

# Population Pharmacokinetic Modeling of TR-700 in Patients with Complicated Skin and Skin Structure Infections

John Mondick<sup>1</sup>, Marc R. Gastonguay<sup>1</sup>, Paul Bien<sup>2</sup>, Carisa DeAnda<sup>2</sup>, Philippe Prokocimer<sup>2</sup>

<sup>1</sup>Metrum Research Group, Tariffville, CT; <sup>2</sup>Trius Therapeutics, San Diego, CA,

## Abstract

**Background:** TR-700 is the microbiologically active moiety of torezolid phosphate (TR-701), an oxazolidinone analog phosphate prodrug active against all clinically relevant gram-positive pathogens and some selected gram-negative pathogens. The goal of this work was to characterize the population pharmacokinetics (PK) and estimate the effects of covariates for TR-700 in patients with complicated skin and skin structure infections (cSSSI).

**Methods:** PK data from a Phase II study in patients with cSSSI (n=175) administered 200, 300, or 400 mg torezolid phosphate QD for 5 to 7 days was used for model development. PK data were analyzed using nonlinear mixed effects modeling. Model qualification included nonparametric bootstrap and predictive checks.

**Results:** The population PK of TR-700 in patients with cSSSI was described by a two-compartment model with zero-order dose delivery to the depot compartment and subsequent first-order absorption, parameterized in terms of apparent oral clearance (CL/F), apparent volume of distribution for central and peripheral compartments (V<sub>c</sub>/F, V<sub>p</sub>/F), inter-compartmental clearance (Q/F), zero-order dose duration (D<sub>1</sub>), and first-order absorption (k<sub>a</sub>). The effects of ideal body weight (IBW) on CL/F and V<sub>c</sub>/F were described using power models normalized to 70 kg, with exponent estimates of 0.414 and 0.940. Age and race effects on CL/F were well defined but were not clinically significant. The typical PK parameters (inter-subject variability) for the reference covariates (white race, IBW = 70 kg, 40 years) were 11.7 (23.9%) L/h, 114 (18.6%) L, 52.4 L, 3.58 L/h, 1.32 (63.5%) h<sup>-1</sup>, and 1.00 h, for CL/F, V<sub>c</sub>/F, V<sub>p</sub>/F, Q/F, k<sub>a</sub>, and D<sub>1</sub>, respectively.

**Conclusions:** The population PK model provided a reasonable description of TR-700 disposition in patients with cSSSI. Although variability in TR-700 PK was primarily affected by IBW, inclusion of covariate factors resulted in a relatively small reduction of unexplained variability.

## Background

Current clinical practice dictates the administration of vancomycin, daptomycin, or linezolid to patients with documented or suspected methicillin-resistant *Staphylococcus aureus* (MRSA) as first-line therapy until culture results become available. The only agent allowing oral treatment of MRSA is Ziyvox® (linezolid), approved in 2000, representing the first (and only) oxazolidinone antibiotic available to practitioners. Linezolid has excellent bioavailability, good efficacy, and an acceptable safety profile. However, reversible myelosuppression (including anemia, leucopenia, thrombocytopenia, or pancytopenia) has been reported in patients treated with linezolid for > 2 weeks [1].

TR-700, the microbiologically active moiety of the prodrug torezolid phosphate (TR-701), is a linezolid analog that inhibits protein synthesis in bacteria and is active against all clinically relevant gram-positive pathogens and some selected gram-negative pathogens. Susceptibility testing against a variety of gram-positive aerobic and anaerobic bacteria demonstrate that TR-700 is 4- to 8-fold more potent than linezolid, generating minimum inhibitory concentration of 90% isolates (MIC<sub>90</sub>) values of 0.25 to 0.5 µg/mL for all staphylococci tested (including MRSA), compared with MIC<sub>90</sub> values of 1 to 4 µg/mL for linezolid [2].

