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Poster Number

Intrapulmonary and Plasma Concentrations of Dalbavancin in Healthy Adults after a Single 1500 mg Infusion

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INTRODUCTION

- Dalbavancin: a lipoglycopeptide antibiotic with a long terminal half-life of 14.4 days
  - -Justifies infrequent dosing
  - -Approved by FDA and EC as single and two-dose treatment of adults with acute bacterial skin and skin structure infections
- Potent activity against staphylococci, including methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-resistant *Streptococcus pneumoniae*
- In vitro activity against gram-positive respiratory pathogens associated with pneumonia
- In vivo activity against *Streptococcus pneumoniae* in murine lung infection model
- Dalbavancin does not appear to be appreciably affected by the presence of surfactant, when tested against *S. aureus* and *S. pneumoniae* in vitro[1]

PURPOSE

- The aim of this study was to evaluate the safety, tolerability, and concentrations of dalbavancin present in lung epithelial lining fluid (ELF) and plasma following a single 1500 mg dalbavancin infusion to Japanese healthy volunteers

METHODS

- Phase 1, open-label, single-dose, safety, tolerability and pharmacokinetic (PK) study of ELF and plasma concentrations of dalbavancin
- 37 healthy, non-smoking Japanese adult subjects received 1500 mg of dalbavancin, infused IV for 30 minutes
- 35 subjects (5 enrolled into each of 7 cohorts) underwent bronchoscopy with bronchial microsampling of ELF at 1 of 7 time points from start of dalbavancin infusion (4, 8, 12, 24, 72, 120 and 168 hrs)
- Plasma levels for PK analyses were drawn in all 37 subjects, at 9 time points from start of dalbavancin infusion (0.5, 1, 2, 4, 8, 12, 24, 72, 120 and 168 hrs), regardless of cohort
- Bronchial microsampling (BMS) technique uses microsampling catheter sponge probes inserted through a fiberoptic bronchoscope to absorb epithelial lining fluid by gentle contact with bronchial lumen, without the requirement of saline[2,3]
- The dalbavancin plasma and ELF concentrations were measured using validated liquid chromatography tandem mass spectrometry (LC-MS/MS) methods
- PK parameters were derived using noncompartmental analysis

RESULTS

- A total of 37 subjects were enrolled; all completed the study
- Mean age was 29.1 years, all subjects were Asian males, with a mean body mass index (BMI) of 23.2 kg/m^2
- 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 free plasma was approximately 36% (Table 2)
- The AUC_{avg}/MIC_{90} ratio of dalbavancin in ELF for *S. pneumoniae* (2509) far exceeded the fAUC/MIC ratios[4] 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[5] associated with stasis (27), 1-log kill (53) and 2-log kill (111)

[§] Based on surveillance data

Table 2. Pharmacokinetic Parameters for Dalbavancin in ELF and Plasma (Mean ± SD)

Parameter	Plasma (n=37)	Epithelial Lining Fluid (n=35)
T_{max}, h[a]	0.5 (0.5 – 0.5)	72
C_{max}, µg/mL	453.41 ± 51.27	4.21
$AUC_{0\text{-}168}$, µg•h/mL	21086.62 ± 2282.37	526.84
CL, mL/h	41.35 ± 5.48	NA
V_{ss}, mL	8109.58 ± 1162.14	NA
Penetration ratio[b]	NA	0.357

a Median (min - max)

b Based on $AUC_{0\text{-}168}$ in ELF to unbound $AUC_{0\text{-}168}$ in plasma assuming no binding in ELF and 93% protein binding in plasma

$AUC_{0\text{-}168}$ = area under the plasma or ELF concentration versus time curve from time 0 to 168 h; CL = total body plasma clearance; C_{max} = maximum plasma or ELF drug concentration; ELF = epithelial lining fluid; max = maximum; min = minimum; SD = standard deviation; T_{max} = time of maximum plasma or ELF drug concentration; V_{ss} = volume of distribution; NA = not applicable

Table 1. Median Dalbavancin Concentrations in ELF and Plasma

Dalbavancin Concentrations (µg/mL)	4 hours	8 hours	12 hours	24 hours	72 hours	120 hours	168 hours
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 1. Median dalbavancin concentrations in ELF and Plasma: Concentration-Time Profile (semi-logarithmic scale)

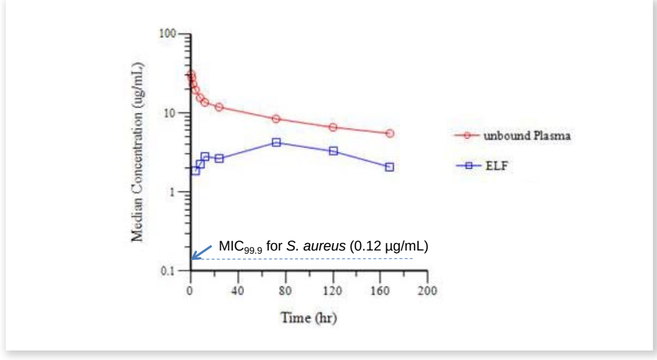
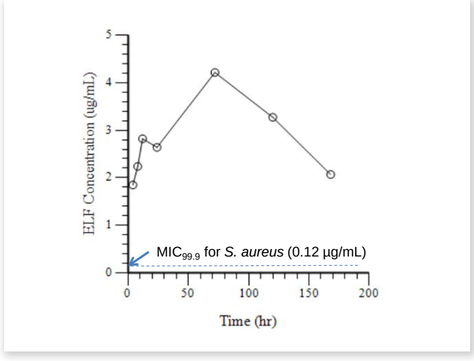


Figure 2. Median dalbavancin concentrations in ELF (linear scale)



- Dalbavancin was safe and well-tolerated in this study with no SAEs reported
- No subject discontinued from study due to an AE
- A total of 5 (13.5%) subjects experienced at least 1 TEAE with the most common being headache and injection-site phlebitis; all TEAEs were mild in intensity
- Drug-related TEAE incidence was low (10.8%)

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*
- Dalbavancin penetrates into lung tissue at a ratio of ~36% relative to free plasma
- These data provide further support for evaluation of a single 1500 mg dose of dalbavancin in the treatment of pneumonia

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DISCLOSURES

This study was sponsored by Durata Therapeutics and Allergan plc. MD, SP were former employees of Allergan, plc and held stock in Durata Therapeutics. UR, SS, DDK are current employees of Allergan, plc. UR holds stock in Allergan, plc and held stock in Durata Therapeutics. JB was an employee of Durata Therapeutics and held stock in the company. All authors met the ICMJE authorship criteria. Neither honoraria nor payments were made for authorship.

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