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Comparison of Linezolid Pharmacokinetics from Phase I Studies of Japanese and Caucasians

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ABSTRACT

Purpose. This bridging analysis compared pharmacokinetic (PK) parameters for linezolid (lzd) observed in Japanese (J) and Caucasians (C) in traditional PK Phase I studies.

Methods. PK data were pooled from 5 studies of lzd administered to healthy males as 125-625mg multiple (BID) IV or oral doses. Non-compartmental methods were used to estimate PK parameters.

Results. PK parameters were pooled from 93 males (57% J) with a mean (SD) age of 24.3 (6.0) years and a mean (SD) weight of 69.0 (10.8) kg. Only CL for C at the 125mg dose level showed large variability. For all other doses the estimated CL values remained in a narrow range in both groups. The range of J CL values was within the range of values for C, while mean (SD) CL for J (dose 250-625mg BID) was lower than that of C (70.44 (16.60) vs. 105.47 (37.81) mL/min). The mean weight-corrected CL estimates were 1.14 (0.27) and 1.38 (0.52) mL/min/kg for the J and C subjects, a difference of 20% that was deemed not to be clinically significant. For distribution volume, differences between the groups were eliminated by correcting for body weight.

Conclusions. Overall, minimal differences in PK were noted. Based in part on this information, lzd was approved for use in Japan/Asia at the same dosage used in the U.S.

INTRODUCTION

- The International Conference on Harmonization (ICH) draft guidelines on "Ethnic Factors in the Acceptability of Foreign Clinical Data" facilitate multi-national regulatory review and approval of medicines.
- The guidance provides a framework for evaluating the impact of ethnic factors upon a drug's effect (i.e., efficacy and safety at a particular dose and regimen).
- The development strategies in the guidance permit adequate evaluation of the influence of ethnic factors while minimizing duplication of clinical studies.
- This bridging analysis addressed the intrinsic ethnic factors relating to potential genetic and physiologic differences between Caucasians and Japanese patients who might receive linezolid for the treatment of infectious disease.
- The analysis compared the pharmacokinetic (PK) parameters for linezolid that were observed in Japanese and Caucasian healthy volunteers enrolled in traditional Phase I studies.

METHODS

Data

- Data was obtained from healthy Japanese and Caucasian (American) volunteers enrolled in five single- and multiple-dose Phase I studies of linezolid described in **Table 1.**

Table 1: Description and Design of the Studies Selected for Inclusion in the Analyses

Site	Study Description	Study Design
Japan	Assessment of safety, tolerance, and pharmacokinetics of 125, 250, 375, 500, and 625 mg BID and 250 mg TID X 8 days in healthy volunteers in Japan.*	Single dose on day 1 after breakfast with 150 mL of water, followed by BID or TID dosing after breakfast, lunch, or dinner for 7 days.
U.S.	Assessment of safety, tolerance, and pharmacokinetics of oral 375, 500, and 625 mg BID X 14.5 days in healthy American volunteers.	Single dose on day 1 followed by BID dosing for 14.5 days in a parallel study. Assessment of PK on first and last doses. All doses were administered in a fasted state.
U.S.	Assessment of safety, tolerance, and pharmacokinetics of IV 500 and 625 mg BID X 7.5 days in healthy American volunteers.	Single dose on day 1 followed by BID dosing for 7.5 days in a parallel study. Assessment of PK on first and last doses. All doses were administered as a 30-minute infusion in a fasted state.
U.S.	Assessment of dose proportionality in healthy American volunteers with doses of 125, 375, and 625 mg.	Single dose on day 1 followed by BID dosing for 4.5 days in a four-way crossover design. Assessment of PK on first and last doses. All doses were administered in a fasted state.
Japan	Assessment of safety, tolerance, and pharmacokinetics of multiple IV doses of linezolid in healthy male volunteers in Japan.	BID dosing following breakfast and dinner, of 300, 400, and 500 mg 30-minute IV infusions in healthy male volunteers.

* Because the US Phase I PK studies did not evaluate a linezolid 250 mg TID regimen, this treatment arm of the Japanese study was excluded.

Pharmacokinetic Analysis

- Standard non-compartmental methods were used to calculate parameter estimates for total clearance and volume of distribution of linezolid.
- Clearance was compared at steady-state after multiple doses to best represent linezolid use in clinical practice.
- Parameter estimates for clearance and volume of distribution were compared with and without normalization for weight (kg).

Statistical Analysis

- Normality of the PK parameter estimates was assessed by evaluating the Shapiro-Wilk statistic generated using SAS© (α = 0.05).
- Subsequent comparisons of parameter estimates from Japanese and Caucasians were performed using the *t*-test or Wilcox rank-sum test (α = 0.05).

RESULTS

Subject Demographics

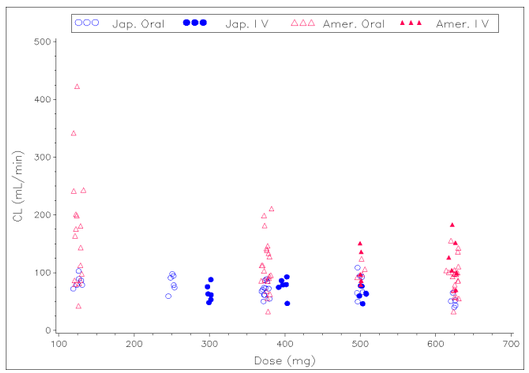
- PK data were pooled from 93 healthy male volunteers described in **Table 2.**

