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

**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: Pharmacometric 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 pharmacometric parameters of linezolid, and their variability, using 3,439 linezolid concentrations from 605 patients enrolled in Phase II trials. NONMEM was used to obtain estimates of exposure for each patient and logistic regression analyses was performed to identify relationships between exposure and efficacy and safety outcomes. Pharmacometric information from Japan/Asia Pacific volunteers was used to demonstrate similarity in pharmacokinetics between Japan/Asia Pacific and US/EU subsets. The PK/PD relationships between exposure and safety and efficacy outcomes were used to evaluate dosing recommendations in Japanese/Asian 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 subsets, a difference of 21%. 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 responses to similar linezolid exposure between Japan/Asia Pacific and US/EU subsets. 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 strategy for 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 strategy for linezolid in the Japan/Asia Pacific region.

**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/PD relationships. 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**

Pharmacometric 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 analysis 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 3,439 plasma linezolid concentrations from 605 patients were available for analysis. The patient population ranged from 18 to 88 years, with a mean(s) of 55.1 (17.7) years. The average weight was 82.2 (24.6) kg with a range of 27.7 to 204 kg. The patient population was 73.6% white, 19.7% black, 3% Asian and 4% other.

- **Phase II Population PK Analysis**
  - A total of 739 plasma linezolid concentrations from 232 patients were available for pharmacokinetic analyses. The patient population ranged from 18 to 85 years, with a mean(s) of 58.1 (18.4) years. The average weight was 77.9 (25.4) kg. The 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 and II studies versus US/EU volunteers and patients in Phase I, II, and III studies. These parameters estimated for assessment of potential hepatotoxicity were gamma-GOT, gamma-GPT, and aspartate aminotransferase (AST) concentrations. Variations in safety outcomes, including complete blood cell counts, were also 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**

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

- After scaling the parameter for total body weight to adjust for the continuing 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 subsets, respectively.

- Although slight differences in the mean values of CL between Japan/Asia Pacific and US/EU subjects were observed, the differences are not likely to be clinically important due to the broad range of values.

- 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, and III NONMEM was used to perform Bayesian parameters estimation from sparse sampling in Phase I and III studies.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
<td>Estimate</td>
<td>Estimate</td>
<td>Estimate</td>
</tr>
</tbody>
</table>
| **AUC** | 620 | 620 | **AUC** increased with increasing dose.
| **MIC** | 20 | 20 | **MIC** decreased with increasing dose.
| **Probability of Cure** | 75% | 75% | **Probability of Cure** increased with increasing dose.

**Phase II Population PK Results - Final Pharmacokinetic Model**

**Phase III Population PK Results - Final Pharmacokinetic Model**

**TABLE 1. Parameter Estimates and Standard Errors for Pharmacokinetic Parameters in Linezolid**

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

**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 inference 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.**