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The Role of Population PK/PD Analysis During the Implementation of a Bridging Strategy for Linezolid

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ABSTRACT

Objectives: To describe the population PK/PD analysis process to support a bridging strategy for regulatory approval of linezolid in Japan/Asia Pacific region.

Methods: Pharmacokinetic data from Phase I healthy volunteers was used to develop a population PK model using the computer program NONMEM. This model was then used to estimate the population pharmacokinetic parameters of linezolid, and their variabilities, using 3,238 linezolid concentrations from 655 patients enrolled in Phase II trials. NONMEM was used to obtain estimates of exposure for each patient and logistic regression analysis was performed to identify relationships between exposure and efficacy and safety outcomes. Pharmacokinetic information from Japan/Asia Pacific volunteers was used to demonstrate similarity in pharmacokinetics between Japan/Asia Pacific and US/EU volunteers. The PK/PD relationships between exposure and safety and efficacy outcomes were used to develop dosing recommendations in Japan/Asia Pacific patients.

Results: The mean weight-corrected clearance estimates were 1.14 (0.27) and 1.38 (0.52) mL/min/kg for the Japan/Asia Pacific and US/EU subjects, a difference of 20%. This difference is well within the range of clearance values observed across the population PK database for US/EU. These findings suggest that the ethnic difference in linezolid PK was not substantial. Overall, there were no clinically significant differences in the hematologic or hepatic response to similar linezolid exposure between Japan/Asia Pacific and US/EU subjects. The subsequent population PK/PD analyses of the Phase II efficacy and safety data supported the use of the 600 mg twice daily regimen for linezolid in Japan/Asia Pacific region.

Conclusions: Population PK/PD analyses using the NONMEM computer program to analyze sparse sampling data from large populations represent a powerful tool for pooling data to estimate pharmacokinetic parameters and the magnitude of variability in patient populations. This is a particularly valuable tool in the implementation of bridging strategies because it permits the pooling of large numbers of patients, each of whom has had limited sampling performed (two or three samples) in order to assess similarity of exposures and outcomes across populations and to develop dosing recommendations.

INTRODUCTION

Population PK/PD analyses have become an important component of drug development because of the ability to combine data from Phase I, II, and III studies. This approach allows sparse sampling strategies to assess population exposures and subsequently to correlate exposure to efficacy and safety outcomes. The approach is well suited for the analysis of multi-national clinical trials. The ability to collect sparse samples from large numbers of patients allows valid assessments of the potential influence of intrinsic and extrinsic ethnic differences, as well as other factors, on PK parameters. These evaluations can play a critical role in the regulatory evaluation of a new medicine.

The goal of this presentation is to describe the population pk/pd analysis process that was implemented to support a bridging strategy for linezolid in the Japan/Asia Pacific region.

METHODS

Pharmacokinetic data from linezolid Phase I, II, and III studies were used to evaluate potential differences in PK between Japan/Asia Pacific and US/EU subjects. The analyses included noncompartmental PK parameter estimation and mixed effect model analysis using NONMEM. Subsequent evaluations of the relationships between exposure and efficacy and safety outcomes during Phase II clinical trials allowed for extrapolation of results and development of dosing recommendations for Japan/Asia Pacific region.

PK Model Development

- NONMEM model building was performed using data from a Phase I dose proportionality study evaluating single- and multiple-dose pharmacokinetics.
- The best population PK model for linezolid following single- and multiple-dose administration was a one-compartment model with first-order absorption and parallel first order and Michaelis-Menten elimination

Phase II Population PK Analysis

- A total of 3,238 plasma linezolid concentrations from 655 patients were available for analysis. The patient population ranged from 18 to 89 years, with a mean(sd) of 50.1 (17.7) years. The average weight was 82.2 (24.0) kg with a range of 37.7 to 204 kg. This patient population was 73.6% white, 19.7% black, 3% Asian and 6.4% other.

Phase III Population PK Analysis

- A total of 729 plasma linezolid concentrations from 232 patients were available for pharmacokinetic analyses. The patient population ranged from 19 to 95 years, with a mean(sd) of 59.1 (18.2) years. The average weight was 77.9 (25.4) kg. This patient population was 61% female.

PK/PD Relationships for Efficacy and Safety

- Relationships between laboratory safety data and linezolid exposure were compared for Japan/Asia Pacific volunteers in Phase I studies versus US/EU volunteers and patients in Phase I, II, and III studies. The parameters examined for assessment of potential hematologic toxicity were hemoglobin [HGB], red blood cell [RBC] counts, white blood cell [WBC] counts, absolute neutrophil count [ANC], and platelet counts. The parameters examined to assess potential hepatic toxicity were alanine transaminase [ALT] and aspartate transaminase [AST] concentrations. Various measures of exposure, including cumulative dose, AUC, and Cmax were evaluated.

Development of Dosing Recommendations for Japan/Asia Pacific Region

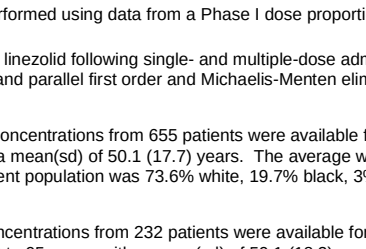
- Monte Carlo simulations were performed to utilize the PK/PD model and efficacy data to develop dosing recommendations for Japan/Asia Pacific region.
- AUC:MIC ratios were simulated using the NONMEM program and the Phase II PK model. The PD model for probability of cure developed from Phase II clinical trial results was then used to simulate efficacy rates.
- The impact of body size and dose on cure rates for various dosing regimens was assessed

RESULTS

Comparison of Clearance for Japan/Asia Pacific and US/EU Subjects and Patients

- After scaling the parameter for total body weight to adjust for the confounding weight effect, the scatter plot of values for US/EU covered the range of values for Japan/Asia Pacific subjects. The mean (SD) weight-corrected clearance estimates, for doses from 250 to 625 mg, were 1.14 (0.27) and 1.38 (0.52) mL/min/kg for the Japan/Asia Pacific and US/EU Phase I subjects, respectively.
- Although slight differences in the mean value of CL between Japan/Asia Pacific and US/EU subjects were observed, the differences are not likely to be clinically significant due to the overall variability in the pharmacokinetics.
- Population PK analysis of Phase II and III data was performed and Bayesian estimates of PK parameters were compared to results for Phase I (see Figure 1).

