PIII-43

Pharmacokinetic/Pharmacodynamic Analysis of Data From a Phase III Trial of Linezolid IV/PO for the Treatment of Resistant Gram-Positive Bacterial Infections in Children

M Vo,[1] C Rubino,[1] B Cirincione,[1] J Bruss,[2] G Jungbluth,[2]

[1]Cognigen Corporation, Buffalo, NY and [2] Pharmacia Corporation, Kalamazoo, MI

ABSTRACT

Purpose. Linezolid (LZD), the first approved oxazolidinone, is effective against Gram-positive infections. Population pharmacokinetic/dynamic (PK/PD) analyses of Phase III data were conducted to evaluate exposure-response relationships in children to support a multiple-dosing regimen.

Methods. Sparse samples were obtained from patients aged birth to 11 years given 10mg/kg LZD every 8 hours. Patients were allowed to switch to oral (microencapsulated suspension) after six intravenous (IV) doses. Previously developed population pharmacokinetic models were used to predict individual pharmacokinetic parameters and exposure by Bayesian method. Relationships between exposure and effectiveness (clinical/microbiological cure) and safety (hematologic labs, adverse events) were explored graphically.

Results. Mean ± SD age and weight were 35 ± 38 months and 13 ± 11 kg. All models predicted individual concentrations with minimal bias and misspecification. Mean ± SD area under the concentration-time curve ($AUC_{0\text{-}24}$) was 147 ± 87 µg•h/mL, lower than adult exposure (179 ± 62 µg•h/mL). Predicted time above MIC_{90} was 54 ± 25% and independent of administration route or age. End-of-treatment and follow-up clinical cure rates were 85% and 90%. Microbiologic success rate was 89%. There was no apparent association between exposures as measured by AUC and effectiveness or safety endpoints.

Conclusions. Previously developed models properly estimated exposure and verify dosing of 10 mg/kg every 8 hours in children aged birth to 11 years. Elimination of oral and IV LZD was comparable. Effectiveness and safety were independent of exposure.

INTRODUCTION

Data from Phase I studies in children have demonstrated that pediatric patients dosed with 10 mg/kg IV have a similar maximum plasma concentration (Cmax) but higher clearance when corrected by body weight, and shorter apparent elimination half-life than adults receiving 600 mg of LZD. Thus, in children, LZD administered every 12 hours intravenously does not appear to exceed the MIC90 values for target pathogens for a sufficient portion of the dosing interval. An every-8-hour dose regimen for children was predicted to be more likely to achieve concentrations required to exceed the MIC90 values for target pathogens for a greater portion of the dosing interval. Because of the high degree of correlation between PK/PD parameters, this regimen would also yield a more favorable AUC:MIC ratio. This analysis of a multiple-dose, population PK study was conducted to evaluate the PK and PD in children receiving IV and oral (PO) LZD 10 mg/kg three times daily (TID).

OBJECTIVES

- To assess the predictive capability of the previously developed model for this Phase III data.
- To predict the population PK parameter estimates and measures of exposure for pediatric patients receiving LZD TID.
- To assess the relationship between effectiveness (clinical and microbiologic outcome) and exposure.
- To assess the effect of LZD exposure on the changes in hemoglobin concentration, platelet count, and absolute neutrophil counts.
- To assess any potential relationship between LZD exposure and reported cardiovascular or neurological adverse events.

METHODS

Study Design

- This was a Phase III, randomized (2:1 LZD to vancomyicn), open-label, comparator-control, multicenter, PK/PD study.
- Patients aged from birth to 11 years including term and preterm infants with suspected or proven resistant Gram-positive bacterial infections were enrolled in the trial.
- Initially, all LZD patients were given IV LZD in 30-120 minute infusions. After at least three days of IV dosing under the investigator's discretion, the patients were allowed to be switched to PO LZD. Patients with documented vancomycin-resistant enterococci (on or before Day 3) who had been randomized to vancomycin were also allowed to switch to LZD.
- Planned duration of therapy was to be at least 10 days with a maximum of 28 days.
- One plasma sample per day for the determination of LZD concentrations was drawn on Days 3, 10, 17, and 24 depending on the duration of LZD therapy.

