

1 Objectives

- to develop a linear mixed effects PK model to describe the FTY720-P (Fingolimod/Gilenya) concentrations at steady-state in the multiple sclerosis (MS) pediatric patient population using data from Study CFTY720D2311 (D2311).
- to assess by performing a visual predictive check (VPC) whether the previously developed adult FTY720-P exposure-lymphocyte count model described the pediatric lymphocyte data from study D2311 and to re-estimate the parameters of the exposure-lymphocyte model using a combined dataset from adult and pediatric patients.

2 Methods

Population PK model

Using the previously developed linear mixed effects PK model (see below) for the adult relapsing-remitting (RR) MS population as a starting point, a linear mixed effect model was developed to describe the FTY720-P concentrations at steady-state in the pediatric MS patients using data from Study D2311 alone. Age, weight and dose group were investigated (both as time-varying and time-invariant) covariates in the present analysis.

$$\mu = (\beta_0 + b_0) + (\beta_1 \cdot \text{weight}) + (\beta_2 \cdot \text{gender}) + (\beta_3 \cdot \text{dose})$$

$$Y \sim MVN \left\{ \begin{bmatrix} \mu_1 \\ \mu_2 \\ \dots \\ \mu_n \end{bmatrix}, \sigma^2 \begin{bmatrix} 1 & \rho & \rho^2 \\ & 1 & \rho \\ & & \dots \\ & & & 1 \end{bmatrix} \right\}, b_0 \sim N(0, \sigma_b^2)$$

where $\mu_1, \mu_2, \dots, \mu_n$ correspond to the log of the estimated mean steady-state FTY720-P concentrations at n visits, β_0 is the intercept and b_0 is the random effect associated with the intercept, β_1 = weight effect on the intercept, β_2 = gender effect on the intercept and β_3 = dose effect on the intercept. The residual model was proposed to be additive on the log-scale.

Exposure-lymphocyte count model

An exploratory VPC was performed to assess whether the previously developed adult exposure-lymphocyte model (see below) described the pediatric lymphocyte data from Study D2311.

$$I_{\max, cov} = I_{\max} \cdot e^{\eta_{I_{\max}}} \cdot (1 + \beta_2 \cdot \text{gender})$$

$$fC_p = \begin{cases} I_{\max, cov} \cdot C_p & \text{for FTY720} \\ 0 & \text{for placebo} \end{cases}$$

$$\mu = \beta_0 + \eta_{BSL} + \beta_1 \cdot (WT - 70) + fC_p$$

$$\log(Y) \sim N(\mu, \sigma_{res}^2) \text{ and } \begin{bmatrix} \eta_{BSL} \\ \eta_{I_{\max}} \end{bmatrix} \sim MVN \left\{ \begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_{BSL}^2 & cov \\ cov & \sigma_{I_{\max}}^2 \end{bmatrix} \right\}$$

where, IC_{50} is the FTY720-P steady-state concentration that achieves 50% of the maximum extent of reduction ($I_{\max}$), β_2 = gender effect on $I_{\max}$, μ = model estimated log absolute lymphocyte count, β_0 = typical log lymphocyte level at baseline in all patients and the steady-state level in placebo-treated patients, β_1 = weight effect on baseline and η_{BSL} and $\eta_{I_{\max}}$ are the random effects associated with the $I_{\max}$ and lymphocyte count at baseline (β_0). σ_{res}^2 is the variance of the additive residual variability on the log scale.

The previously developed model in adults did not describe the pediatric data and therefore the parameters of the exposure-lymphocyte model were re-estimated using a combined dataset from adult and pediatric patients to determine which parameters were different between the adult and pediatric populations. A binary covariate on each model parameter (baseline, IC_{50} and $I_{\max}$) was added to estimate the difference between adult and pediatric data.

The final population PK and exposure-lymphocyte count models were evaluated by performing a prediction-corrected VPC. NONMEM® program version VII level 3.0 was used for all analyses using PDx-Pop (Version 5.2) as an interface.

