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# Tedizolid Population Pharmacokinetics, Exposure-Response, and Target Attainment

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## BACKGROUND

- Tedizolid phosphate is a novel antibiotic prodrug rapidly converted by phosphatases to its active moiety tedizolid after administration[1]. Tedizolid is 4-16 fold more potent in vitro than linezolid against Gram-positive pathogens, incl. methicillin-resistant *Staphylococcus aureus* and strains resistant to linezolid or vancomycin[2-4] and is rapidly bactericidal in vivo[5]. Tedizolid phosphate is administered once daily (orally or IV at identical dosage).
  - In clinical studies, tedizolid has demonstrated a favorable pharmacokinetic (PK) profile in healthy volunteers, including a long half-life, minimal accumulation over time, high oral bioavailability (> 80%), and low inter-patient variability in drug exposure levels[1].
  - Once daily dosing regimens of 200, 300, or 400 mg resulted in similar efficacy outcomes in a Phase 2 study[6].
  - In two recent Phase 3 trials, a 6-day course of tedizolid phosphate 200 mg once/day demonstrated non-inferior efficacy to a 10-day course of linezolid 600 mg twice/day for the treatment of acute bacterial skin and soft tissue infections (ABSSSI), with improved gastrointestinal tolerability and a reduced potential for hematological toxicity[7,8].
- A population pharmacokinetic model was developed to evaluate the impact of tedizolid exposures on efficacy and safety, factors influencing PK and PK/pharmacodynamic (PK/PD) variability, and the probability of attaining the tedizolid PK/PD target measure.

## METHODS

- Data were obtained from four densely sampled Phase 1 studies (PK data), one sparsely sampled Phase 2 study (PK and safety data), and two sparsely sampled Phase 3 studies (PK, safety, and efficacy data).
- The following prospectively collected efficacy outcomes were utilized in the PK/PD analysis: early clinical response (with ≥ 20% decrease in lesion area) at the 48-72 hour visit; clinical response (investigator assessed) at the post-therapy evaluation (PTE; 7-14 days after end-of-therapy); and microbiologic response at end-of-therapy and the PTE.
- The following safety outcomes were utilized in the PK/PD analysis: treatment-emergent adverse events (TEAEs); TE gastrointestinal AEs; changes in absolute neutrophil counts and in platelet counts.
- The final PK model was based on data from the six clinical studies and included ideal bodyweight (IBW) and total bilirubin as statistically significant covariates.
- The model was used to generate empiric Bayesian estimates of $AUC_{(0\text{-}24)}$, $AUC_{(0\text{-}24)}$/MIC ratio, minimum observed drug concentration ($C_{min}$), and maximum observed drug concentration ($C_{max}$), at Day 1 and steady-state.
- Logistic regression analysis was used to examine the effects of drug exposure on each of the efficacy and safety endpoints. The influence of covariates was to be evaluated only if an exposure-response relationship was identified.
- The probability of attaining the PK/PD target measure (Day 1 $AUC_{(0\text{-}24)}$/MIC ratio) associated with tedizolid efficacy was estimated from 100,000 simulated patients (100 trials of 1000 virtual patients each).
  - The MIC susceptibility breakpoint was defined as the highest clinically relevant MIC value with a ≥ 90% probability of PK/PD target attainment.

## RESULTS

**TABLE 1. Parameter Estimates From the Final Population Pharmacokinetic Model for Tedizolid**

| Parameter | Final Parameter Estimate | | Interindividual Variability / Residual Variability | |
|---|---|---|---|---|
| | Typical Value | % SEM | Magnitude | % SEM |
| $k_a$: First-order absorption rate constant (1/h) | 1.99 | 13.0 | 194 % CV | 11.0 |
| CL: Clearance (L/h) | 6.69 | 2.28 | 31.0 % CV | 8.70 |
| Power term for the effect of IBW on CL | 0.811 | 11.9 | | |
| Slope for the effect of total bilirubin on CL (L/h/mg/dL) | -0.851 | 13.1 | | |
| $V_c$: Central volume (L) | 69.0 | 2.58 | 13.4 % CV | 33.1 |
| Power term for the effect of IBW on $V_c$ | 1.32 | 8.92 | | |
| Q: Intercompartmental CL (L/h) | 0.959 | 10.3 | NE | NE |
| $V_p$: Peripheral volume (L) | 13.6 | 6.30 | | |
| F1: Absolute bioavailability | 0.859 | 2.47 | | |
| DUR: Duration of zero order absorption (h) | 1.62 | 8.90 | | |
| RV for Phase 1 studies (log units) | 0.148 | 17.1 | 0.384 SD | NA |
| RV for Phase 2/3 studies (log units) | 0.210 | 5.37 | 0.458 SD | NA |

CV, coefficient of variation; IBW, ideal body weight; NA, not available; NE, not estimated; RV, residual variability; SD, standard deviation; % SEM, standard error of the mean expressed as a percentage.