Data Management

Real-time data assembly (RTDA) was conducted to ensure the quality of the data for the population pharmacokinetic analysis. Please refer to poster PIII-10 for more details.

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Vd: volume of distribution; Km: Michaelis constant;
Vm: maximum rate of elimination; CL: clearance
GAGE: gestational age; PNA: postnatal age in weeks;
WTKG: weight in kg; AGEW: age in weeks

Bayesian Prediction

- Three separate datasets were built for the samples collected from this study; one for plasma samples collected after IV administration; one for plasma samples collected after PO administration; and one for all samples combined, IV and PO.
- Since the population models described (**Table 1**) above were developed using plasma samples obtained after IV administration (IV model), the models were modified to accommodate for the PO concentrations (PO model).
- Due to the sparse sampling scheme, absorption rate constant (Ka) could not be estimated. A sensitivity analysis was conducted by evaluating the fit of several models in which Ka was fixed to different values within +/- 100% of the adult Ka value (0.37 /hr).
- Thus, there were two models available for Bayesian prediction. The IV model was applied to the IV concentrations. The PO model was applied to the PO concentrations. Since the only difference between the models was the presence of a Ka term in the PO model, the PO model was also applied to all concentrations combined (PO and IV).

Methods for Model Evaluation

- Goodness-of-fit plots: individual predicted versus measured concentrations and individual weighted residuals versus individual predicted concentrations
- Bias: percent error prediction

$$PEP_{ij} = \left(Cp_{ij} - PRED_{ij}\right) / PRED_{ij} * 100$$

- Precision: absolute percent error of prediction

$$APEP_{ij} = \left|PEP_{ij}\right|$$

Derived PK Parameter Calculations

- Individual Bayesian PK parameter estimates were used to predict a concentration-time profile at increments of 30 minutes out to 8 hours post-dose.

Exposure-Response Analyses

The exposure-response relationships were only evaluated graphically. No statistical analyses were performed.

RESULTS

Data

- 376 LZD concentrations from 195 patients were available for the PK analysis.
- Demographic characteristics of this population are provided in **Table 2**.
- 144 patients with clinical outcome assessment and 89 patients with microbiologic outcome assessment were available for the effectiveness analysis.
- 195 patients with at least one clinical lab value were available for the safety assessments.

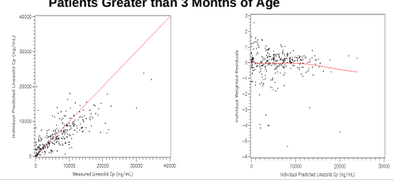
Table 2: Demographic Characteristics of Patients

Variable	Birth to 3 Months of Age	3 Months to 12 Years of Age
Number	41	154
Gestational Age (Weeks)		
Mean (SD)	32 (5)	Not Reported
Min-Max	24-42	
Age (weeks)		
Mean (SD)	3.6 (2.7)	190 (163)
Min-Max	0.9-12.3	14.0-612
Weight (kg)		
Mean (SD)	2.0 (1.2)	15.6 (10.3)
Min-Max	0.5-5.4	2.8-68.9
Gender-n (%)		
Males	23 (56)	85 (55)
Females	18 (44)	69 (45)

Bayesian Prediction

- Sensitivity analysis found the absorption rate constant of 0.37 hr^{-1} obtained from studies in an adult population to be appropriate for use in this pediatric population.
- No trend of biases or model misspecification was observed in the fitting of the IV and PO models to the data.

