm)	Baseline Hemoglobin (mg/dL)	Baseline Albumin (mg/dL)	Baseline Serum Creatinine (mg/dL)	Ideal Body Weight (kg)	Body Surface Area (m^2)	Truncated Creatinine Clearance (mL/min)	Maximum Dose (mg)
Age (yrs)	1	0	0.04	0.05	-0.16	0.28	0.07	0.02	-0.52	-0.06
Weight (kg)	0	1	0.5	0.13	0.01	0.21	0.51	0.94	0.49	0.82
Height (cm)	0.04	0.5	1	0.08	-0.08	0.19	0.99	0.76	0.25	0.49
Baseline Hemoglobin (mg/dL)	0.05	0.13	0.08	1	0.19	0.11	0.13	0.13	0.06	0.12
Baseline Albumin (mg/dL)	-0.16	0.01	-0.08	0.19	1	0.12	-0.09	-0.03	-0.06	-0.03
Baseline Serum Creatinine (mg/dL)	0.28	0.21	0.19	0.11	0.12	1	0.22	0.23	-0.62	0.1
Ideal Body Weight (kg)	0.07	0.51	0.99	0.13	-0.09	0.22	1	0.76	0.24	0.49
Body Surface Area (m^2)	0.02	0.94	0.76	0.13	-0.03	0.23	0.76	1	0.46	0.81
Truncated Creatinine Clearance (mL/min)	-0.52	0.49	0.25	0.06	-0.06	-0.62	0.24	0.46	1	0.48
Maximum Dose (mg)	-0.06	0.82	0.49	0.12	-0.03	0.1	0.49	0.81	0.48	1

Methods

- Data processing and graphics were performed using S-PLUS (6.1 Pro/Win, Insightful, Seattle, WA). Data were analyzed via nonlinear mixed-effects population PK-PD modeling using the First-Order estimation method of NONMEM (V,l.1, GloboMax, Hanover, MD) and Compaq Visual Fortran 6.6B. Computations were performed on Intel-based personal computers, under the WindowsXP operating system.
- A base model, which simultaneously described EFP plasma and RBC concentrations as well as p50 values, was initially developed.
- A full covariate model was subsequently developed and covariate-parameter relationships were estimated.
- Covariate-parameter relationships were described with a power model and were chosen based on scientific interest, mechanistic plausibility and exploratory graphics, with care to avoid collinearity in predictors.

Methods

- Full model goodness-of-fit was assessed through typical diagnostic plots, and changes in the Akaike Information Criterion, which was based on the NONMEM minimum objective function value (OFV) and total number of parameters (P). Models were also investigated for any remaining trends between random effects (ETAs) and all covariates in the population PK-PD database.
- Parameters of the full model (and asymptotic standard errors) were estimated and 95% confidence intervals were obtained by non-parametric bootstrap.
- Inferences about clinical importance of covariate effects were based on point and interval estimates of parameters rather than by stepwise hypothesis testing.
- A predictive check model evaluation was conducted to investigate the performance of this model as a Monte Carlo simulation tool.

Categorizing Covariate Effects with Full Model

- **Clinically Important (CI):** Point estimate and 95% confidence interval of covariate effect parameter results in clinically important change in PK (e.g. greater than +/- 30% of null value).
- **Not Clinically Important (NCI):** 95% confidence interval of covariate effect parameter lies within a pre-defined, unimportant effect size (e.g. less than +/- 30% of null value).
- **Insufficient Information (II):** 95% confidence interval of covariate effect is broad and spans across values of covariate effect that are both clinically important and not clinically important.

Results

- A linear, 2-comparment PK model with RBC:plasma proportionality constant and a linear RBC concentration - p50 response provided a simultaneous description of EFP PK-PD across doses and across broad ranges of covariate factors that was without systematic bias (Figures 1-3).
- The relationship between RBC EFP concentration and p50 response was characterized by a linear model with minimal variability relative to PK endpoints (Equation1, Table 3).
- Structural model parameter estimates were consistent with previously reported values and were precisely estimated (Table 3).
- The inclusion of individual-specific covariate factors resulted in discernable improvements in model goodness of fit criteria and decreases in the estimated random inter-individual variances.

Results

- With the full model, no remaining trends were observed when exploring relationships between inter-individual random effects and individual-specific covariates.
- Covariate effects were estimated with varying degrees of precision (Table 4).
- Clinically important (CI) covariate effects included BSA on central volume of distribution and age on clearance (Tables 4 & 5).
- Point estimates for some effects, such as BSA on inter-compartmental clearance (Table 4), were small but estimates were poorly defined due to insufficient information (II) in the data.
- Other covariate effects had minimal impact but were well-defined (NCI), such as the relative PD slope for CATP2 and the age and dose effects on SLPRBC (Tables 4 & 5).

