Intrapulmonary and plasma concentrations of dalbavancin in healthy adults after a single 1500 mg infusion

Michael Dunne*[1], Urania Rappo[2], Sailaja Puttagunta[3], James Baldassarre[4], Shengfang Su[2], Daksha Desai-Krieger[5], Megumi Inoue[6]

[1]*Old Saybrook, Old Saybrook, Ct, United States*

[2]*Allergan Plc, Jersey City, United States*

[3]*Indus Hospital, Visakhapatnam, India*

[4]*Johnson & Johnson, Summit, Nj, United States*

[5]*Allegan Plc, Jersey City, United States*

[6]*Ita-Med, Tokyo, Japan*

Background: Dalbavancin is a lipoglycopeptide antibiotic with a prolonged half-life that justifies infrequent dosing and is approved for treatment of adults with acute bacterial skin and skin structure infections. As part of an effort to understand the potential for activity in pneumonia, this Phase 1 study evaluated dalbavancin levels in epithelial lining fluid (ELF).

Material/methods: Thirty-seven healthy, non-smoking Japanese adult subjects were included, of whom 35 underwent bronchoscopy with bronchial microsampling of ELF at 1 of 7 time points (4, 8, 12, 24, 72, 120 and 168 hrs) after a single 1500 mg dose of IV dalbavancin. Plasma concentrations of dalbavancin were also collected. The dalbavancin plasma and ELF concentrations were measured using validated LC-MS/MS bioanalytical methods. PK parameters were derived using noncompartmental analysis.

Results: Median ELF levels exceeded the MIC_{90} of *S. aureus* (MIC_{90} = 0.06 µg/mL) and *S. pneumoniae* (MIC_{90} = 0.03 µg/mL) at 4 hours and through 7 days (Table 1). Based on area under the concentration curve (AUC), the ratio of dalbavancin ELF levels relative to plasma was approximately 36%. The AUC_{avg}/MIC_{90} ratio of dalbavancin in ELF for *S. pneumoniae* (2509) far exceeded the fAUC/MIC ratios in a murine thigh infection model associated with stasis (18), 1-log kill (21) and 2-log kill (24), where AUC_{avg} = $AUC_{168}/7$. Similarly, the AUC_{avg}/MIC_{90} ratio in ELF for *S. aureus* (1254) far exceeded the fAUC/MIC ratios associated with stasis (27), 1-log kill (53) and 2-log kill (111).

Table 1. Median Dalbavancin Concentrations in ELF and Plasma

Dalbavancin Concentrations (µg/mL)	4 h	8 h	12 h	24 h	72 h	120 h	168 h
Measured plasma (N=37)	279	222	194	169	120	93.8	78.5
Calculated free plasma (N=37)*	19.5	15.5	13.6	11.8	8.4	6.6	5.5

| ELF (N) | 1.85 (5) | 2.24 (5) | 2.82 (5) | 2.64 (5) | 4.21(5) | 3.27 (5) | 2.07 (5) |

* 7% of total plasma concentration; 2 subjects did not have bronchoscopy

Figure. Median dalbavancin concentrations in ELF and Plasma: Concentration-Time Profile (semi-logarithmic scale)
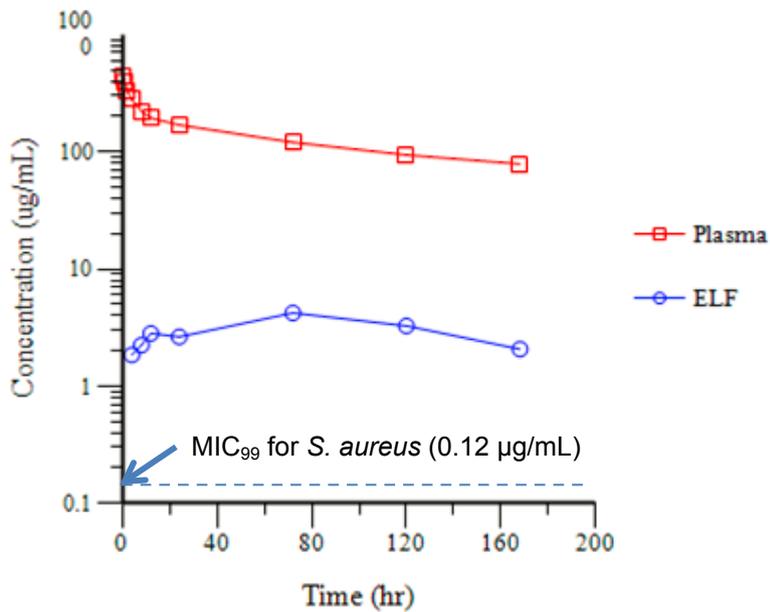
Conclusions: Intrapulmonary concentrations of dalbavancin that exceed the MIC_{90} of *S. pneumoniae* and *S. aureus* are achieved early after a single 1500 mg IV infusion and are sustained for at least 7 days. Prior PK/PD modeling and the AUC_{avg}/MIC_{90} ratio of dalbavancin in ELF suggest that high levels of target attainment would be achieved in patients with pneumonia due to *S. aureus* and *S. pneumoniae*. These data support further evaluation of this antibiotic in the treatment of pneumonia.