

Posterior predictive check to assess similarity of systemic exposure profiles of an inhaled drug product pre- and post- manufacturing modification

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Background

- Cystic fibrosis (CF) is the most common life-shortening monogenetic disorder in Caucasians, characterized by a gradually progressive obstructive lung disease due to the accumulation of viscous endobronchial secretions in the airways.
- Acquisition of chronic *P. aeruginosa* in the lungs of CF patients is associated with accelerated lung function decline.
- Tobramycin Inhalation Powder (TIP) is a novel drug-device combination designed to deliver tobramycin, an aminoglycoside antibiotic active against gram-negative bacteria, to the lungs. Tobramycin has been shown to have negligible bioavailability from the gastrointestinal tract.
- The manufacturing process of TIP was modified to improve emulsion stability and yield, and produce the drug product consistently on a commercial scale; no changes to the pharmaceutical formulation were made.

Objective

- To assess similarity of tobramycin concentration-time profiles in serum of Phase III product (TIP-PhIII) and the marketed product (TIP-Mkt).

Methods

- The population PK model of TIP-PhIII was a two-compartment model with 1st-order absorption and 1st-order elimination, developed in NONMEM VI.
- A total of 662 concentration observations from 139 CF patients receiving single dose 28, 56, 84 and 112 mg, and 112 mg b.i.d. were included (Table 1).
- Typical apparent clearance CL/F was estimated 14.5 L/h, apparent central volume of distribution (Vd/F) 85.1 L, apparent peripheral volume of distribution (Vp/F) 210 L, absorption rate constant (Ka) 2.39 1/h and apparent intercompartmental clearance (Q/F) 6.43 L/h.
- Vd/F was found to increase nonlinearly with increasing body-mass index (BMI), and decrease with increasing FEV1% predicted.

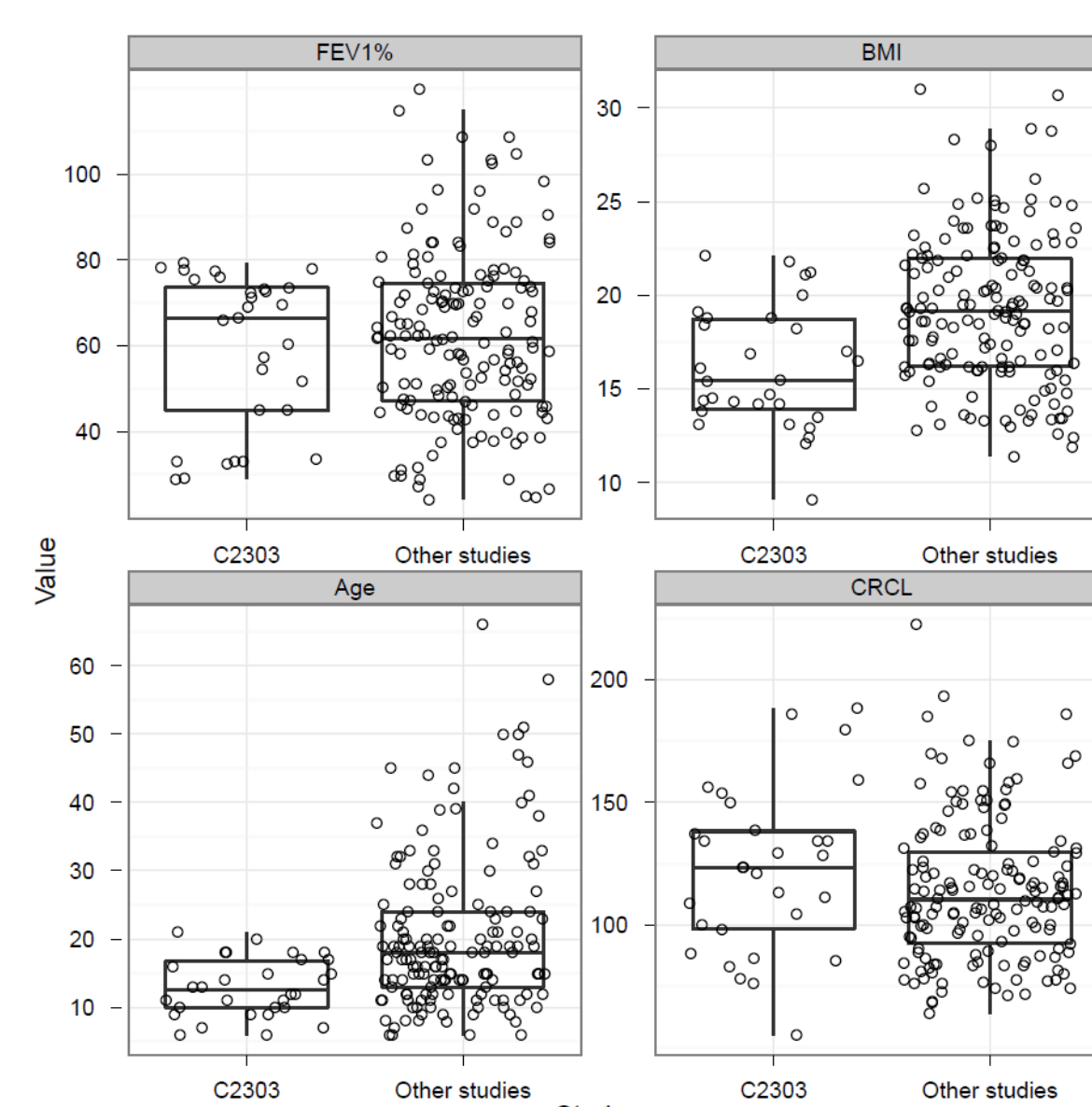
$$Vd / F = 85.1 \cdot \left(\frac{FEV1\%}{62.1} \right)^{-0.303} \cdot \left(\frac{BMI}{18.8} \right)^{0.624}$$