Results

- The predictive check model evaluation indicated that simulations with the final model adequately described the expected central tendency and population variability for the endpoints analyzed across most of the range of observed data, but provided biased distributions at the high end of the RBC and p50 data ranges (Figure 4).
- Given this inadequacy of the simulation model, further investigations about the proposed EFP dosing rule were conducted using simulations based on conditional estimates of random effects from subjects in this database, rather than by generating pseudo-random variates using Monte Carlo simulation.
- Simulations with conditional estimates revealed that the per-protocol dosing rule provided adequate control of exposure and response in this patient population (Figure 5).

Equation 1: Full Covariate Model

PK Model

$$
\begin{aligned}
CL_i &= \theta_{CL} \cdot \left(\frac{BSA_i(m^2)}{1.8(m^2)}\right)^{\theta_{CL\sim BSA}} \cdot \left(\frac{AGE_i(yrs)}{60(yrs)}\right)^{\theta_{CL\sim AGE}} \cdot \exp^{\eta_{CL}} \\
V1_i &= \theta_{V1} \cdot \left(\frac{BSA_i(m^2)}{1.8(m^2)}\right)^{\theta_{V1\sim BSA}} \cdot \left(\frac{AGE_i(yrs)}{60(yrs)}\right)^{\theta_{V1\sim AGE}} \cdot \left(\frac{BALB_i(g/dL)}{3.5(g/dL)}\right)^{\theta_{V1\sim BALB}} \cdot \exp^{\eta_{V1}} \\
Q_i &= \theta_Q \cdot \left(\frac{BSA_i(m^2)}{1.8(m^2)}\right)^{\theta_{Q\sim BSA}} \cdot \exp^{\eta_Q} \\
V2_i &= \theta_{V2} \cdot \left(\frac{BSA_i(m^2)}{1.8(m^2)}\right)^{\theta_{V2\sim BSA}} \cdot \left(\frac{AGE_i(yrs)}{60(yrs)}\right)^{\theta_{V2\sim AGE}} \cdot \left(\frac{BALB_i(g/dL)}{3.5(g/dL)}\right)^{\theta_{V2\sim BALB}} \cdot \exp^{\eta_{V2}} \\
CP_i &= A1_i / V1_i
\end{aligned}
$$

PD Model

$$
\begin{aligned}
SLPRBC_i &= \theta_{SLPRBC} \cdot \left(\frac{MDOS_i(mg)}{6800(mg)}\right)^{\theta_{SLPRBC\sim MDOS}} \cdot \left(\frac{AGE_i(yrs)}{60(yrs)}\right)^{\theta_{SLP\sim AGE}} \\
&\quad \cdot \left(\frac{BALB_i(g/dL)}{3.5(g/dL)}\right)^{\theta_{SLP\sim BALB}} \cdot \exp^{\eta_{SLPRBC}} \\
CRBC_i &= SLPRBC_i \cdot CP_i \\
INTp50_i &= \theta_{INTp50} \cdot \exp^{\eta_{INTp50}} \\
SLPP50_i &= \theta_{SLPP50} \cdot (\theta_{SLPP50\sim CA2})^{CA2} \cdot (\theta_{SLPP50\sim CA3})^{CA3} \cdot (\theta_{SLPP50\sim CA4})^{CA4} \cdot \exp^{\eta_{SLPP50}} \\
p50_i &= INTp50_i + SLPP50_i \cdot CRBC_i
\end{aligned}
$$

