**TITLE:** Pharmacokinetics of dalbavancin (DAL) in bone and associated tissues in patients undergoing orthopedic surgical procedures

**ABSTRACT**

**BACKGROUND:** Osteomyelitis (OM) is an infection requiring prolonged antimicrobial therapy. Dalbavancin (DAL) may be an ideal antimicrobial agent for OM based on its potent activity against S. aureus, and a long terminal half-life.

**OBJECTIVE:** The objective of this study was to characterize the PK of DAL in bone and associated tissues in patients undergoing joint surgery.

**METHODS:** Adults scheduled for joint surgery (N = 31) were administered 1 g of DAL infused over 30 minutes prior to scheduled surgery. Patients were assigned to 1 of 6 cohorts and had serial plasma PK samples collected up to 1080 h post-dose plus 1 bone PK sample collected at 12, 24, 72, 168, 240 or 336 h post-dose. Samples were analyzed for DAL in plasma, synovial fluid, skin, cartilage and bone. A population model was fit to plasma and bone PK data and covariate analysis was performed. Allometry was used to determine the total amount of bone tissue and to estimate the amount of DAL in bone.

**RESULTS:** DAL concentrations in bone, synovial fluid, skin, cartilage and bone and the measured CLcr and BSA as statistically significant predictors of dalbavancin CL and Vc, respectively. The mean of the individual bone:plasma AUC penetration ratio was calculated to be 0.139 ± 0.13%.

**CONCLUSIONS:** Dalbavancin was well tolerated as used in this study. The most common treatment related AE of dizziness. One subject was hospitalized for pulmonary embolism at Day 14 and again at Day 28, which was unrelated to study drug and resolved. One subject died after giving consent but before receiving study drug.

**METHODS**

**INTRODUCTION**

**RESULTS**

Thirty one subjects were enrolled, received treatment and contributed six plasma samples each to the plasma PK analysis. For one subject, the bone PK sample was mishandled and rendered unusable; thus 30 evaluable bone PK samples were available for analysis. Mean ± SD of bone tissue levels for dalbavancin are shown in Table 1. The observed dalbavancin concentrations in each of the matrices evaluated were analyzed for DAL in plasma, synovial fluid, skin, cartilage and bone. A population model was fit to plasma and bone PK data and covariate analysis was performed. Allometry was used to determine the total amount of bone tissue and to estimate the amount of DAL in bone.

**RESULTS:**

**Table 1. Dalbavancin Tissue Concentration, Mean ± SD**

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<th>Tissue Type</th>
<th>Mean ± SD (µg/mL)</th>
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<tr>
<td>Plasma</td>
<td>37.2 ± 19.7</td>
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<tr>
<td>Bone</td>
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</tr>
<tr>
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**DISCUSSION**

- In this study, a single 1000 mg dose of dalbavancin was safe and well tolerated.
- Mean dalbavancin concentrations of >15 µg/mL in plasma were observed through Day 14.
- Mean dalbavancin concentrations observed in bone (4.1 µg/mL) and in associated tissues (>6.2 mg/g) through Day 14 were well above MIC90 for S. aureus; population mean dalbavancin concentrations in bone were predicted to exceed the 5 µg/mL MIC of 10µg/mL for >28 days.
- Although the proportion of dalbavancin measured in tissues that is free to interact with microbes is not yet characterized, the measured concentrations were several fold higher than the MIC90 for S. aureus through Day 14.
- Based upon this study, dalbavancin may be suitable for administration as a one or two dose regimen in the treatment of osteomyelitis.
- Application of population PK analysis methods allowed for estimation of the time course of dalbavancin in plasma and bone, enabling evaluation of the relative exposure in both matrices.
- Several limitations to the PK modeling were noted, including insufficient data to clearly depict the removal of dalbavancin from bone given the PK sampling strategy utilized. In addition, the number of patients at each sampling point for the bone and associated tissues was also small. Given these findings, the model parameters should be interpreted with caution.

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Based upon this study, dalbavancin was well tolerated as used in this study. The most common treatment related AE of dizziness. One subject was hospitalized for pulmonary embolism at Day 14 and again at Day 28, which was unrelated to study drug and resolved. One subject died after giving consent but before receiving study drug.

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