Table 2: Subject Demographic Characteristics Stratified by Race

Parameter		Combined N = 93	Japanese N = 53	Caucasian N = 40	P-Value
Age (yrs)	Mean (SD)	24.26 (6.00)	22.49 (2.56)	26.61 (8.12)	0.0224
	Range	18.5 - 53.7	20.00 - 35.00	18.50 - 53.70	
Height (cm)	Mean (SD)	175.22 (7.12)	172.65 (5.55)	178.67 (7.55)	0.0001
	Range	156.60 - 191.3	156.60 - 182.3	160.00 - 191.3	
Weight (kg)	Mean (SD)	68.60 (10.80)	62.11 (7.24)	77.17 (8.55)	0.0001
	Range	44.2 - 94.8	44.20 - 80.70	60.60 - 94.80	

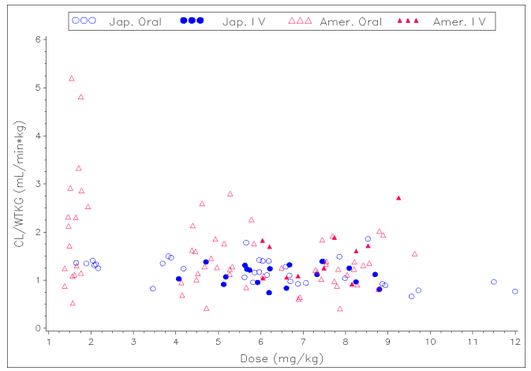
- PK profiles of Japanese and Caucasian subjects were compared using a plot of clearance (CL) values for each subject versus dose (**Figure 1**).

Figure 1: Clearance Values (mL/min) for Japanese and Caucasians by Dose (mg)



- Based on the plotted data, only CL for the Caucasians at the 125 mg dose showed large variability. For all other dose levels in Japanese and Caucasians, the estimated CL values remained within a narrow range.
- The range of Japanese CL values was within the range of values for Caucasians, however the mean CL for Japanese was lower than that of Caucasians. **Figure 2** illustrates weight-corrected CL estimates plotted versus dose.

Figure 2: Weight-Adjusted Clearance Values (mL/min*kg) for Japanese and Caucasians by Dose (mg/kg)



- The mean (SD) weight-corrected clearance estimates, for doses from 25-625 mg, were 1.14 (0.27) and 1.38 (0.52) mL/min/kg for the Japanese and Caucasian subjects. Due to overall variability in PK, this difference of approximately 20% was deemed not to be clinically significant.
- Similarly, the mean (SD) volumes of distribution were 38.40 (6.41) and 52.08 (16.05) L for the Japanese and Caucasian subjects respectively, but the difference was eliminated by correcting for total body weight (**Figures 3-4).**

Figure 3: Volume of Distribution Values (L) for Japanese and Caucasians by Dose (mg)

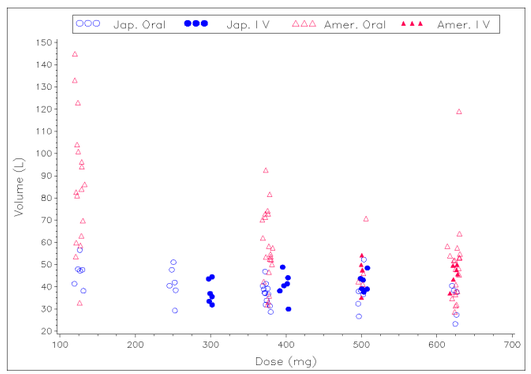
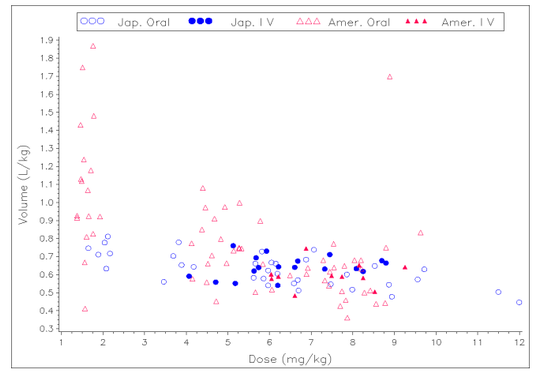


Figure 4: Weight-Adjusted Volume of Distribution (L/kg) for Japanese and Caucasians by Dose (mg)



- **Table 3** summarizes the Japanese-Caucasian comparisons of PK parameter estimates.

Table 3: Japanese/Caucasian Comparisons of Phase I Pharmacokinetic Parameter Estimates Pooled Across Dose Groups (250-625 mg) and Administration Method

Parameters		Japanese	Caucasian	P-Value
CL (mL/min)	N	47	57	<0.0001
	Mean (SD)	70.44 (16.60)	105.47 (37.81)	
	Median	70.60	99.00	
	Min-Max	39.90 - 109.0	33.00 - 211.0	
CL (mL/min*kg)	N	47	57	0.0211
	Mean (SD)	1.14 (0.27)	1.38 (0.52)	
	Median	1.12	1.27	
	Min-Max	0.66 - 1.86	0.42 - 2.80	
Volume (L)	N	47	57	<0.0001
	Mean (SD)	38.40 (6.41)	52.80 (16.05)	
	Median	38.40	50.00	
	Min-Max	23.30 - 52.30	28.80 - 119.0	
Volume (L/kg)	N	47	57	0.3761
	Mean (SD)	0.62 (0.08)	0.67 (0.21)	
	Median	0.63	0.64	
	Min-Max	0.45 - 0.78	0.36 - 1.70	

*N = number of parameter estimates available for comparison

CONCLUSIONS

- Overall minimal differences in pharmacokinetics were noted between the Japanese and Caucasians that were deemed not to be clinically significant due to the overall variability in the pharmacokinetics.
- Based in part on these pharmacokinetic comparisons, linezolid was approved for use in Japan/Asia at the same dosage used in the US.