2012). The AUC_{0-24} was 2896 ± 2755 and 8892 ± 5589 for the 0.2- and 1-mg doses, respectively. On the fourth day, the daptomycin concentrations were 20 ± 14 and 80 ± 56 mg/l for the 0.2- and 1-mg doses, respectively. On day 7 these concentrations were 3 ± 1.6 and 25 ± 20. The elimination half-life ($t_{1/2}$) of daptomycin was independent of the administered dose (38.8 ± 16.5 and 40.9 ± 6.7 hours, respectively, for the 0.2- and 1-mg doses) and was significantly longer than the $t_{1/2}$ of vancomycin (20.5 ± 2.0 hours for the vancomycin, 1 mg, group) ($p < 0.05$) (Lefèvre *et al.*, 2012). However, the use of daptomycin as an intravitreal injection seems limited by toxicity. Four doses of intravitreal daptomycin were injected into rabbit eyes. The 75- and 188-μg doses of daptomycin demonstrated acceptable safety profiles when injected intravitreally in Dutch-belted rabbits. However, there was a dose-dependent increase in cataract formation, electroretinogram suppression, and photoreceptor damage with higher doses (Comer *et al.*, 2011).

A rabbit model was also used to study the penetration of daptomycin in the aqueous humor. After topical application on the corneal epithelium of rabbit eyes of a single drop of 50 μl containing 1% daptomycin, 30 minutes later the concentration of daptomycin in the aqueous humor was undetectable for both scraped and nonscraped epithelium. The application regimen of drops every 15 minutes for 1 hour resulted in concentrations in the aqueous humor of 1.90 ± 0.15 and 1.71 ± 0.42 mg/l at 1 and 2 hours, respectively, after the last drop for the nonscraped group. For the scraped group these concentrations were 5.19 ± 0.5 and 4.96 ± 0.47 mg/l, respectively (Sakarya *et al.*, 2013).

5c. Clinically important pharmacokinetic and pharmacodynamic features

Daptomycin displays concentration-dependent activity that is best characterized by the pharmacodynamic indices AUC/MIC or C_{max}/MIC. The pharmacodynamics of daptomycin for *S. pneumoniae, S. aureus,* and *E. faecium* were characterized in the neutropenic mouse model (Safdar *et al.*, 2004). Free daptomycin exhibited concentration-dependent killing. The pharmacodynamic indices that correlated best with *in vivo* efficacy were 24-hour AUC/MIC ratio (R^2 = 86%) and C_{max}/MIC (R^2 = 83%) for standard strains of *S. aureus* and *S. pneumoniae*. The C_{max}/MIC ratios required for a bacteriostatic effect ranged from 12–36 for *S. pneumoniae*, from 59–94 for *S. aureus*, and from 0.14–0.25 for *E. faecium*. The AUC/MIC ratios required for a bacteriostatic effect ranged from 75–237 for *S. pneumoniae*, from 338–537 for *S. aureus*, and from 0.94–1.67 for *E. faecium*. The free daptomycin concentrations needed were an average of one to two times the MIC over 24 hours to produce a bacteriostatic effect, and two to four times the MIC over 24 hours to produce greater than 99% killing. Translating this information to the human situation, it can be calculated that a mean AUC of approximately 400 mgh/l (as reached with a dose of 4 mg/kg in humans) and a mean MIC of an *S. aureus* strain of approximately 0.25 mg/l result in mean AUC/MIC ratios that should be sufficient for a bactericidal effect. However, in the case of lower AUCs owing to increased clearance of the drug or a higher MIC, higher doses are likely to be needed.

The daptomycin free (*f*)AUC/MIC ratio for a static effect and 3-log reduction in viable MRSA count was also determined in a pharmacokinetic *in vitro* model. The *f*AUC/MIC ratios for a static effect and 1-log and 3-log drop were 37.2 +/– 16.5, 40.6 +/– 17.8 and 49.8 +/– 19.2, respectively. A higher inoculum reduced the antibacterial effects (Bowker *et al.*, 2009).

In clinical studies a clear relationship between exposure and outcome was not consistently found. In 55 patients with an *S. aureus* skin infection treated with 4 mg/kg of daptomycin daily, there was no relation between AUC/MIC and the probability of clinical success (OR: 1.03; 95% CI: 0.73–1.45) or of microbiological success (OR: 0.94; 95% CI: 0.81–1.09) (Takesue *et al.*, 2015). On the other hand, in 35 patients with severe Gram-positive infections and various creatinine clearances treated with two dosing regimens of daptomycin, an AUC/MIC < 666 was associated with increased mortality. Other factors, such as infection acquired in the intensive care unit and hypoalbuminemia, were also associated with increased mortality (Falcone *et al.*, 2013a).

With the help of the available literature, Monte Carlo simulations were performed to determine the probability of bacteriologic efficacy for various dosing regimens and MICs. By considering a probability of target attainment of > 90% as being adequate as well as the risk for toxicity, it was determined that the most favorable dosing regimen in the treatment of microorganisms with an MIC of ≤ 1 mg/l was 10 mg/kg/day (Soon *et al.*, 2013). However, a 90% probability of target attainment is often considered too low, and even higher doses may therefore be needed.

By using the known relationship between exposure to daptomycin and clinical outcome in patients with *S. aureus* bacteremia as well as by using Monte Carlo simulations, a U-shaped exposure-response relationship for clinical response was found. This indicates that the AUC/MIC ratio resulted in a favorable clinical outcome in the case of a low ratio (AUC/MIC ≤ 1081) and in the case of a high ratio (AUC/MIC > 2337). The clinical success rates were 100% and 75% for the groups with the low and the high AUC/MIC ratios, respectively. The middle-range group had clinical success in 60.5% of cases. It appeared that the group with the low AUC/MIC ratio had a more favorable profile in regard to other variables, such as better renal function, higher albumin level, and a greater percentage of patients with uncomplicated bacteremia. This might explain the high success rate in this group (Bhavnani *et al.*, 2015). The probability of success improved substantially in subgroups of patients, such as patients with left-sided endocarditis, good renal function, and a higher albumin concentration, after optimizing the exposure (from 0.577–0.832). Time to decreased susceptibility was also analyzed at day 30 after start of therapy. The probability of decreased susceptibility was high (0.278) in the middle AUC/MIC range (between 1480 and 1970). In the case of a low AUC/MIC ratio, the probability of decreased susceptibility