Table 1. Study designs and PK sampling times for studies contributing to the population PK analysis. Cycle is 28 days on, 28 days off treatment. All subjects were CF patients.

Study	Population	Treatment	Sampling times
TPI001	>=6 years old	Single dose of 28, 56, 84 and 112 mg TIP-PhIII	Pre-dose, 0.5, 1, 2, 4, 8, 12 hours post-dose for 64 subjects with PK data
C2301	Between 6 and 21 years old, FEV1 >= 25% to <= 80% predicted	Multiple dose 112 mg TIP-PhIII b.i.d. for two cycles	Pre-dose and 1 hour post-dose on day 1 and day 28 of each cycle for 62 subjects with PK data
C2302	>= 6 years old, FEV1 >= 25% to <= 75% predicted	Multiple dose 112 mg TIP-PhIII b.i.d. for two cycles	Pre-dose, one sample each in windows 0-2 and 2-5 hours post-dose on day 1 and day 28 of each cycle for 13 subjects with PK data
C2303	Between 6 and 21 years old, FEV1 >= 25% to <= 80% predicted	Multiple dose 112 mg TIP-Mkt b.i.d. for one cycle	Pre-dose, one sample each in windows 0-1, 1-2 and 2-6 hours post-dose on day 1 and day 28 of a cycle for 30 subjects with PK data

- Covariate values for patients administered TIP-Mkt were in the range of covariates in previous studies of TIP-PhIII (Figure 1).

Figure 1. Distributions of FEV1% predicted at baseline, body-mass index (kg/m²), age (years) and creatinine clearance (mL/min) for the PK analysis population of study C2303 (TIP-Mkt), contrasted with distributions for pooled PK analysis populations of other studies TPI001, C2301 and C2302 that were used to develop the population PK model of TIP-PhIII.



- Posterior predictive check (PPC) simulation was performed to assess whether the population PK model of TIP-PhIII is compatible with TIP-Mkt serum concentration data.
- We simulated 1000 concentration-time profiles using the population PK model of TIP-PhIII, sampling model parameters using the multivariate normal distribution with the approximate variance-covariance matrix returned by NONMEM. Covariate values BMI and FEV1% at baseline were sampled with replacement from values of patients in the PK population of Study C2303 (TIP-Mkt). Simulation was implemented in R 2.10.1.
- The normalized prediction distribution error (NPDE) analysis was performed on simulated and observed data using R package npde version 1.2.1.
- All statistical tests were performed at the pre-specified significance level of 0.05.
- Visual predictive check (VPC) plots were constructed to assess the overall agreement between simulated and observed data.

Results

- Predictive simulations of serum concentration profiles using the population PK model for TIP-PhIII showed that the majority of observed concentrations for TIP-Mkt fall within the 90% predictive interval; proportion of data points outside the interval (13%) is close to expected 10% if the procedure was repeated on independent realizations of PK data with identical study design.
- Model adequately described the central tendency and variability of observed concentrations of the modified product (Figure 2 and Figure 3).
- Diagnostic plots and results of tests for normality of the NPDE distribution showed that null hypothesis that the distribution is normal is not rejected at pre-specified level of 0.05 (Figure 4).