## Objectives

Describe the population pharmacokinetics (PK) of TR-700 when administered as torezolid phosphate in patients with cSSSI and to quantify the effects of individual-specific covariate factors that are predictive of unexplained random variability in TR-700 PK.

## Methods

### Study Data

- Concentration-time data from a multicenter, randomized, double-blind, non-controlled Phase 2 study with oral torezolid phosphate for the treatment of cSSSI in adults was used for model development.
- Patients were randomized to receive torezolid phosphate at doses of 200, 300, or 400 mg once daily (QD). Patients were administered at least 5 but no more than 7 days of torezolid phosphate therapy.
- Plasma samples for population PK analysis were obtained in all patients on day 3 (predose, 1 hour) and on the last day of therapy (predose, 1, 2, 4, and 8 hours).
- Population PK data were assembled and formatted for analyses using the R software (version 2.72; R Development Core Team; www.rproject.org).

### Model and Modeling Assumptions

- Data were analyzed using nonlinear mixed-effects modeling with the NONMEM software, Version V1, Level 1.0 [3].
- Model selection was guided by various goodness-of-fit criteria, including diagnostic scatter plots, convergence with at least 2 significant digits, plausibility of parameter estimates, precision of parameter estimates, correlation between model parameter estimation errors < 0.95, and the Akaike information criterion (AIC), given the minimum objective function value and number of estimated parameters.
- Covariate modeling was conducted using a full model approach emphasizing parameter estimation rather than stepwise hypothesis testing [4].
- Continuous covariate effects were modeled using a normalized power model while the effects of categorical covariates were similarly described.
- Individual, clinical and demographic covariate factors included in the population PK data set were: sex, weight (kg), ideal body weight (kg), age (years), race, hepatic function (AST, ALT, total bilirubin) and Cockcroft-Gault calculated creatinine clearance.
- Log-normal distributions were assumed for all random effects. Inter-individual variability (IIV) was estimated for CL/F, V<sub>c</sub>/F, and k<sub>a</sub>. Inter-occasion variability (IOV) was estimated for F<sub>1</sub>, D<sub>1</sub>, and k<sub>a</sub>.
- Residual error was described by proportional error model.
- Parameter precision was investigated via non-parametric bootstrap (1000 replicates with replacement using the individual as the sampling unit) [5].
- The final model was evaluated using a predictive check (500 Monte Carlo simulation replicates of the original data) [6].

## Results

### Analysis Population and Data Characteristics

- Of the 188 patients enrolled, 175 patients contributed 1142 plasma TR-700 concentrations to the PK data set.
- The study population consisted of 115 males and 60 females with ages ranging from 18 to 68 years and weights ranging from 47 to 118 kg.
- The majority of enrolled patients were Caucasian (n=132) or African American (n=40), with 1 Asian, 1 Pacific Islander, and 1 patient designated as "other race"

## Results (cont)

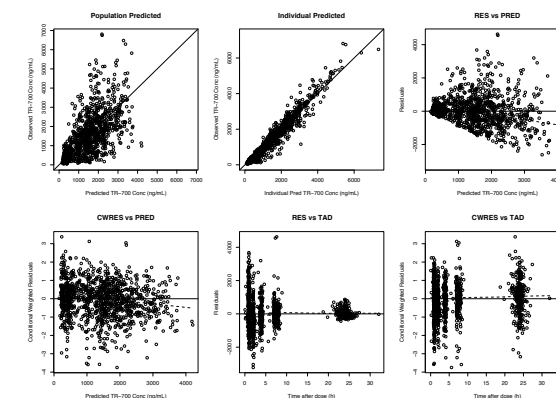
Table 1: Summary of Continuous Covariates