## RESULTS continued

- A 2-compartment model with sigmoidal absorption, absolute bioavailability, and linear elimination sufficiently described the data. Variability was low, with a 31% and 13.4% coefficient of variation for clearance and volume, respectively. Absolute bioavailability was high (86%).
  - Population parameter estimates for the final PK model are shown in Table 1.
- No clinically relevant covariate effects on tedizolid PK were found (Table 2).
- Exposure-response analyses based on data from the Phase 3 studies using 200 mg once/day in ABSSSI showed no relationship between exposure and clinical or microbiologic response, representing the flat portion of the exposure-response relationship.
- Safety analyses, including patients receiving up to 400 mg per day, showed a modest increase in the probability of experiencing an AE with increasing exposure. No such relationship was observed with the standard 200 mg dose that was evaluated in Phase 3 trials.
  - There were no trends in the plots of minimum or maximum decrease in neutrophil counts or platelet counts versus tedizolid exposure measures at Day 1 or at steady-state across all doses.
- The target attainment simulation indicated a high probability of attaining the PK/PD target measure (fAUC/MIC ratio of 3, corresponding to a total AUC/MIC ratio of 15 with typical plasma protein binding of 80%[9]) with a susceptibility breakpoint of 0.5 µg/mL for 200 mg tedizolid phosphate (Figure 1).
- There was no apparent drop in microbiological efficacy across a wide range of AUC/MIC ratios observed in the Phase 3 trials .

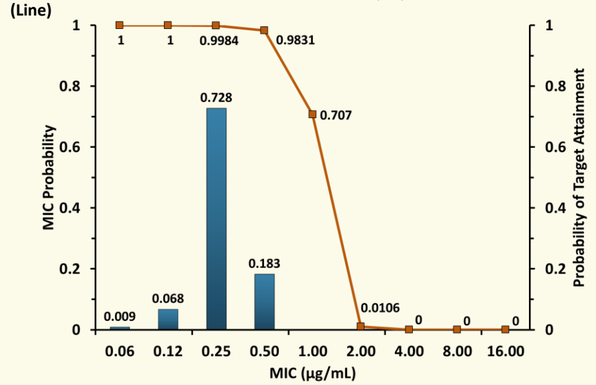
**TABLE 2. Assessment of Clinical Relevance of Effects of Statistically Significant Covariates in the Final Model for Tedizolid**

| Covariate in Final Population Pharmacokinetic Model | | | Predicted $AUC_{ss}$ Ratio |
|---|---|---|---|
| IBW | 5th Percentile of Covariate: Median Value | 52 kg: 64.65 kg | 1.193 |
| | 95th Percentile of Covariate: Median Value | 77.6 kg: 64.65 kg | 0.862 |
| | 5th Percentile of Covariate: 95th Percentile of Covariate | 52 kg: 77.6 kg | 1.384 |
| Total bilirubin | 5th Percentile of Covariate: Median Value | 0.1 mg/dL: 0.4 mg/dL | 0.963 |
| | 95th Percentile of Covariate: Median Value | 1 mg/dL: 0.4 mg/dL | 1.083 |
| | 5th Percentile of Covariate: 95th Percentile of Covariate | 0.1 mg/dL: 1 mg/dL | 0.89 |

$AUC_{ss}$ = area under the concentration-time curve at steady-state; IBW = ideal body weight.

## RESULTS continued

**Figure 1. MIC Frequency Distribution (Bars) and Probability of PK/PD Target Attainment for Tedizolid Phosphate at the $AUC_{(0\text{-}24)}$/MIC Ratio Breakpoint of 15 (Line)**




## CONCLUSIONS

- This population PK model supports the selection of 200 mg tedizolid phosphate once/day as the optimum dose for the treatment of Gram-positive infections:
  - There was no relationship between tedizolid exposure and efficacy as all evaluated doses demonstrated similar efficacy results.
  - At 200 mg once/day, tedizolid phosphate did not appear to result in exposures associated with increased AEs, while slight increases in AEs (but not in hematological changes) were seen with exposures resulting from higher doses.
  - The 200 mg dose had a high probability of attaining the PK/PD target measure with a susceptibility breakpoint of 0.5 µg/mL.
- No covariates exerted any clinically significant effect on tedizolid PK, suggesting that the 200 mg dose does not need to be adjusted for any patient sub-population.

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