Figure 2. Comparison of simulated and observed serum concentration time profiles for TIP-Mkt in Study C2303 on day 1 (visit 2). Data: white circles, cubic spline fit of the data: dashed line, mean of simulated concentrations: solid line, 5th and 95th percentiles of the predictive concentration distribution: gray area.

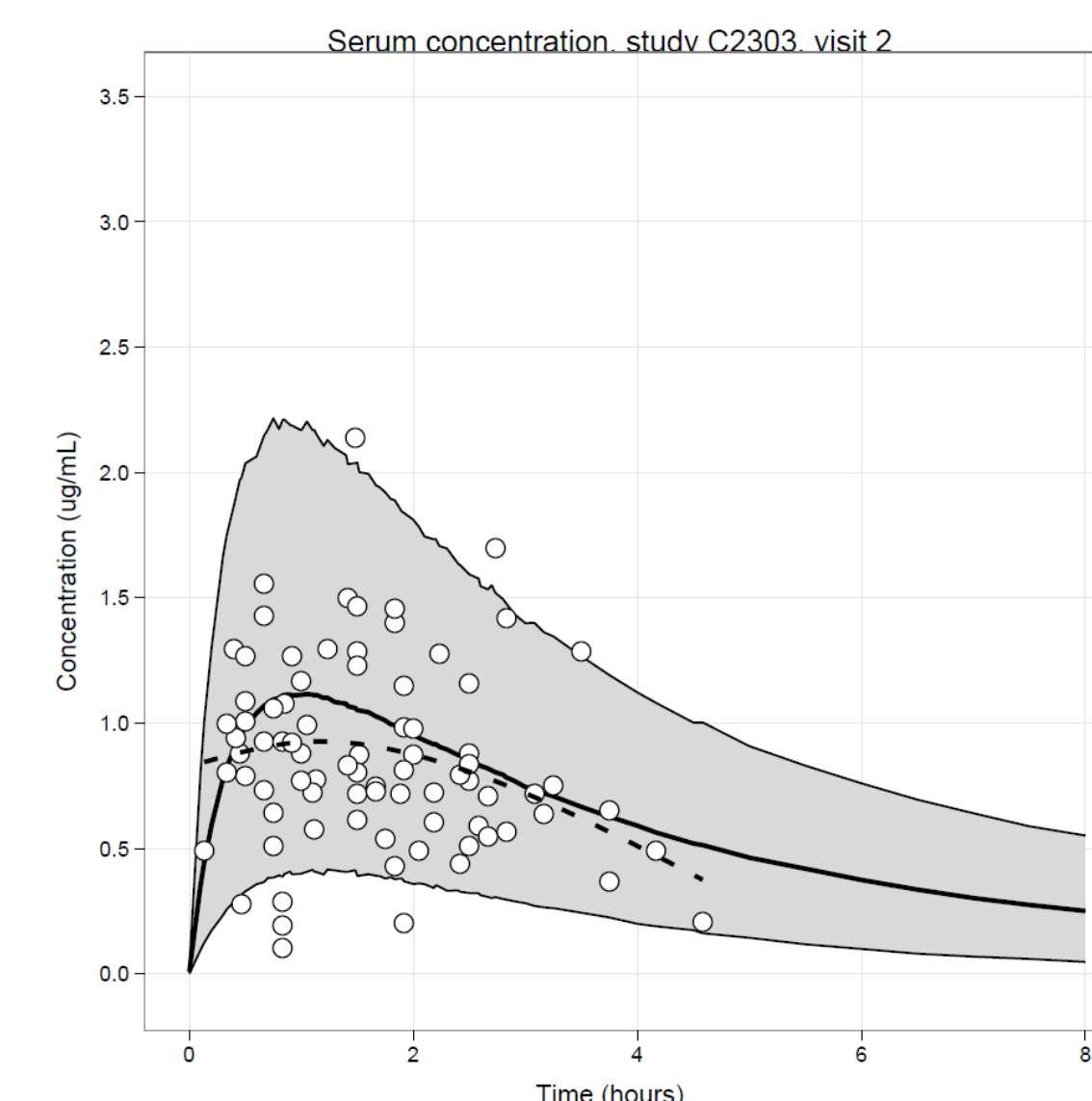


Figure 3. Comparison of simulated and observed serum concentration time profiles TIP-Mkt in Study C2303 on day 28 (visit 3). Data: white circles, cubic spline fit of the data: dashed line, mean of simulated concentrations: solid line, 5th and 95th percentiles of the predictive concentration distribution: gray area