FIGURE 1. Weight-adjusted clearance values for subjects and patients in Phase I, II, III traits NONMEM was used to perform Bayesian parameters estimations from sparse sampling in Phase II and III studies.



Phase II Population PK Results – Final Pharmacokinetic Model

TABLE 1. Parameter Estimates and Standard Final Pharmacokinetic Model of Linezolid Applied to the Phase II Dataset – Final Errors

	Population Mean		Magnitude of Interindividual Variability (% CV)	
Parameter	Final Estimate	% SEM	Final Estimate	% SEM
$Ka(1/hr)$	0.802	30.7	101.00	49.7
$Km(mg)$	378	16.7	56.83	23.3
K^{int} $(1/hr)$	0.0135	42.8	65.88	54.8
K^{race}	1.11	55.0		
V^{int} (L)	23.4	16.8	18.38	23.1
V^{WTKG} (L/Kg)	0.351	17.6		
V^{frac}_{Age} (L/yrs)	-0.0088	35.0		
V^{gender}	0.124	40.5		
$Vm(mg/hr)$	75.5	11.7		

$K(1/hr) = K^{int} \bullet \left(1 + K^{race} \bullet RACEN\right)$ where RACEN=0 for white, 1 for all others

$V(L) = \left[V^{int} + \left(V^{WTKG} \bullet WTKG\right) + \left(V^{int} \bullet V^{frac}_{Age} \bullet (Age - 50)\right)\right] \bullet \left(1 + V^{gender}(1 - GENDER)\right)$

- Based on the parameter estimates for the final model, the total clearance for a 52 year old white male patient weighing 84.4 kg was estimated to be 10.99, 6.96, and 4.51 at steady-state concentration values of 1.02, 5.86, and 13.94. The non-linear component of clearance represented 92.73, 88.53, 82.30 percent of the total clearance.
- Covariate analysis indicated that the first-order elimination process was influenced by race, however no changes in total clearance were identified and dosage adjustment is not required. Weight, age and gender also were significant covariates of volume of distribution.

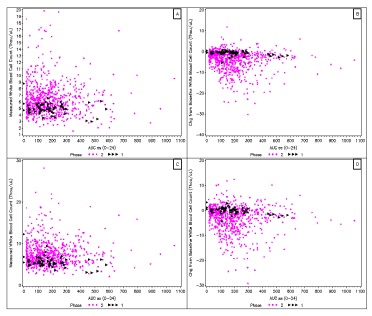
Simulations

- No accumulation because of non-linear pathway is anticipated based on simulations to 60 days (see Figure 2).

FIGURE 2. Boxplots of simulated peak and trough concentrations associated with BID oral dosing to 60 days.

Safety Evaluation

FIGURE 3. WBC counts versus AUC for phase I and II studies.



Laboratory safety data for all subjects and patients in Phase I and II trials were evaluated for an association between exposure and change in values over the study period. NONMEM was used to perform Bayesian parameter estimation using sparse sampling in Phase II studies (see Figure 3).

Dosing Extrapolations Based on Population PK/PD Model

- The simulations performed using the PK/PD model were used to develop dosing recommendations for Japan/Asia Pacific patients. Figure 4 shows the probablity densities of the AUC:MIC ratio for patients receiving 500 mg versus 600 mg of linezolid administered twice daily. These simulation results were then combined with the PD model for efficacy to predict population cure rates (see Table 2).
- These results support a 600 mg BID dosing regimen for linezolid. For every 100 patients treated with linezolid, 4 to 5 additional patients would be cured using the 600 mg BID regimen compared to a 500 mg BID regimen.

FIGURE 4. Probability density of Monte Carlo simulated AUC:MIC ratio.

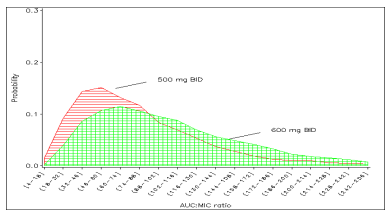


TABLE 2. Expected Cure Rates for Patients Receiving Linezolid 500 and 600 mg BID Stratified by Weight

Weight (kg)	BID Dose (mg)	Expected Cure Rate (%)	95% Confidence Intervals about the Cure Rate
82.2 kg	500	70.0	(69.8, 70.2)
	600	74.1	(73.8, 74.3)
65 kg	500	71.6	(71.4, 71.8)
	600	76.0	(75.8, 76.3)

CONCLUSIONS

- **Population PK/PD analysis of data collected during drug development is a powerful tool for assessing possible ethnic differences in PK and evaluating relationships between exposure and efficacy and safety outcomes.**
- **Population PK analysis allows for the influence of intrinsic and extrinsic factors to be assessed in representative patient populations, using sparse sampling to minimize expense and patient discomfort, while improving the quality and quantity of data available for regulatory review.**
- **Monte Carlo simulations, using the models defined during data analysis, permit an assessment of the clinical implications of the PK/PD models and the exploration of possible outcome for various dosing regimens based on efficacy and/or safety outcomes as appropriate.**