Dalbavancin Population Pharmacokinetic Modeling and Target Attainment Analysis

TJ Carrothers1,* and Jason Chittenden2

1 Allergan, Jersey City, NJ; 2 qPharmetra LLC, Andover, MA

Objectives: To evaluate single dose population pharmacokinetics and support determination of a PK/PD breakpoint for dalbavancin.

Methods: Population pharmacokinetic (popPK) modeling, exploratory exposure-response analysis, and target attainment simulation were conducted following the conclusion of a pivotal single dose study in patients. This study compared a single IV dose of 1500 mg to the previously approved two-dose regimen of 1000 mg (Day 1) and 500 mg (Day 8). The popPK dataset utilized the current study as well as three prior Phase 2/3 studies. Covariate analysis was conducted to characterize the impact, if any, of intrinsic factors on dalbavancin exposures. Exploration of exposure-response used logistic regression. Using the final popPK model, target attainment was simulated for the non-clinical free AUC/MIC stasis target of 27.1 h.

Results: A three compartment distribution model with first-order elimination provided an appropriate fit to the observed data. Inter-individual variability for clearance and central volume were low, at 22% and 24%, respectively. Statistically significant (p<0.05) covariate relationships with total clearance were found for creatinine clearance, weight, and albumin, although their clinical importance was limited. Dose-adjustment is only indicated for creatinine clearance under 30 mL/min. The efficacy endpoints showed no statistically significant relationships with any PK/PD indices (e.g., cumulative AUC/MIC), which was unsurprising given the high success rates and low PK variability. Nonclinical target attainment simulations projected more than 90% of simulated subjects to achieve the nonclinical target at MIC <= 2 mg/L, although relatively few isolates above 0.25 mg/L have been observed in clinical studies or surveillance.

Figure 1: Mean Concentrations after Day 1 Dose (mg)

Conclusions: The pharmacokinetic profile (Figure 1) of dalbavancin was well-characterized, with low intersubject variability and a limited impact of intrinsic factors, other than severe renal impairment, observed. Clinical exploration of exposure-response was limited by the high rate of clinical success observed for dalbavancin in the ABSSSI pivotal studies. Nonclinical target attainment simulations supported a PK/PD breakpoint up to 2 mg/L for both approved dosing regimens.