Figure 1: Goodness-of-Fit Plots (All Concentrations Combined) Patients Greater than 3 Months of Age



Exposure

- Mean predicted $AUC_{0\text{-}24}$ in patients aged 0 to 11 years (147 ± 87.0 µg•h/mL) was slightly lower than the adult exposure (179 ± 62 µg•h/mL) following a 600 mg every-12-hour regimen.
- The population mean predicted Cmax after IV administration was higher than that after PO administration. In contrast, the population mean predicted Cmin after IV infusion was lower than that after PO administration.
- One-hundred thirty-six patients had available MIC data to be used for AUC:MIC ratio calculation. The mean (SD) predicted AUC:MIC was 75.9 (116) ranging from 11.0 to 788.
- Patient predicted time above MIC_{90} (fixed at µg 4 /mL) was approximately 54% of the dosing interval.
- The summary statistics for AUC:MIC ratios using fixed MICs of 0.5, 1, 2, and 4 for all 195 patients are provided in **Table 4**.

Table 3: Summary Statistics of the Predicted Steady-State Exposure Measures

	IV/PO	Intravenous (IV)			Oral (PO)		
	$AUC_{0\text{-}24}$ (mcg*hr/mL)	Cmax (mcg/mL)	Cmin (mcg/mL)	Time Above MIC_{90}* %	Cmax (mcg/mL)	Cmin (mcg/mL)	Time Above MIC_{90}* %
Birth to 90 days (n)	41	41	41	41	5	5	5
Mean (SD)	175 (128)	14.4 (6.3)	4.12 (5.18)	61.4 (30.7)	9.19 (5.51)	5.31 (4.84)	62.5 (40.5)
90 days to 4 yrs (n)	109	105	105	105	58	58	58
Mean (SD)	121 (56.2)	12.6 (2.80)	1.50 (1.70)	46.1 (22.0)	6.44 (2.30)	2.59 (1.66)	55.8 (33.2)
5 to 11 years (n)	45	45	45	45	26	26	26
Mean (SD)	187 (81.6)	14.3 (3.45)	3.06 (2.79)	65.6 (21.0)	10.4 (3.26)	5.98 (3.05)	83.4 (17.8)
All Patients (n)	195	191	191	191	89	89	89
Mean (SD)	147 (87.0)	13.4 (4.03)	2.43 (3.20)	54.0 (25.3)	7.74 (3.33)	3.73 (2.83)	64.3 (32.1)

Table 4: Predicted AUC:MIC Ratio at Fixed MIC Values (n=195)

MIC	0.5 mcg/mL	1 mcg/mL	2 mcg/mL	4 mcg/mL
Mean (SD)	295 (174)	147 (87.0)	73.7 (43.5)	36.9 (21.8)
Median	251	125	62.6	31.3
Min	27.3	13.7	6.82	3.41
Max	1330	666	333	167

Exposure-Response Relationship

- No apparent association between exposure (AUC or T>MIC_{90}) and effectiveness was observed (**Figures 2** and **3**).
- Clinical cure rate was 85% and 90% for end-of-treatment and follow-up, respectively.
- Microbiologic success rate was 89%.
- No association between exposure and clinical lab values was identified (**Figures 4** and **5**).
- No apparent relationship between the reported adverse event and exposure was observed (**Figure 6**).

Figure 2: Frequency Distribution Histogram of Individual $AUC_{0\text{-}24}$ Values Stratified by Clinical Response at End-of-Treatment

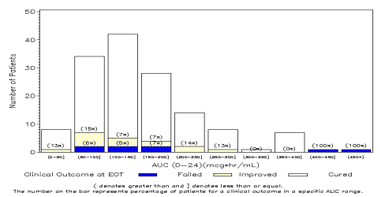
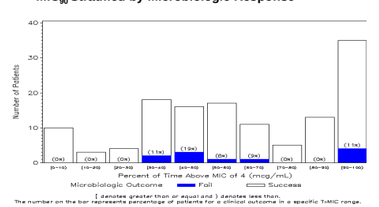


Figure 3: Frequency Distribution Histogram of Percent Time above MIC_{90} Stratified by Microbiologic Response



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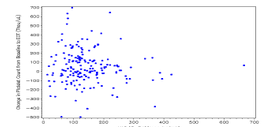

