

Population Pharmacokinetic (PK) Pharmacodynamic (PD) Evaluation of Eritoran (E5564) in Patients with Severe Sepsis

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ABSTRACT

Objectives: Eritoran is a synthetic analogue of the Lipid A portion of the lipopolysaccharide (endotoxin) molecule and an antagonist of TLR4 (toll-like receptor 4). Eritoran suppresses endotoxin-induced TNF production and is being investigated for treatment of patients with severe sepsis (SPAT). The objective was to develop a population PK / PD (mortality) model for eritoran in SPATs. **Methods:** Eritoran concentrations were from a double blind randomized placebo controlled study in ICUs. Approximately 300 SPATs who met study enrollment criteria each received either placebo, 45 mg or 105 mg eritoran IV divided over 6 days, doses given every 12h. Sparse sampling involved taking samples at 3 of the following times: For dosing-interval (DI) 1: pre-dose (0 hr), 4 and 8 hours after start of infusion. For the next 9 DIs: 0, 4 and 7 hours after start of infusion. For final DI: 0, 7, 12 hr, and 2, 4, 6 and 8 days after start of infusion. Eritoran concentrations were used for PK modeling. Exposure was correlated with survival using binomial logistic regression. Data were analyzed using NONMEM V Level 1.1. **Results:** PK was described using a linear two compartment model. Clearance (CL) was estimated as $CL = 0.11 \cdot (IL6/10) \cdot 0.061 \cdot (HDL/80) \cdot 0.209 \cdot (BSA/1.8) \cdot 0.87$, central volume (V1) as $V1 = 3.65 \cdot (BSA/1.8) \cdot 1.02$, inter-compartmental clearance (Q) as $Q = 0.0357 \text{ L/h}$ and peripheral volume (V2) as $V2 = 1.73 \text{ L}$. After including covariates in the model, inter-individual variability (IIV) reduced from 56% to 46% and from 39% to 36.6% for CL and V1, respectively. The final PD model was a logistic regression model where baseline age, APACHE II Score, PROM Score and IL6 were identified as covariates. The model based $C_{ss,avg}$ showed a trend that correlated with higher rate of survival but did not reach statistical significance. As an example using this PD model, we can estimate that a patient (age=25 years, PROM=40, IL6=500, APACHE=30) has a survival probability of 55% if untreated and 74% with a $C_{ss,ave} = 10,000 \text{ ng/ml}$ (corresponding to 105 mg of eritoran). **Conclusions:** Eritoran PK is well described by the linear two compartment model. This PK / PD model, incorporating four covariates (age, PROM, IL6, APACHE), may predict survival rates based on $C_{ss,avg}$.

METHODS

Study Design

This was a double blind randomized placebo controlled study in SPATs with 100 SPATs per treatment group. The Eritoran dose regimen is presented in Table 1. PK samples were taken at 3 randomly selected points from the following specified times: pre-dose (0 hr), end of infusion (4 hr) and 8 hours after starting the first infusion. For the next 9 doses samples were at 0, 4 and 7 hours after starting. For final dose samples were at 0, 7, 12 hr, and 2, 4, 6 and 8 days after dose. Patient survival was also recorded.

Table 1 – Dose Regimen

Load Dose Hour 0	Load Dose 2 Hour 12	Maintenance Dose q12h	Total (mg)
3 mg/h x 4 h	3 mg/h x 2 h	1.5 mg/h x 2 h	45
7 mg/r x 4 h	7 mg/h x 2 h	3.5 mg/h x 2 h	105

PK Database

The final data base used for the PK analysis consisted of 466 observations from 182 SPATs (2.6 samples per patient). A listing of demographic information for the PK database is in Table 2.

Table 2 – Baseline Demographics for PK Database

Demog (Units)	Mean (SD)	Median	Range
Age (y)	56.1 (16.33)	57.0	19.0-84.0
Weight (kg)	89.0 (33.0)	84.0	42.3-327
BMI (m ² /kg)	31.5 (10.9)	29.1	16.5-98.8
BSA (m ²)	2.05 (0.39)	2.02	1.35-4.30
Bilirubin (umol/L)	25.0 (33.6)	13.84	0-219
ALT (IU/L)	149 (538)	33.0	7-4816
AST (IU/L)	179 (485)	42.0	6-3457
LDL (mmol/L)	1.26 (0.76)	1.14	0-4.0145
HDL (mmol/L)	0.68 (0.40)	0.62	0.026-2.23
IL6 (pg/mL)	22257 (80227)	341	5-533692
Endotoxin	0.51 (1.27)	0.30	0.01-14.4
Apache II	24.6 (5.46)	25.0	14.0-36.0
PROM	53.2 (17.8)	56.0	20.0-80.0
Dose (mg)	45mg = 99; 105mg = 83		
Sex	Males = 88; Females = 94		
Shock	Yes = 96; No = 86		
Race	Caucasian = 126; Non Caucasian = 56		

PD Database

Survival data from 276 SPATs were used for the PD evaluation. The database included all SPATs receiving placebo and all SPATs on Eritoran who had evaluable PK. Summary statistics of exposure were included in the PKPD database (Treatment status, dose and $C_{ss,avg}$). The demographics were similar to the PK database.