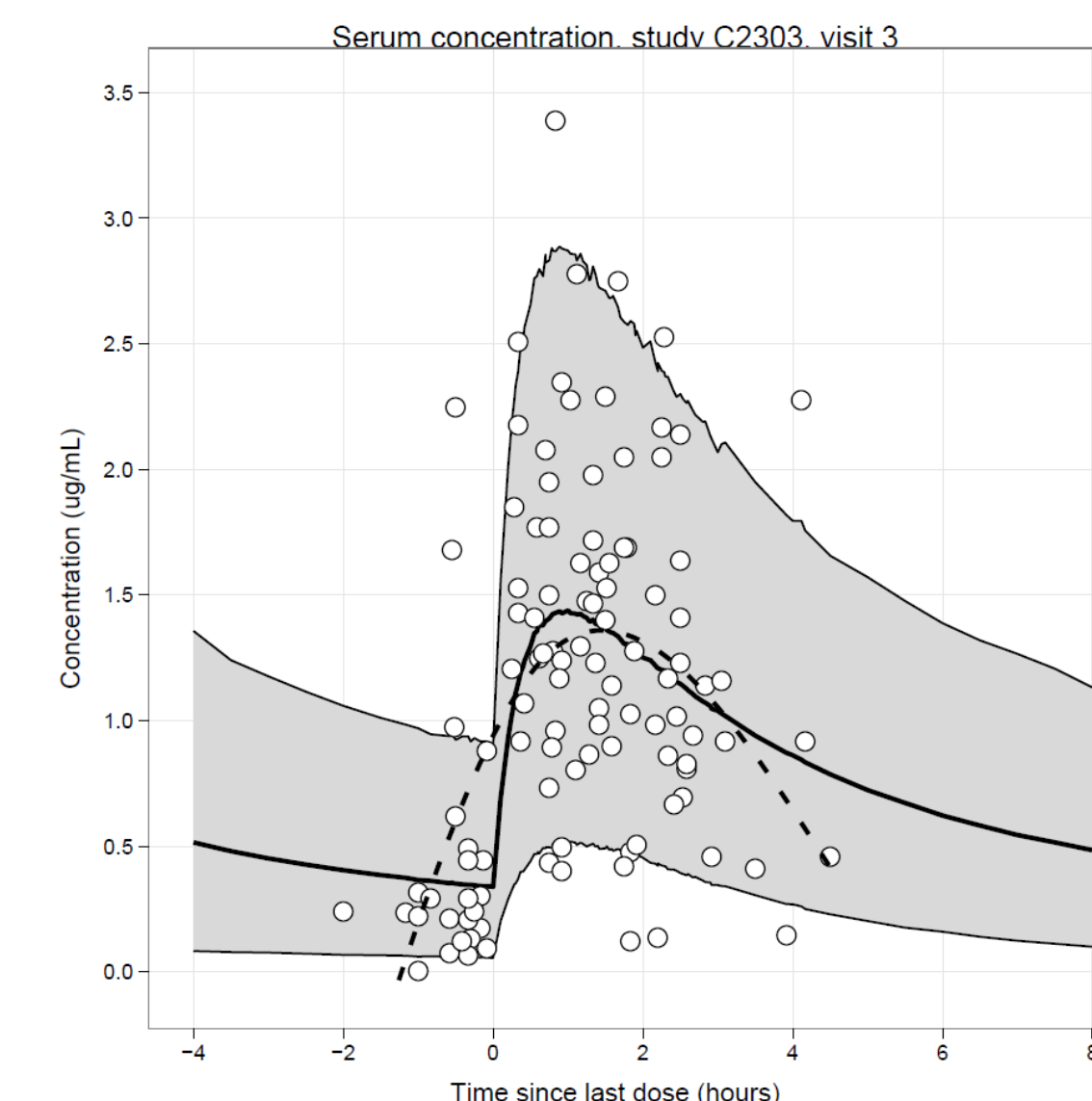
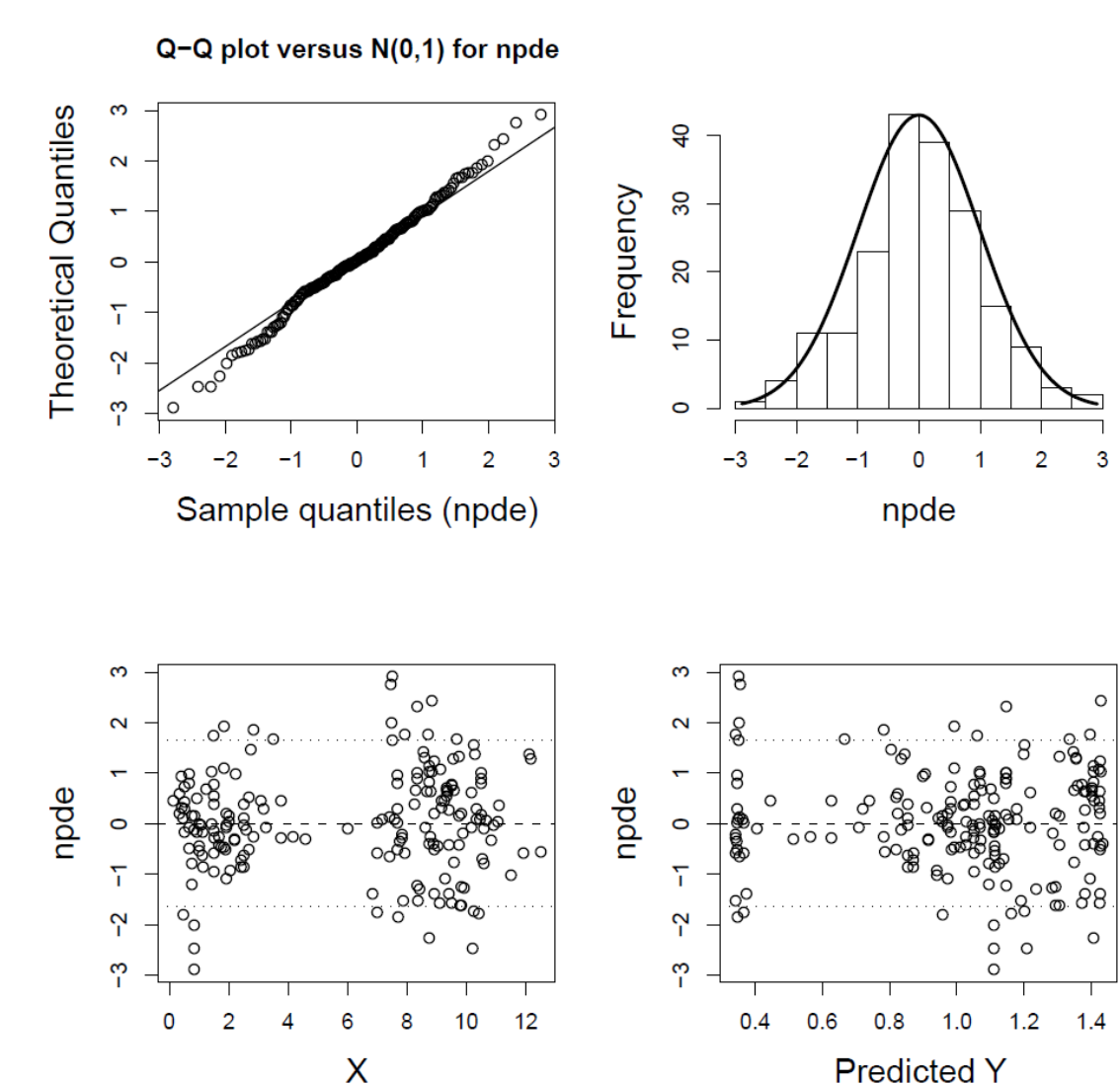


Figure 4. Distribution of normalized prediction distribution errors (NPDE) is not different from a standard normal distribution at pre-specified significance level 0.05, indicating that systemic exposure profiles of TIP-Mkt (Study C2303) are consistent with the population PK model of TIP-PhIII.



Conclusions

- Serum exposure profiles of tobramycin after inhalation of TIP-Mkt are not statistically significantly different from exposure after inhalation of TIP-PhIII expected based on the population PK model of TIP-PhIII.
- Statistical equivalence of exposures implies that estimates of PK model parameters and effect of covariates reported in the existing population PK model apply to TIP-Mkt as well.

Clinical implications

- Predicted bioavailabilities of TIP-Mkt and TIP-PhIII after administration of the same dose and formulation are similar to such a degree that no clinical difference is expected between their effects, with respect to both efficacy and safety.

References

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