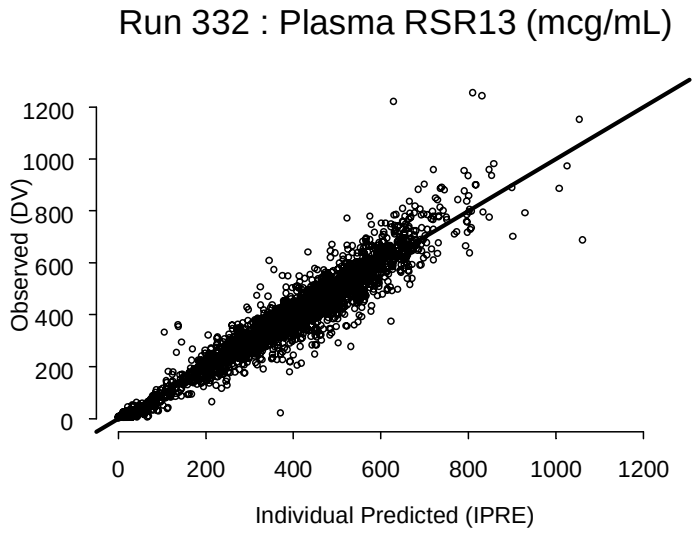
Table 3: Full Model Parameter Estimates

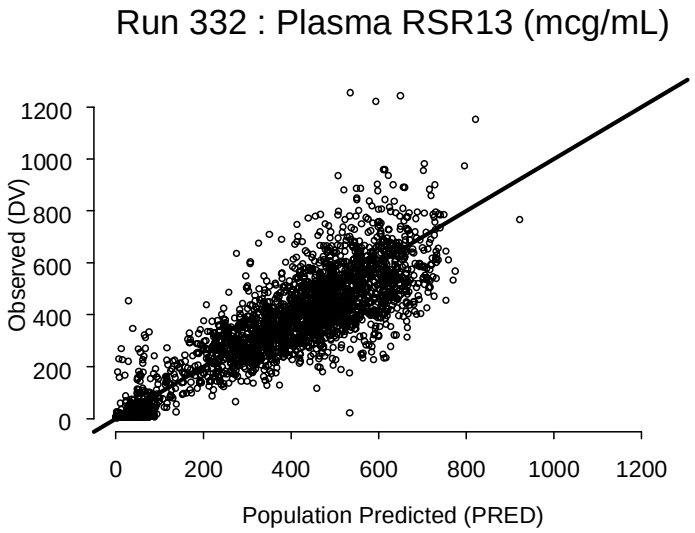
Structural Model and Interindividual Variance Parameters		
Parameter	Typical Value (%SE)	Interindividual Variance (%SE)
CL (L/hr)[a,b]	1.88 (8%)	0.283 (21%) CV%=53%
$\theta_{CL\sim BSA}$	0.528 (101%)	N/A
$\theta_{CL\sim AGE}$	-1 (25%)	N/A
V1 (L)[a,c]	10.5 (2%)	0.0324 (14%) CV%=18%
$\theta_{V1\sim BSA}$	1.15 (11%)	N/A
$\theta_{V1\sim AGE}$	-0.282 (27%)	N/A
$\theta_{V1\sim BALB}$	0.357 (47%)	N/A
Q (L/hr)	2.58 (12%)	0.154 (30%) CV%=39%
$\theta_{Q\sim BSA}$	0.199 (426%)	N/A
V2 (L)[b,c]	18.1 (10%)	4.66 (55%) CV%=216%
$\theta_{V2\sim BSA}$	2.62 (29%)	N/A
$\theta_{V2\sim AGE}$	0.524 (81%)	N/A
$\theta_{V2\sim BALB}$	-2.35 (57%)	N/A
SLPRBC	0.982 (1%)	0.0176 (15%) CV%=13%
$\theta_{SLPRBC\sim MDSA}$	-0.125 (42%)	N/A
$\theta_{SLPRBC\sim AGE}$	-0.109 (49%)	N/A
$\theta_{SLPRBC\sim BALB}$	0.367 (38%)	N/A
INTp50	26.9 (0%)	0.00217 (25%) CV%=5%
SLPp50	0.0193 (5%)	0.0568 (26%) CV%=24%
$\theta_{SLPp50\sim CATP2}$	1.11 (8%)	N/A
$\theta_{SLPp50\sim CATP3}$	1.28 (18%)	N/A
$\theta_{SLPp50\sim CATP4}$	0.854 (11%)	N/A

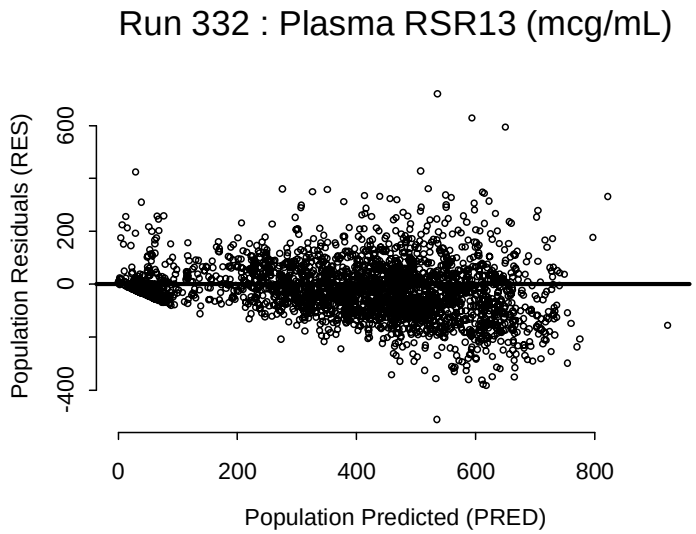
Residual Error	
Parameter	Estimate
$\sigma^2_{Plasma,\ add}$	SD=24.74 (26%)
$\sigma^2_{Plasma,\ prop}$	CV%=12.96% (11%)
$\sigma^2_{RBC,\ add}$	SD=15.62 (27%)
$\sigma^2_{RBC,\ prop}$	CV%=15.56% (15%)
$\sigma^2_{p50,\ prop}$	CV%=6.86% (18%)