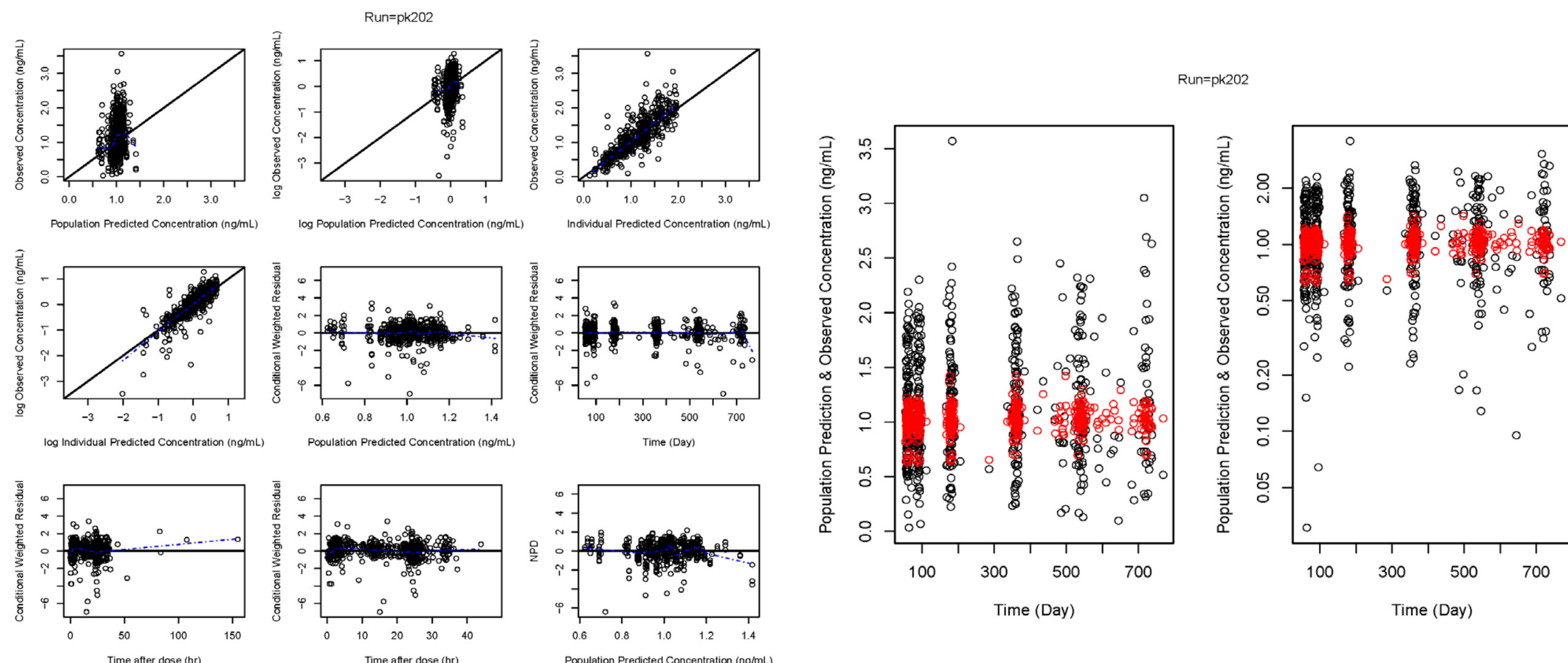
3 Results

Population PK model

- Following administration of 0.5 mg per day of FTY720 in a pediatric population, the typical steady-state FTY720-P concentration for a body weight of 70 kg (0.978 ng/mL) was within the 90% CI around the median of the adult target FTY720-P steady-state concentration and higher than the 65% relative bound (0.878 ng/mL) of the adult target FTY720-P steady-state concentration level.
- The steady-state FTY720-P concentrations were 49% lower following administration of 0.25 mg capsule compared to following administration of 0.50 mg capsule formulation thus confirming the dose-proportionality between the two dose levels.
- The steady-state FTY720-P concentrations decreased slightly with increasing body weight. The decrease in concentration was non-linear. An increase of 10 kg weight from 20 to 30 kg and from 70 to 80 kg resulted in a 15.2% and a 5.3% decrease in FTY720-P concentrations, respectively.

