exposure-response model for dalbavancin was well described by the pharmacodynamic (PD) index AUC/MIC ($R^2 = 0.86$). Against *S. aureus* isolates (MIC range 0.12–0.5mg/l), including VISA, the free drug AUC/MIC targets for stasis, 1-log kill, and 2-log kill were 27, 53, and 111, respectively (Lepak *et al.,* 2015).

The 7-day AUC for dalbavancin (1000 mg) in humans is 8992 mgh/l (Marbury *et al*., 2009). Using protein binding in humans of 93%, the average daily (24-hour) free drug AUC over the treatment period is 89.9 mgh/l. These findings suggest that the current human dosing regimen could achieve a 1-log kill for *S. aureus* strains with dalbavancin MICs of ≤ 1 mg/l (Lepak *et al*., 2015). In population parametric models, the standard dose of dalbavancin demonstrated that the free plasma concentrations of dalbavancin remain above 1 mg/l for 14 days (Dowell *et al*., 2008). The likelihood of target attainment was near 100% at dalbavancin MICs up to 0.5 mg/l against *S. aureus* isolates. A similar finding was demonstrated in a recent study with 10,000 Monte Carlo simulations of dalbavancin, 1000 mg, followed by 500 mg 1 week later. The results showed a 100% probability of target attainment for MRSA isolates with dalbavancin MICs up to 0.12 mg/l (Salem *et al*., 2014).

A pharmacokinetic analysis of a single dalbavancin dose (1000 mg if > 60 kg or 15 mg/kg if < 60 kg) in children 12–17 years of age demonstrated dose proportionality, with similar $t_{1/2}$ and plasma exposures between the two doses (Bradley *et al*., 2015). Although the AUC in children was ~30% lower than in adults, the volume of distribution at steady state was similar (Bradley *et al*., 2015).

5d. Excretion

In a phase I study, nearly 34% of dalbavancin was excreted unchanged in the urine, suggesting that nonrenal methods of elimination play an important role in the metabolism of dalbavancin (Leighton *et al*., 2004). A different elimination route for dalbavancin was found in a rat study, as 3.7%, 17.4%, and 22.3% of dalbavancin were recovered in feces at 1, 36, and 70 days, respectively, following a 20 mg/kg dose (Cavaleri *et al*., 2005).

5e. Drug interactions

To date, major drug interactions with dalbavancin have not been identified. It is not a substrate, inhibitor, or inducer of CYP450 isoenzymes (Buckwalter and Dowell, 2005).

6. ADVERSE REACTIONS AND TOXICITY

In a phase I dose-escalation study, dalbavancin was well tolerated with no serious AEs in 39 evaluated subjects (Leighton *et al*., 2004). Although 68% experienced at least one AE, most events were considered mild. The most common AEs were pyrexia (50%) and headache (25%), which were also experienced by patients receiving placebo (pyrexia, 38%; headache, 31%). No auditory toxicity was detected at any time point (2, 7, 14, or 21 days after drug administration) for all subjects within the conventional (0.25–8 kHz) and high-frequency (9–16 kHz) range, as specified by the American Speech–Language–Hearing Association 1994 criteria (Campbell *et al*., 2003). No vestibular dysfunction was observed according to the Dizziness Handicap Inventory, with a zero score at all time-points in all subjects (Campbell *et al*., 2003). Dose-related effects were not seen over the range of doses tested with the single-dose group (140–1120 mg) and the multiple-dose group given as a loading dose on the first day, followed by daily maintenance doses for 6 days (300/30–1000/100 mg) (Leighton *et al*., 2004).

A safety database was compiled from seven different phase II and III studies between 2002 and 2013 evaluating dalbavancin against different comparator agents (cefazolin, nafcillin, oxacillin, vancomycin, and linezolid) for the treatment of uncomplicated and complicated skin infections, catheter-related bloodstream infections, and ABSSSIs (Dunne *et al*., 2016b). The database contains 1778 subjects who received dalbavancin and 1224 subjects who received a comparator agent. Approximately 85% and 86.5%, respectively, of the subjects completed the study drug course of therapy. Treatment-related AEs for dalbavancin and comparator agents are displayed in Table 47.4. Overall, most AEs experienced with dalbavancin were gastrointestinal in nature, of mild to moderate intensity, and comparable to comparator agents. Relative to those treated with comparator, patients receiving dalbavancin experienced fewer treatment-emergent AEs (44.9% vs. 46.8 %, respectively; $p = 0.012$), fewer treatment-related AEs (18.4% vs. 20.1%, respectively; $p = 0.014$), and fewer treatment-related serious AEs (0.2% vs. 0.7%, respectively; $p = 0.021$). However, in subjects with normal hepatic function at baseline, determined by alanine aminotransferase levels, 218 (15.2%) subjects receiving dalbavancin had alanine aminotransferase levels above the upper limit of normal compared with 139 (14.3%) subjects receiving the comparator post-therapy. There were no treatment-related serious AEs involving the renal, nervous, auditory, or vestibular systems. The rate of discontinuations due to AE was found to be low for dalbavancin (3.0%), similar to comparator agents (2.9%). Ten deaths were observed in the dalbavancin group, whereas 14 deaths occurred in the comparator group.

Dunne and colleagues (2015a) specifically looked at the effect that dalbavancin has on QT prolongation. Fifty patients in each group received dalbavancin at 1000 mg, dalbavancin at 1500 mg, placebo i.v., or 400 mg of oral moxifloxacin. The findings showed that dalbavancin did not exert a relevant effect on heart rate or PR or QRS intervals. Doses up to 1500 mg of dalbavancin did not prolong the QTc interval and had no effect on heart rate or PR and QRS intervals.

7. CLINICAL USES OF THE DRUG

Leading up to the FDA's approval of the two-dose dalbavancin regimen for ABSSSIs, one phase II trial and three phase III trials for the treatment of skin and skin structure