[a]interindividual covariance CL, V1 = 0.0264 (26%)
[b]interindividual covariance CL, V2 = -0.41 (49%)
[c]interindividual covariance V1, V2 = 0.0341 (96%)
%SE = % standard error
SD = standard deviation
CV% = percent coefficient of variation
N/A = not available

Figure 1: EFP (RSR13) Plasma Concentration Final Model Goodness of Fit







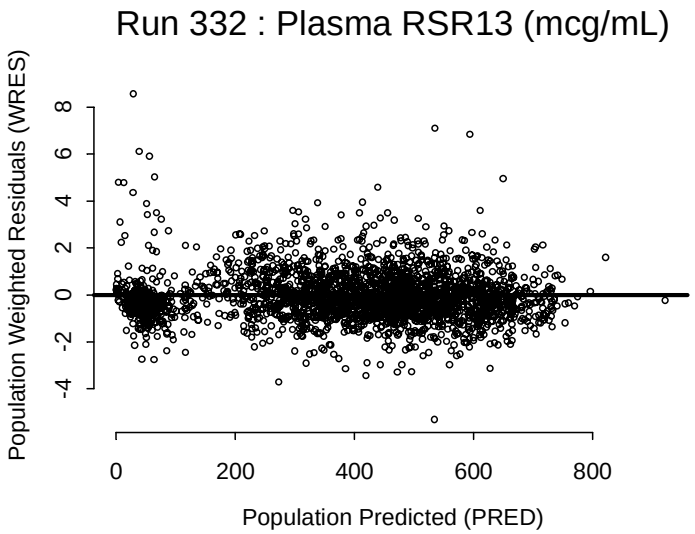
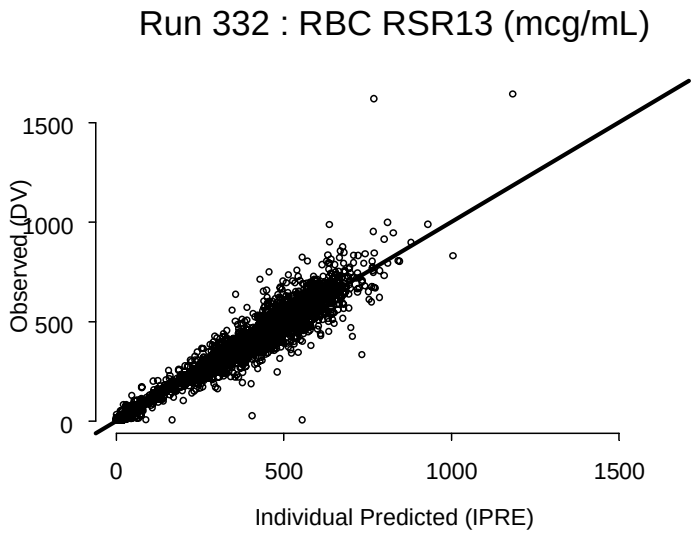
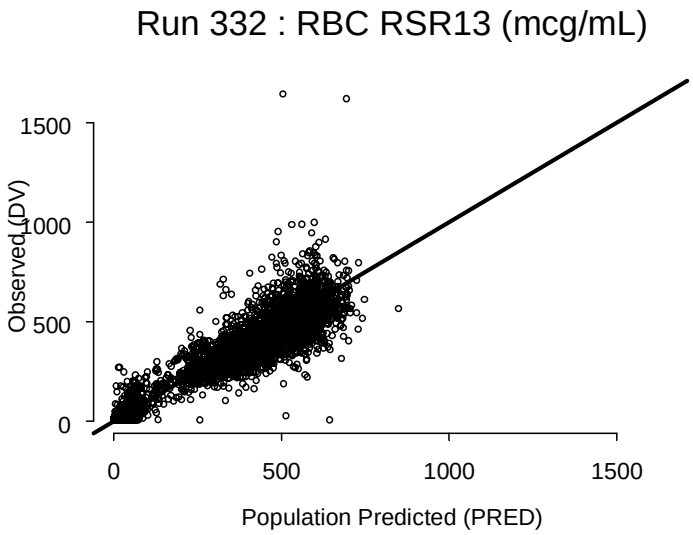
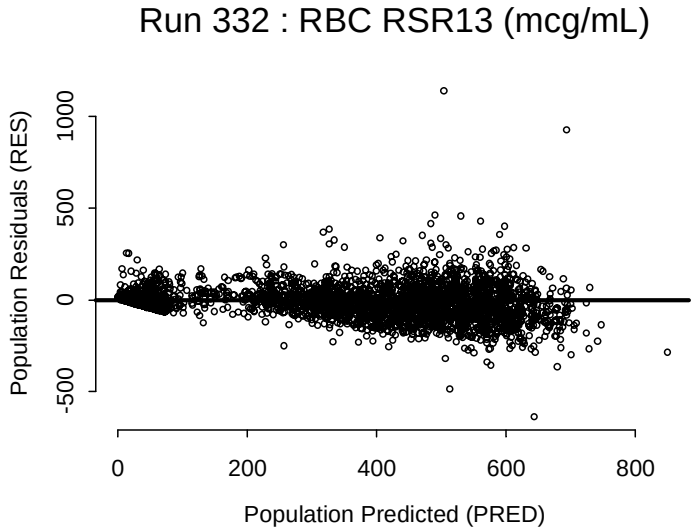