Model Based Evaluation

NONMEM, version V, Level 1.1 and Compaq Digital Visual Fortran 6.6.3C was used. The First Order Conditional Estimation (FOCE) Method with interaction was used for the PK analysis. The Conditional method with LAPLACIAN and LIKELIHOOD options was used for PD. For PK, covariates had to reduce the objective function by at least 10 points (p<0.001), and improve one or more of the following: prediction of observed concentrations, lower inter-individual variance and residual variability. A lower level of significance (p<0.05) was used for the PD evaluation. Both PK and PD models were evaluated using nonparametric bootstrap. A visual predictive check was also performed. A permutation test was conducted for the PD model to establish the validity of the relationship of survival to Eritoran exposure

RESULTS

PK Model

The final PK model was a two-compartment model with first-order elimination. The model was parameterized for CL, V1, Q, and V2, with terms for inter-individual variability on CL, V1 and covariance between these two parameters. The PK model parameters are defined below.

$$CL = \theta_1 \cdot \left(\frac{IL6}{10} \right)^{\theta_2} \cdot \left(\frac{HDL}{80} \right)^{\theta_3} \cdot \left(\frac{BSA}{1.8} \right)^{\theta_4} \cdot \exp(\eta_1)$$

$$V1 = \left(\theta_5 \cdot \left(\frac{BSA}{1.8} \right)^{\theta_6} \right) \cdot \exp(\eta_2)$$

$$Q = \theta_7$$

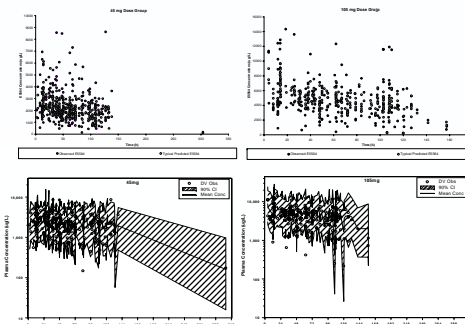
$$V2 = \theta_8$$

The final PK parameter estimates are listed in Table 3.

Table 3 – Final PK Model Parameters

Parameter (Units)	Population Mean (SE)	%CV Inter-Individual Variance (SE)
CL (L/h) Effect of IL6 Effect of HDL Effect of BSA	01 05 06 07	0.11 (7.2) 0.061 (19.5) -0.209 (20.6) 0.873 (23.6)
V1 (L) Effect of BSA	02 08	3.65 (7.0) 1.02 (27.7)
Q (L/h)	03	0.0357 (26.6)
V2 (L)	04	1.73 (38.8)
CCV Residual Error (as %CV)	23.8 (17.7)	
Additive Residual Error (ug/L)	37.3 (283)	
SE – standard error; NE – not estimated		

Adding 4 covariates reduced the objective function by 64.4 points (p<0.001). IIV on CL reduced from 56% to 46%; IIV on V1 reduced from 39% to 36.6%. Based on the covariate models, when HDL and IL6 are constant, CL increases 3.4-fold with a 4 fold increase in BSA. When BSA and IL6 are constant, CL decreases 2.7-fold as HDL increases 150-fold. When BSA and HDL are constant CL increases 1.4 fold as IL6 increases 200-fold. These ranges were represented in the database. Diagnostic plots are shown below



PD Model

The final PD model showed that probability of survival was dependent on APACHE II score, PROM score, IL6, age and calculated $C_{ss,avg}$. The best function is shown below:

$$\text{Logit} = -6.56 + 10.9 \cdot \frac{APACHE}{40} - 2.45 \cdot \frac{PROM}{50} + 0.00699 \cdot \frac{IL6}{1000} + 1.26 \cdot \frac{AGE}{50} - 0.0823 \cdot \frac{C_{ss}}{1000}$$

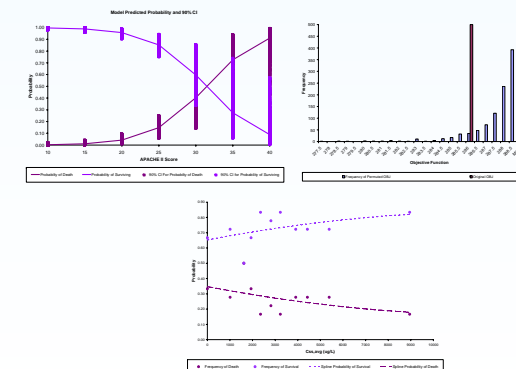
The final PD parameter estimates are provided in Table 4.

Table 4 – Final PD Model Parameters

Parameter	Population Mean	Standard Error*	
Baseline Probability	θ_1	-6.56	18.3
Scale for APACHE	θ_2	10.9	31.8
Scale for PROM	θ_3	-2.45	52.7
Scale for IL6	θ_4	0.00699	33.8
Scale for AGE	θ_5	1.26	38.8
Scale for CSS	θ_6	-0.0823	69.1

* - SE given as %CV

The effects of APACHE II and PROM scores were evaluated for collinearity as these two scores are related, however the removal of either covariate resulted in a substantial increase in the objective function. The permutation test supported the inclusion of these covariates. The condition number for the final model was 34.7. Diagnostic plots are provided below



CONCLUSIONS

Eritoran PK were best described with a 2 compartment model. IL6, HDL and BSA affected CL, BSA affected V1. Apache II Score, PROM Score and IL6 were predictors of survival in SPATs. Individual Eritoran exposure ($C_{ss,avg}$) conferred a survival advantage, but was not statistically significant. Subset analysis comparing 105 mg to placebo showed a statistically significant effect of treatment. Interaction analysis showed a different treatment effects on mortality at different APACHE II scores. These findings were consistent with the traditional statistical evaluations.