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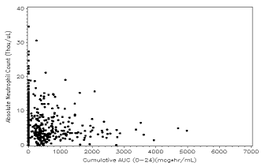

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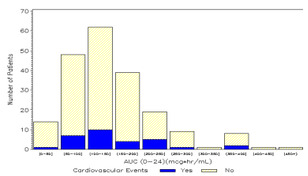

CONCLUSIONS

- The pharmacokinetics between the linezolid oral formulation and the intravenous formulation were comparable.
- Exposure in children receiving 10 mg/kg linezolid every 8 hours is comparable to that in adults receiving 600 mg linezolid every 12 hours.
- Mean (SD) predicted percent of a dosing interval spent above an MIC_{90} (4 mcg/mL) was 54.0 (25.3)%.
- The mean percent time above MIC_{90} after oral administration was higher than after intravenous administration (63% for oral and 54% for intravenous).
- Mean (SD) predicted AUC:MIC ratio, in patients with an MIC value, was 75.9 (116).
- Clinical and microbiologic success rates were high (>80%) and independent of levels of exposure ($AUC_{0\text{-}24}$ and T>MIC).
- No association was observed between exposure and safety indices.
- These population PK/PD analyses helped support the current indication for linezolid in children.

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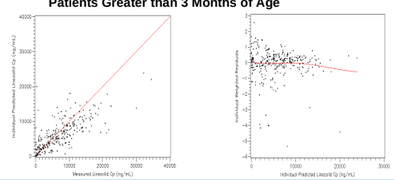

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Exposure-Response Relationship

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- Microbiologic success rate was 89%.
- No association between exposure and clinical lab values was identified (**Figures 4** and **5**).
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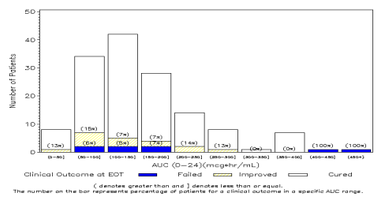

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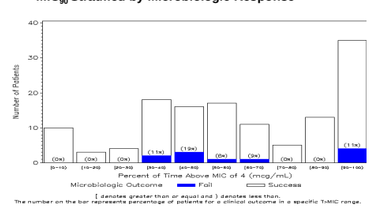
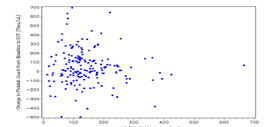


Figure 4: Scatterplot of Change in Platelet Count from Baseline to End-of-Treatment



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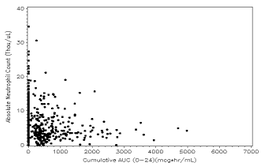
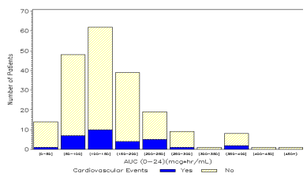


Figure 6: Frequency Distribution Histogram of Individual $AUC_{0\text{-}24}$ Values with Patients with Any Cardiovascular Adverse Event Highlighted



CONCLUSIONS

- The pharmacokinetics between the linezolid oral formulation and the intravenous formulation were comparable.
- Exposure in children receiving 10 mg/kg linezolid every 8 hours is comparable to that in adults receiving 600 mg linezolid every 12 hours.
- Mean (SD) predicted percent of a dosing interval spent above an MIC_{90} (4 mcg/mL) was 54.0 (25.3)%.
- The mean percent time above MIC_{90} after oral administration was higher than after intravenous administration (63% for oral and 54% for intravenous).
- Mean (SD) predicted AUC:MIC ratio, in patients with an MIC value, was 75.9 (116).
- Clinical and microbiologic success rates were high (>80%) and independent of levels of exposure ($AUC_{0\text{-}24}$ and T>MIC).
- No association was observed between exposure and safety indices.
- These population PK/PD analyses helped support the current indication for linezolid in children.