Figure 2: EFP (RSR13) RBC Concentration Final Model Goodness of Fit







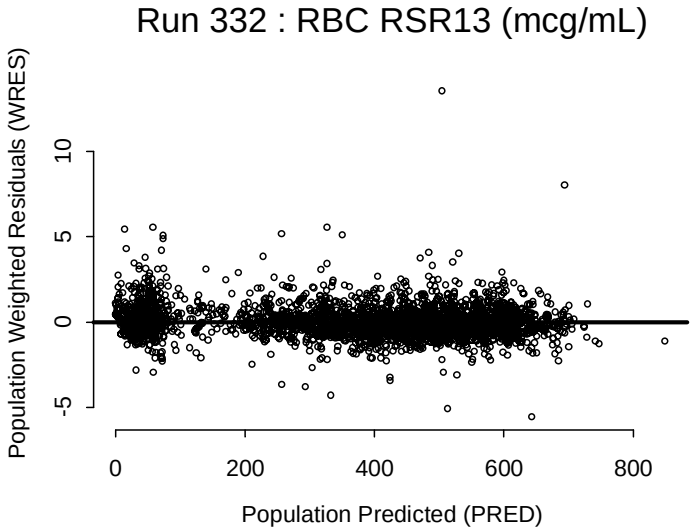
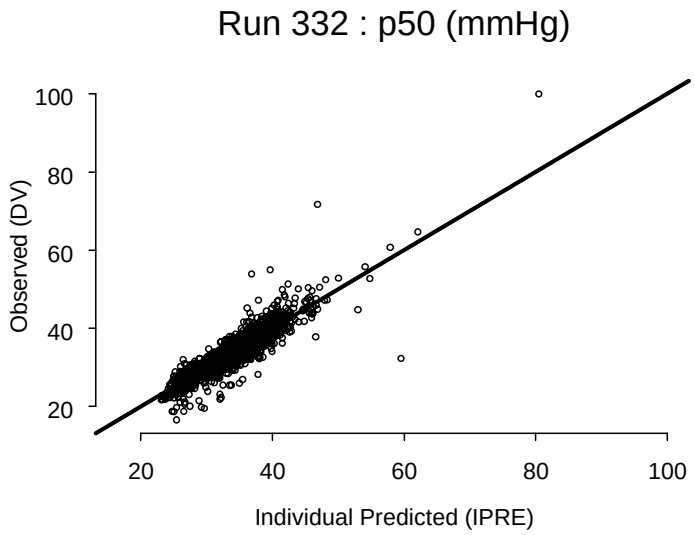
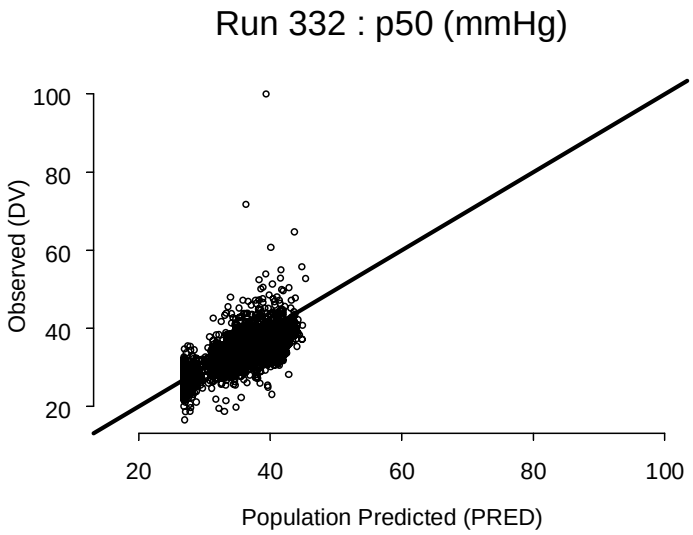
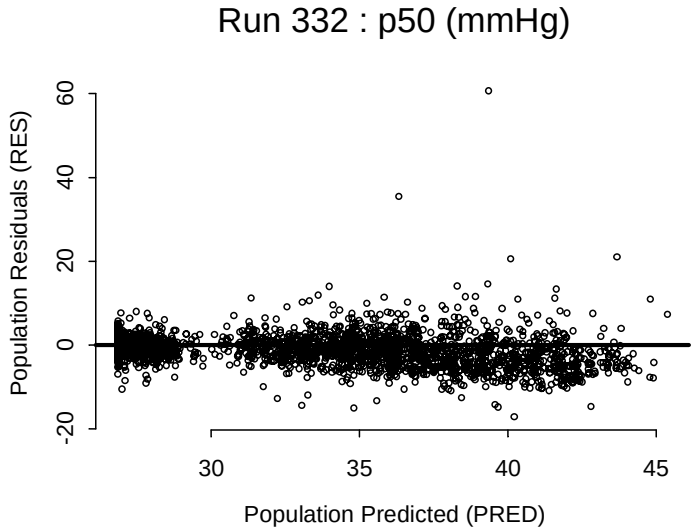