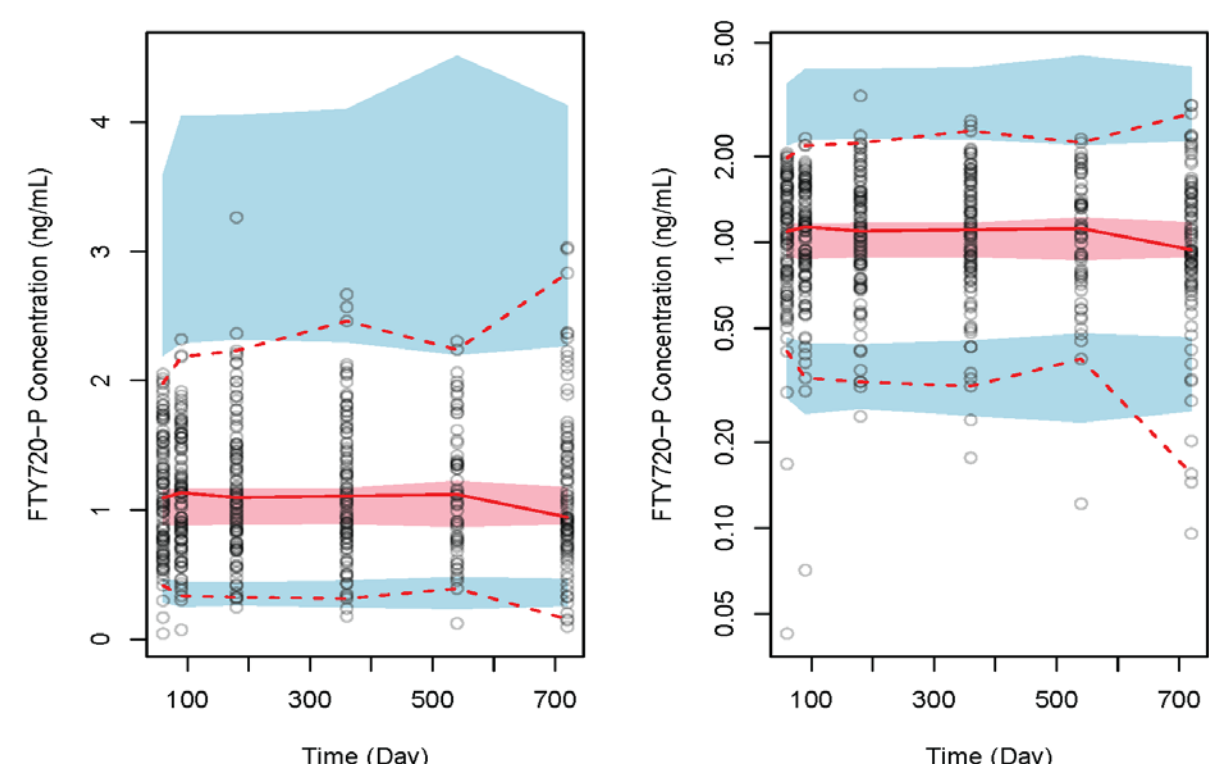
Goodness-of-fit plots for the final population PK model

Black circles: Observed concentrations, Red circles: Population predicted concentrations, Blue dashed line: Local regression (Loess) smoothing line



Prediction-corrected VPC for the final population PK model

Open Circle: Observed Lymphocyte Count; Solid Line: Median of Observed Lymphocyte Count; Dashed Lines: 5th and 95th percentile of Observed Lymphocyte Count. Red Shaded Region: 95% Prediction Interval for Median of Predicted Lymphocyte Count; Blue Shaded Regions: 95% Prediction Intervals for the 5th and 95th percentiles of Predicted Lymphocyte Count



Results (cont'd.)

