dalbavancin concentrations in cortical bone 12 hours after a single 1000-mg i.v. infusion were 6.3 μg/g and 2 weeks later were 4.1 μg/g (Dunne *et al*., 2016b). This study also suggested that a regimen of 1500 mg given on day 1 and again on day 8 will result in dalbavancin exposure at or above the *S. aureus* $MIC_{99.9}$ for dalbavancin 0.12 mg/l for the entire osteomyelitis treatment duration with an adverse event (AE) profile similar to that of a 1000-mg dose (Dunne *et al*., 2016b).

A phase I blister study identified favorable penetration into the skin (60%) with a mean AUC of 6438 ± 1238 mgh/l for blister fluid vs. 10806 ± 1926 mgh/l for plasma, after a 1000-mg dose (Nicolau *et al*., 2007). Dalbavancin concentrations in blister fluid (30.3 ± 4.4 mg/l) were sustained well above the MIC over 7 days, regardless of protein binding. Concentrations in blister fluid in ratio to plasma were found to be 0.83–1.11, supporting dalbavancin's FDA approval for ABSSSIs (Leighton *et al*., 2004).

Dalbavancin has moderate penetration into macrophages, where the intracellular concentration increases with growing extracellular concentrations (Bulgheroni *et al*., 2004). In comparison with vancomycin and teicoplanin, dalbavancin has better penetration into these cells, although its intracellular concentration is still considerably lower than oritavancin.

5c. Clinically important pharmacokinetic and pharmacodynamic features

Time-kill experiments with staphylococci reiterate dalbavancin's antibacterial activity compared with traditional glycopeptides (Candiani *et al*., 1999; Lin *et al*., 2005a; Lopez *et al*., 2005). Dalbavancin produced a 3-log kill at four times the MIC over 24 hours against six strains (grouping of methicillin-susceptible and methicillin-resistant *S. aureus* and CoNS) (Lin *et al*., 2005a). Only oritavancin and daptomycin matched dalbavancin's activity, whereas vancomycin and teicoplanin were bactericidal against just four strains and linezolid and quinupristin–dalfopristin against none. Like vancomycin and teicoplanin, dalbavancin is slower in reaching its bactericidal activity and generally requires 24 hours to achieve the requisite bactericidal kill of 3 logs (Lin *et al*., 2005a; Lopez *et al*., 2005). An earlier study by Jones *et al*. (2001) conversely discovered bacteriostatic (1.0- to 2.3-log kill) results for dalbavancin against two *S. aureus* strains and one *S. epidermidis* strain at four to eight times MIC in 24 hours.

Serum bactericidal activity experiments against two MRSA strains showed bactericidal activity up to 7 days after dalbavancin administration (Leighton *et al*., 2004). Blood samples taken from subjects who received single doses ≥ 500 mg or any multiple doses revealed reciprocal serum bactericidal activity titers that increased along with plasma drug concentrations. It appears that drug concentrations ≥ 20 mg/l in plasma yield detectable bactericidal titers. Cavaleri *et al*. (2002) attempted to explain how dalbavancin is capable of bactericidal activity within the serum, despite the high protein binding, by means of isothermal titration microcalorimetry. It seems that dalbavancin has a high capacity but a low affinity for human plasma proteins. Its high protein capacity is responsible for creating high concentrations of dalbavancin and for its long $t_{1/2}$, but the low affinity for protein allows enough unbound dalbavancin to be present to generate bactericidal activity *in vitro*.

Goldstein *et al*. (2007) demonstrated that minimal bactericidal concentrations (MBCs) for dalbavancin were ≤ 0.5 mg/l for eight staphylococcal isolates; for six of these strains, including one VISA isolate, the MBCs were equal to or within one doubling dilution of the MIC. Dalbavancin MBCs were 0.008–0.25 mg/l for three *S. pyogenes* strains, which were identical to the MICs for two of the three isolates (0.008 mg/l). In time-kill studies conducted with a different set of seven strains, including MSSA, MRSA, VISA, and *S. pyogenes*, all strains exhibited a ≥ 3 $\log_{10}$ decrease in their viable counts when they were exposed to ≥ 1 mg/l of dalbavancin for 24 hours.

In a time-kill study with 10 pneumococci strains of assorted resistant types, dalbavancin was bactericidal at two to four times the MIC in 24 hours against 10 strains, and at one times the MIC in 8 of 10 (Lin *et al*., 2005b). In another time-kill study, dalbavancin was determined to be bacteriostatic (0- to 1.4-log kill) against single isolates of *E. faecalis* and vancomycin-resistant *E. faecium* at four to eight times the MIC in 24 hours (Jones *et al*., 2001).

Unlike glycopeptides that have time-dependent killing, dalbavancin displays concentration-dependent activity, which is best characterized by AUC/MIC ratios (Bowker *et al*., 2006; Andes and Craig, 2007; Lepak *et al*., 2015). An *in vitro* model with simulated free concentrations against several *S. aureus* (MSSA, MRSA, VISA) isolates similarly found correlations between AUC/MIC and antibacterial activity, whereas C_{max}/MIC was determined to be less relevant (Bowker *et al*., 2006). In this study, free AUC/MIC of 36–100 was sufficient for a bacteriostatic effect, and an increase to 214–331 produced a 2-log bactericidal kill. In murine thigh and lung infection models studying multiple doses of dalbavancin (twofold increasing total doses divided into 2, 4, 6, or 12 doses over a period of 6 days), high doses given less frequently were the most effective regimens in producing the greatest bacterial kill. C_{max} and AUC had the greatest impact on efficacy compared with time above MIC (T > MIC) for both *S. aureus* and S. *pneumoniae*, based on free (i.e. unbound) drug concentrations. AUC/MIC (R^2 = 0.77) was more strongly associated with efficacy than C_{max}/MIC (R^2 = 0.57) for *S. aureus*, whereas C_{max}/MIC (R^2 = 0.90) was the predictive index for S. *pneumoniae* vs. AUC/MIC (R^2 = 0.78). Free AUC/MIC ratios of 160 ± 67 and 7.2 ± 4.52 were associated with bacteriostatic effect for *S. aureus* and *S. pneumoniae*, respectively, with the less frequent dosing regimen (every 72 hours), and exposures required for a 2-log kill were only slightly greater (less than twofold). Overall, less drug exposure (approximately 10-fold) was necessary against *S. pneumoniae* than *S. aureus* (Andes and Craig, 2007). Comparatively, a recent neutropenic murine thigh infection model demonstrated lower AUC/MIC target values. In this study, the