Figure 3: p50 Final Model Goodness of Fit







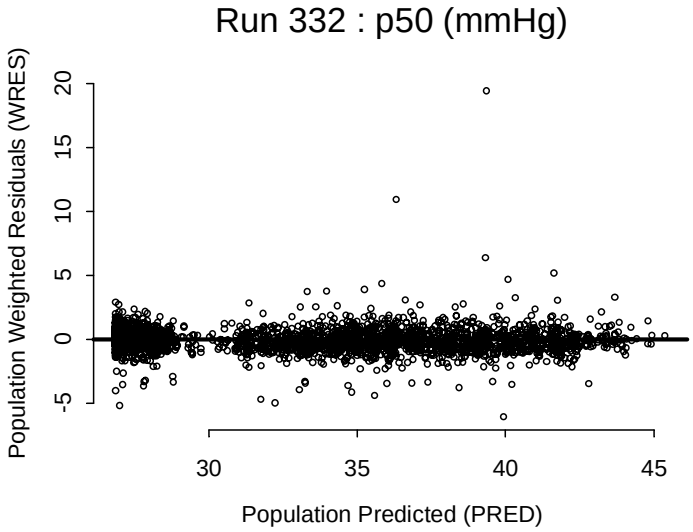


Table 4: Inference about Covariate Effects

Continuous covariates (null=0)

Categorical covariates (null=1)

Parameter	Typical Value (95% CI)	Covariate Classification
CL (L/hr)	1.88 (1.29, 2.1)	
$\theta_{CL\sim BSA}$	0.528 (-1.18, 1.93)	II
$\theta_{CL\sim AGE}$	-1 (-1.76, -0.497)	CI
V1 (L)	10.5 (9.04, 11)	
$\theta_{V1\sim BSA}$	1.15 (0.491, 1.47)	CI
$\theta_{V1\sim AGE}$	-0.282 (-0.49, -0.133)	II
$\theta_{V1\sim BALB}$	0.357 (0.0236, 0.759)	II
Q (L/hr)	2.58 (1.67, 7.95)	
$\theta_{Q\sim BSA}$	0.199 (-1.8, 5.24)	II
V2 (L)	18.1 (7.38, 43.7)	
$\theta_{V2\sim BSA}$	2.62 (-3.6, 3.84)	II
$\theta_{V2\sim AGE}$	0.524 (-0.602, 3.74)	II
$\theta_{V2\sim BALB}$	-2.35 (-3.56, 3.89)	II
SLPRBC	0.982 (0.956, 1.03)	
$\theta_{SLPRBC\sim MDSA}$	-0.125 (-0.22, -0.0222)	NCI
$\theta_{SLPRBC\sim AGE}$	-0.109 (-0.197, 0.0267)	NCI
$\theta_{SLPRBC\sim BALB}$	0.367 (-0.0528, 0.618)	II
INTp50	26.9 (26.6, 27)	
SLPp50	0.0193 (0.0167, 0.0218)	
$\theta_{SLPp50\sim CATP2}$	1.11 (0.946, 1.3)	NCI
$\theta_{SLPp50\sim CATP3}$	1.28 (1, 2.07)	II
$\theta_{SLPp50\sim CATP4}$	0.854 (0.464, 1.12)	II

Table 5: Covariate Effects on PK-PD Parameters

Parameter	Covariate	Lower[a]	Median[b]	Upper[c]
CL (L/hr)	BSA (m^2)	1.68	1.89	2.11
CL (L/hr)	**Age (years)**	**3.05**	**1.98**	**1.49**
V1 (L)	**BSA (m^2)**	**8.21**	**10.6**	**13.4**
V1 (L)	Age (years)	12	10.7	9.83
V1 (L)	Albumin (mg/dL)	9.47	10.6	11.5
Q (L/hr)	BSA (m^2)	2.47	2.58	2.69
V2 (L)	BSA (m^2)	10.3	18.5	31.7
V2 (L)	Age (years)	14	17.6	20.5
V2 (L)	Albumin (mg/dL)	35.7	16.9	10
SLPRBC	Maximum Dose (mg)	1.04	0.983	0.936
SLPRBC	Age (years)	1.04	0.988	0.957
SLPRBC	Albumin (mg/dL)	0.883	0.992	1.08