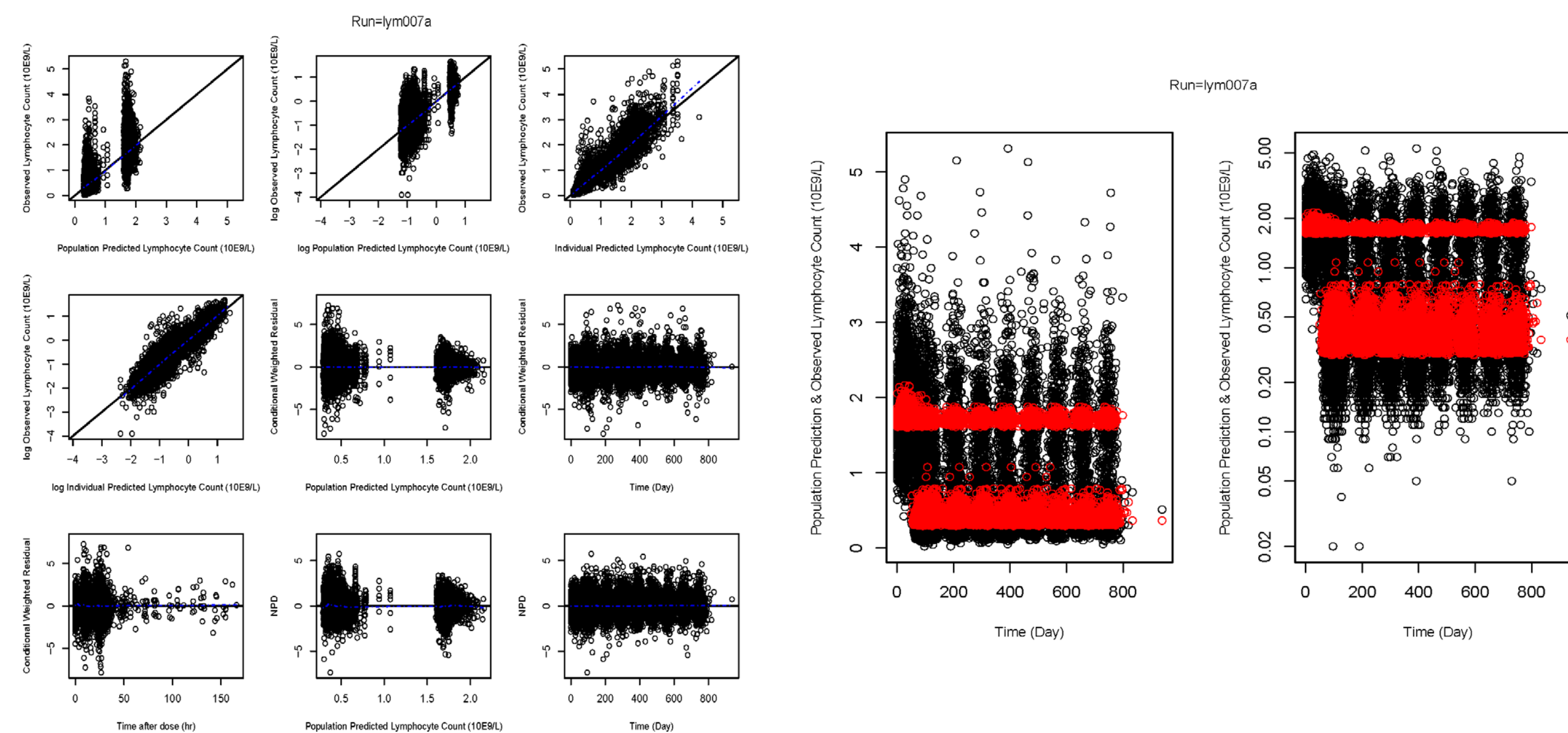
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Exposure-lymphocyte count model

- The FTY720-P exposure-lymphocyte relationship in adults is an $I_{\max}$ model relating the estimated FTY720-P concentrations at steady state to the absolute lymphocyte count.
- The baseline lymphocyte count was estimated to be 17.2% higher in pediatric patients compared to the adult population. Both $I_{\max}$ and IC_{50} were comparable between pediatric and adult populations with $I_{\max}$ 6% lower and IC_{50} 12% lower in pediatric versus adult patients.
- The baseline lymphocyte count was slightly higher for higher baseline weights. A 10-kg increase in weight (from 70 to 80 kg) resulted in only a 2% increase in lymphocyte count.