Covariate	N	Minimum	Maximum	Median	Mean	SD
Age (y)	175	18.0	68.0	35.0	36.20	12.20
Weight (kg)	175	47.0	118.0	79.8	81.50	14.50
Body Mass Index (kg/m <sup>2</sup> )	175	18.5	36.0	26.7	27.00	4.37
Ideal Body Weight (kg)	175	43.2	93.7	68.4	67.60	9.60
Lean Body Mass (kg)	175	36.9	82.4	58.7	58.60	9.20
Creatinine CL (mL/min)	175	58.8	150.0	128.0	124.00	24.40
AST (U/L)	175	10.0	116.0	20.0	25.30	14.90
ALT (U/L)	175	4.0	155.0	19.0	26.80	21.80
Total Bilirubin (µM)	175	2.0	29.0	7.0	7.26	4.68

### Population PK Modeling

- The population PK of TR-700 in patients with cSSSI was described by a two-compartment model with zero-order dose delivery to the depot compartment and subsequent first-order absorption.
- Diagnostic plots revealed that the model was consistent with the observed data and no systematic bias was evident (Figure 1).
- Effects of renal and hepatic function on TR-700 PK were poorly defined, with few patients exhibiting measures outside of normal ranges. Therefore, hepatic and renal function were not considered in the full covariate model.
- The full covariate model (Equation 1) included effects of IBW, age, and race (dichotomized to Caucasian and non-Caucasian) on CL/F and IBW on V<sub>c</sub>/F.
- Full model results and 95% CIs from the bootstrap analysis are provided in the Table 2.
- Normalized typical value parameter distributions for covariates relative to the reference population were plotted to examine the magnitude of covariate effects (Figure 2).

Figure 1: Full population PK model diagnostic plots



## Results (cont)

$$\frac{CL}{F_1} = \theta_{CL/F} \cdot \left( \frac{IBW_i(\text{kg})}{70(\text{kg})} \right)^{0.75} \cdot \left( \frac{AGE_i(\text{years})}{40(\text{years})} \right)^{\theta_{AGE}} \cdot \theta_{RACE} \cdot \exp^{\theta_{F1}} \quad (1)$$

$$V_c = \theta_{V_c/F} \cdot \left( \frac{IBW_i(\text{kg})}{70(\text{kg})} \right)^{0.75} \cdot \exp^{\theta_{V_c/F}}$$

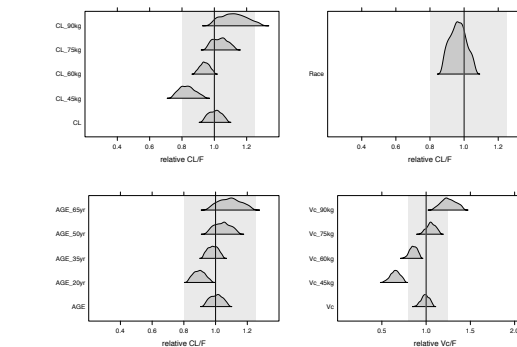
Table 2: Parameter Estimates from Final Population Pharmacokinetic Model

	Point Estimate	%RSE	95% CI	IIV	IOV
CL/F	11.7 (L/h)	4.25	(10.8, 12.8)	23.9%	
· (IBW/70) <sup>0.414</sup>	0.414	44.0	(0.0306, 0.798)		
· (AGE/55) <sup>0.08</sup>	0.156	56.3	(-0.0111, 0.345)		
· θ <sub>RACE,CL</sub>	0.964	5.58	(0.857, 1.09)		
V <sub>c</sub> /F	114 (L)	4.18	(69.1, 124)	18.6%	
· (IBW/70) <sup>0.940</sup>	0.940	19.2	(0.571, 1.75)		
V <sub>p</sub> /F	52.4 (L)	21.8	(33.6, 90.3)		
Q/F	3.58 (L/h)	19.1	(2.06, 71.6)		
k <sub>a</sub>	1.32 (h <sup>-1</sup> )	9.33	(1.01, 1.78)	63.5%	92.0%
D <sub>1</sub>	1.00 (h)	6.23	(0.845, 1.2)		105%
F <sub>1</sub>	1	Fixed			21.9%

Residual Variability  
Prop. Error CV 23.4 (CV%)