[a]Parameter estimate at lower bound of observed 95% variability interval for specified covariate

[b]Parameter estimate at observed median for specified covariate

[c]Parameter estimate at upper bound of observed 95% variability interval for specified covariate

Figure 4: Predictive Check Results

Quantile-quantile plots compare distributions of simulated and observed values. Top Left: Simulated Plasma EFP (RSR13) (mcg/mL) vs. Observed Plasma EFP (mcg/mL) at a low dose group of 75 mg/kg; Top Center: Simulated Red Blood Cell EFP (mcg/mL) vs. Observed Red Blood Cell EFP (mcg/mL) at a low dose group of 75 mg/kg; Top Right: Simulated p50 (mmHg) vs. Observed p50 (mmHg) at a low dose group of 75 mg/kg; Bottom Left: Simulated Plasma EFP (mcg/mL) vs. Observed Plasma EFP (mcg/mL) at a high dose group of 100 mg/kg; Bottom Center: Simulated Red Blood Cell EFP (mcg/mL) vs. Observed Red Blood Cell EFP (mcg/mL) at a high dose group of 100 mg/kg; Bottom Right: Simulated p50 (mmHg) vs. Observed p50 (mmHg) at a high dose group of 100 mg/kg

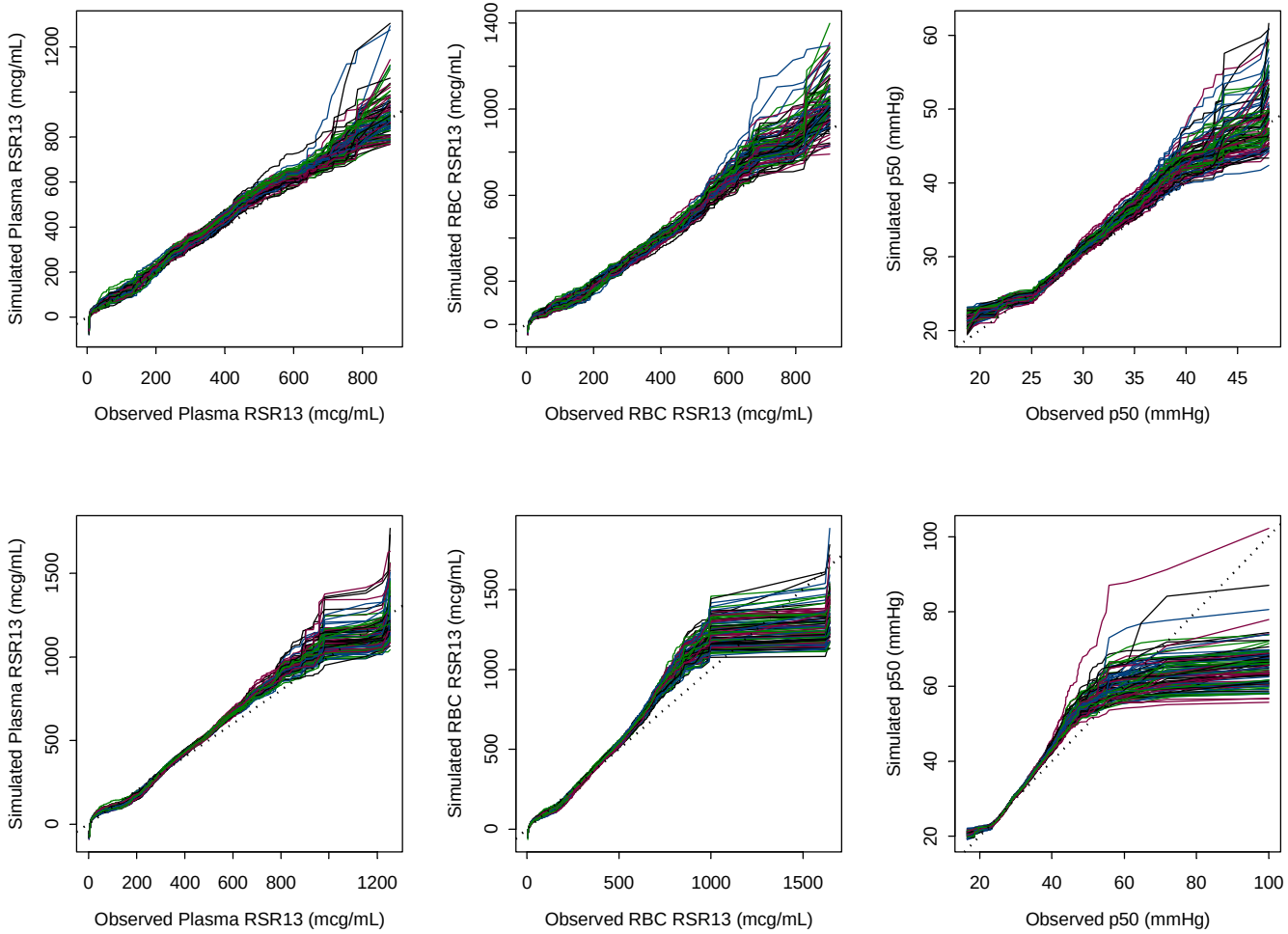
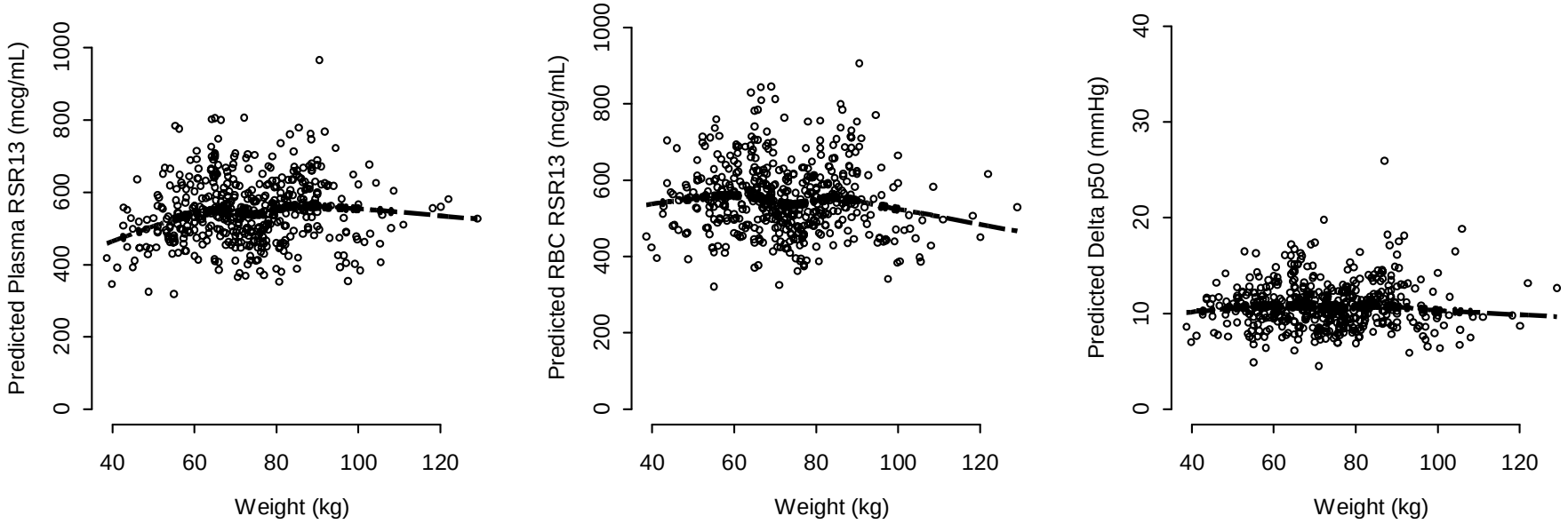