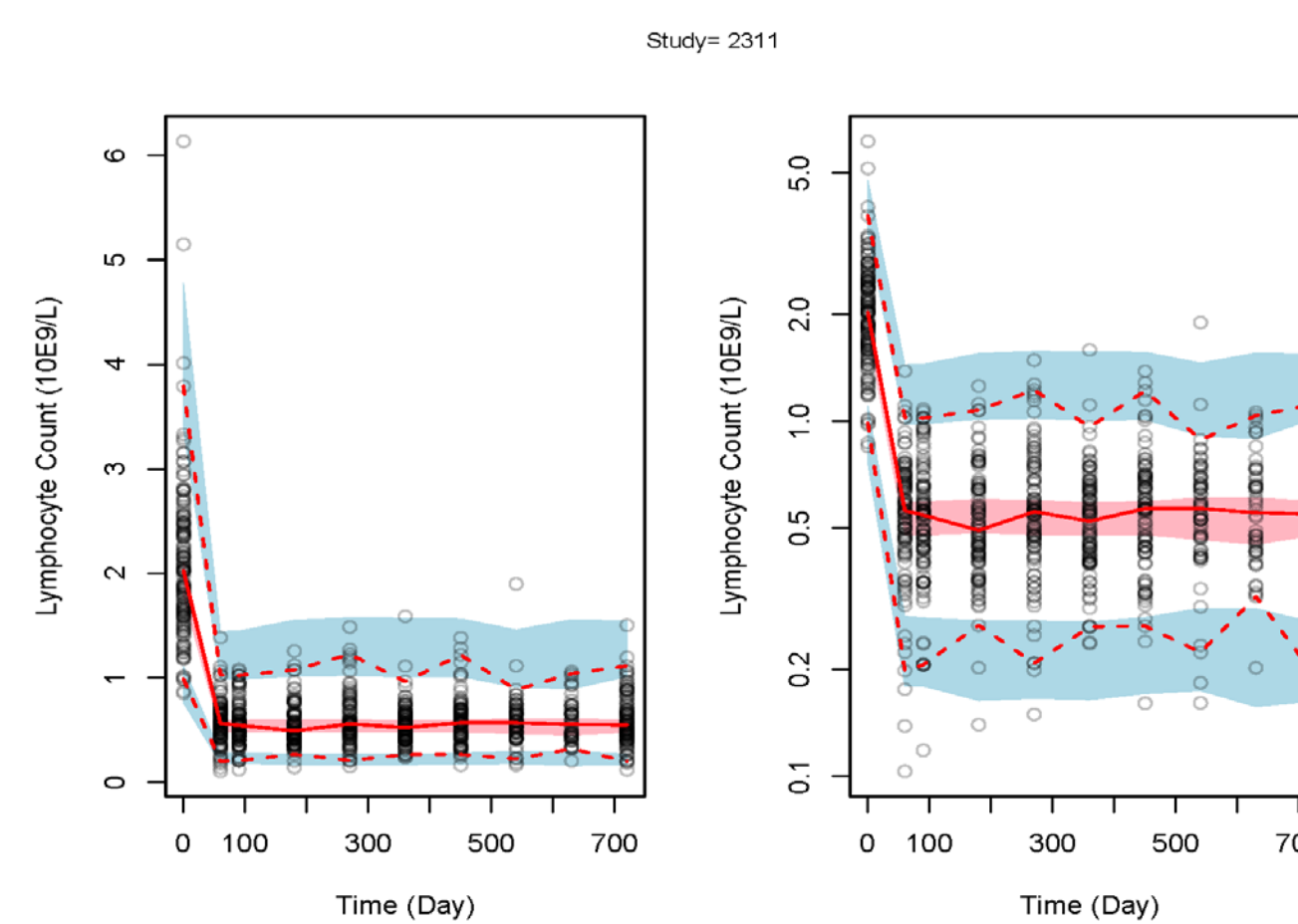
Goodness-of-fit plots for the final exposure-lymphocyte count model

Black circles: Observed lymphocyte count, Red circles: Population predicted lymphocyte count, Blue dashed line: Local regression (Loess) smoothing line