%RSE = percent relative standard error of the parameter estimate, IIV = inter-individual variability, IOV = inter-occasion variability, CL/F = apparent oral clearance, V<sub>c</sub>/F = apparent volume of distribution in the central compartment, V<sub>p</sub>/F = apparent volume of distribution in the peripheral compartment, Q/F = apparent inter-compartmental clearance, D<sub>1</sub> = zero-order absorption duration, k<sub>a</sub> = first-order absorption rate, F<sub>1</sub> = bioavailability

Figure 2: Covariate Effects on CL/F and V<sub>c</sub>/F. Typical values are presented for the reference 70 kg (IBW), 40 year old, Caucasian patient. Distributions for relative parameter values are presented for patient ideal body weights of 45, 60, 75, and 90 kg, and ages of 20, 35, 50, and 65 years. The gray shaded area represents a range of 80% to 125% of the reference value where little clinical impact would be expected.



## Conclusions

- The population PK of TR-700 in patients with cSSSI was well-described by a two-compartment model with zero-order dose delivery to the depot compartment and subsequent first-order absorption.
- The TR-700 population PK model evaluation results, which included the results of a predictive check and a non-parametric bootstrap, revealed that the final model provided a reliable description of the data with good precision of structural model and variance parameter estimates.
- Variability in CL/F and V<sub>c</sub>/F was primarily affected by IBW. Comparing the extremes of the weight range in the study, the typical values of CL/F and V<sub>c</sub>/F are expected to be 1.35-fold and 1.91-fold greater, respectively, for a 90 kg subject compared with a 45 kg subject.
- Age did not affect CL/F. The probability for the typical patient at ages of 20, 35, 50, and 65 years to have CL/F values within the 80-125% boundaries of the null effect was near 100%.
- Effects of race on CL/F were well-defined but were not significantly different between Caucasian and non-Caucasian populations, which was largely comprised of African American patients. Therefore, race effects when comparing whites to African Americans are likely to be clinically unimportant.
- Effects of renal and hepatic function on TR-700 PK were poorly defined, with few patients exhibiting measures of renal or hepatic function outside of the normal ranges. Renal and hepatic function measures were not included in the full covariate model.
- The addition of covariate factors resulted in a relatively small reduction of unexplained inter-individual variability. Unexplained random variability was slightly reduced for CL/F (23.9 %CV) and V<sub>c</sub>/F (18.6 %CV) in the final model, when compared to the base model CL/F (24.7 %CV) and V<sub>c</sub>/F (21.9 %CV) variance estimates.
- The high potency and PK disposition of TR-700 should allow for a once daily torezolid phosphate dosing regimen, lower dose, and shorter course of therapy than linezolid and provide a comparable level of efficacy.

## References

- French G. Safety and tolerability of linezolid. J Antimicrob Chemother. 2003 May; 51 Suppl 2:i45-53
- Lemaire S, Van Bambeke F, Appelbaum PC, Tulkens PM. Cellular pharmacokinetics and intracellular activity of torezolid (TR-700): studies with human macrophage (THP-1) and endothelial (HUVEC) cell lines. J Antimicrob Chemother. 2009 Nov; 64(5):1035-43.
- Beal, S.L., Sheiner, L.B. and Boeckmann, A.J., (eds.). NONMEM Users Guide: Part-VII, (1989-2006) (Icon Development Solutions, Ellicott City, Maryland, USA)
- Burnham, K.P. and Anderson, D.R. Model selection and multimodel inference: A practical information-theoretic approach (Springer-Verlag, New York, 2002).
- Gobburu, J.V. and Lawrence, J. Application of resampling techniques to estimate exact significance levels for covariate selection during nonlinear mixed effects model building: some inferences. Pharmaceutical Research 19 (2002): 9298.
- Yano, Y., Beal, S.L. and Sheiner, L.B. Evaluating pharmacokinetic/pharmacodynamic models using the posterior predictive check. Journal of Pharmacokinetics and Biopharmaceutics 28 (2001): 171192.