Figure 5: Predicted PK-PD for Per-Protocol Dosing

Predicted PK and PD responses after a 30-minute infusion of EFP (RSR13) (dichotomous dosing rule: 100 mg/kg for males <= 95 kg and females <= 70 kg; 75 mg/kg for males > 95 kg and females > 70 kg) are plotted versus weight (kg). Predicted values are indicated by open circles and a dashed lowess (local regression smoother) trend line. Left: Predicted Plasma EFP (mcg/mL) vs. Weight (kg); Center: Predicted Red Blood Cell EFP (mcg/mL) vs. Weight (kg); Right: Predicted Change from Baseline p50 (mmHg) vs. Weight (kg). One individual (ID = 84, PATID = 60019) was removed from these plots because of unrealistically high p50 values > 70 mmHg.



Conclusions/Discussion

- The per-protocol dosing rule appears to have provided adequate control of EFP exposure variability for this patient database
- Body size, as depicted by BSA, was the most important covariate factor for predicting variability in EFP disposition.
- EFP exposure increased with age, an effect which may be related to a decrease in renal function
- Differences in PK-PD response due to cancer type were small in magnitude and were confounded by study-related differences.
- Considerable unexplained variability (inter-individual and residual) remained even after covariate-PKPD modeling
- Bias in the predictive check may be due to biased estimation of variance parameters and/or limited data at the high end of RBC and p50 values
- Unlike stepwise regression, the full model approach allowed for the direct assessment of clinical importance of covariate effects and provided an explanation for the apparent absence of an effect (e.g. true lack of an effect vs. lack of information about that effect).

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