Prediction-corrected VPC for the final exposure-lymphocyte count model

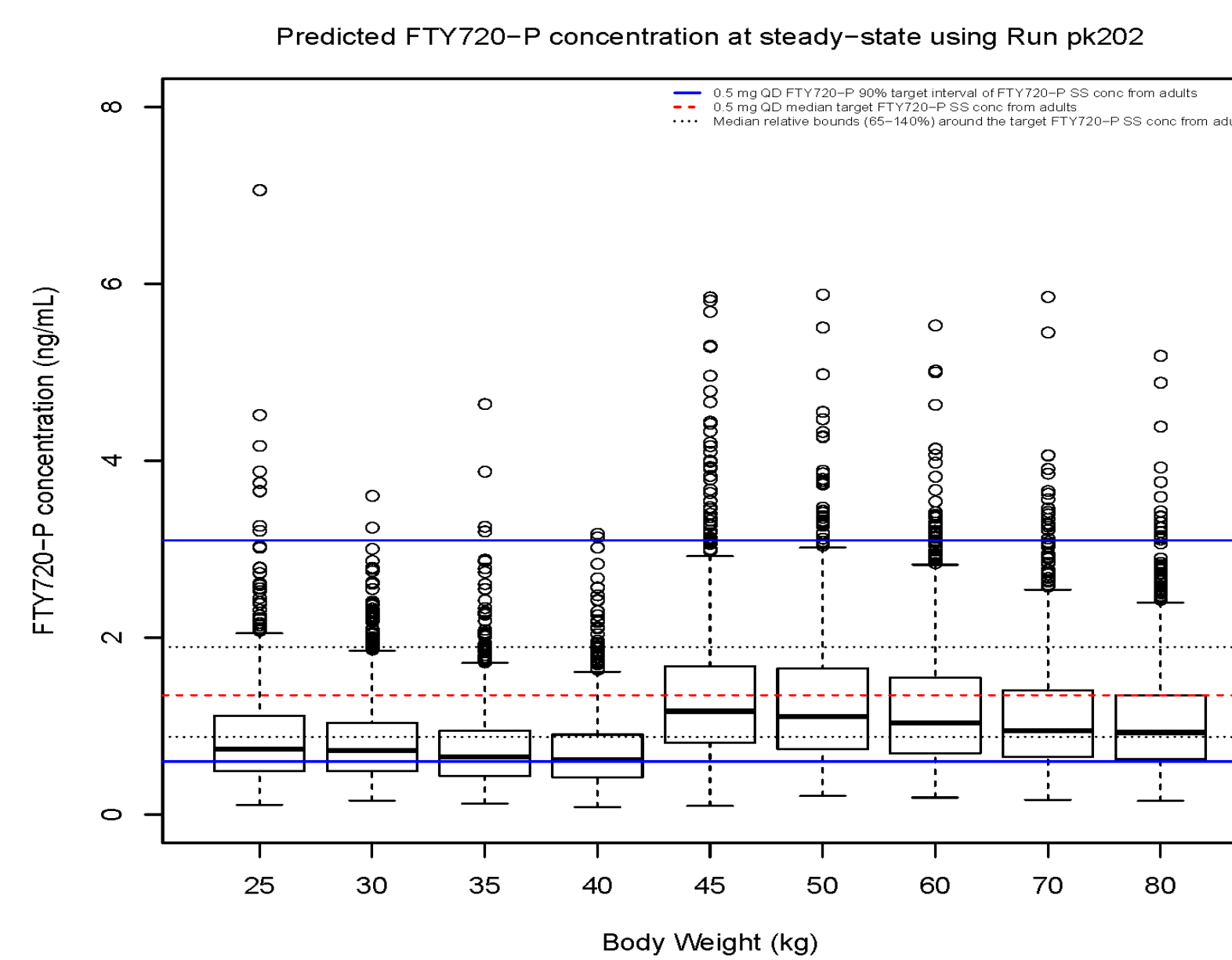
Open Circle: Observed Lymphocyte Count; Solid Line: Median of Observed Lymphocyte Count; Dashed Lines: 5th and 95th percentile of observed concentrations. Red Shaded Region: 95% Prediction Interval for Median of Predicted Lymphocyte Count; Blue Shaded Regions: 95% Prediction Intervals for the 5th and 95th percentiles of Predicted Lymphocyte Count



Simulations

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Predicted FTY720-P Steady-State Concentrations Using Final Population PK Model



Conclusions

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Population PK model

- Following administration of 0.5 mg per day of FTY720 in a pediatric population, the typical steady-state FTY720-P concentration for a body weight of 70 kg (0.978 ng/mL) was slightly below the adult target FTY720-P steady-state concentration level (median: 1.35 ng/mL, (90% CI: 0.62, 3.1)) but within the 90% CI around the median of the adult target FTY720-P steady-state concentration. The typical steady-state FTY720-P concentration in pediatric patients was also higher than the 65% relative bound (0.878 ng/mL) of the adult target FTY720-P steady-state concentration level.
- The steady-state FTY720-P concentrations were dose proportional following 0.25 mg and 0.50 mg capsule formulation of FTY720 in the pediatric population.
- The steady-state FTY720-P concentrations decreased slightly with an increasing weight. The decrease in concentration was non-linear. An increase of 10 kg weight from 20 to 30 kg and from 70 to 80 kg resulted in a 15.2% and a 5.3% decrease in FTY720-P concentrations, respectively.

Exposure-lymphocyte count model

- The baseline lymphocyte count was estimated to be 17.2% higher in pediatric patients compared to the adult population.
- Both $I_{\max}$ and IC_{50} were comparable between pediatric and adult populations with $I_{\max}$ 6% lower and IC_{50} 12% lower in pediatric versus adult patients.
- The baseline lymphocyte count was slightly higher for the higher baseline weight. A 10-kg increase in weight (from 70 to 80 kg) resulted in only a 2% increase in lymphocyte count.