CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-572

Clinical Pharmacology and Biopharmaceutics Review

NDA#	21-572
PRODUCT	Daptomycin (Cubicin™)
FORMULATION	Sterile powder for injection
DOSAGE STRENGTH	250 mg and 500 mg vials
SUBMISSION DATES	12/19/02, 3/17/03, 3/26/03, 3/27/03, 4/11/03, 5/19/03, 5/20/03, 5/28/03, 5/29/03, 6/19/03, 8/8/03, 9/3/03
SUBMISSION TYPE	New Molecular Entity, 1P
SPONSOR	Cubist Pharmaceuticals, Inc., Lexington, MA 02421
OCPB DIVISION	Division of Pharmaceutical Evaluation III
MEDICAL DIVISION	Division of Anti-Infective Drug Products
REVIEWER	Charles R. Bonapace, Pharm.D.
PM REVIEWER	Jenny J. Zheng, Ph.D.
TEAM LEADER	Philip M. Colangelo, Pharm.D., Ph.D.

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

I: EXECUTIVE SUMMARY

Cubist Pharmaceuticals, Inc. submitted a priority review New Drug Application for Cubicin™ (daptomycin for injection) on December 19, 2002. Daptomycin is a cyclic lipopeptide antibiotic derived from the fermentation of a strain of *Streptomyces roseosporus* that demonstrates *in vitro* activity against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus*. The proposed dosing regimen of daptomycin is 4 mg/kg intravenously administered over 30 min q24h for 7 to 14 days. The sponsor is seeking an indication for complicated skin and skin structure infections —— —— caused by susceptible strains of the following Gram-positive organisms: *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subsp. *equisimilis*, *Enterococcus faecalis* (vancomycin-susceptible strains only), ——.

Daptomycin represents a new class of antibacterial agents with a novel mechanism of action that involves binding to the bacterial cell membrane followed by membrane depolarization and cell death. Since the mechanism of action of daptomycin is different from other antimicrobial agents, it may offer a therapeutic alternative in select cases of antimicrobial resistance. The goal of Cubist continues to be focused on delivering daptomycin to the market as quickly as possible to address the pressing public health need for new classes of antibiotics effective in treating serious and life-threatening infections caused by Gram-positive pathogens, particularly *Staphylococcus aureus* (including methicillin-resistant strains).

Several review issues have been identified that impact the quality of data submitted for review. These issues consist of the analytical methodology in the renal impairment study, the impact of using estimated creatinine clearance (Cockcroft and Gault equation) vs. measured creatinine clearance, the unusually large degree of inter-study variability among studies with healthy adult subjects, and the impact of this variability in assessing a dosage recommendation in elderly subjects.

In the renal impairment study (Study DAP-00-01), plasma concentrations of daptomycin were initially determined by a validated —— method for all subjects (controls and renal impairment). Since plasma concentrations of daptomycin were greater than other phase 1 studies with the same once-daily dose, the sponsor determined the concentration of daptomycin in subjects with normal renal function using a validated —— assay. The —— method overestimated the plasma concentrations of

daptomycin by an average of 46% (accuracy ranged from 73% to 187%). Thus, the sponsor converted plasma concentrations of daptomycin determined by — to the — for all subjects in study DAP-00-01 using the equation derived from the linear relationship between samples determined by — The accuracy of daptomycin concentrations exceeded 100 ± 15% in 34% of plasma samples as determined by the reviewer. The sponsor re-assayed all plasma samples from Study DAP-00-01 (subjects with normal and impaired renal function) using the validated — assay.

Also in Study DAP-00-01, the sponsor assigned subjects for the pharmacokinetic analysis to treatment groups based on estimated creatinine clearance (CL_{CR}) using the Cockcroft & Gault equation and ideal body weight (IBW). However, many of the subjects were obese based on a mean body mass index of 31.1 kg/m^2 that ranged from — kg/m^2. The reviewer assigned subjects to treatment groups based on their measured creatinine clearance. Due to differences between the estimated CL_{CR} using Cockcroft & Gault and the measured CL_{CR}, only one subject remained in the 30-50 mL/min treatment group.

In a second renal impairment study (Study DAP-MDRI-01-09), the sponsor enrolled eight subjects with moderate renal impairment (CL_{CR} 30-50 mL/min). The sponsor did not enroll a control group. All subjects had a CL_{CR} of 30-50 mL/min using IBW, three subjects had a CL_{CR} of 30-50 mL/min using actual body weight, and one subject had a CL_{CR} of 30-50 mL/min based on a measured creatinine clearance. This study was unable to provide information about the pharmacokinetics of daptomycin in subjects with CL_{CR} 30-50 mL/min.

The mean daptomycin C_{max} ranged from 42.3 to 62.4 µg/mL (1.48-fold) and the $AUC_{0-\infty}$ ranged from 301 to 517 µg*hr/mL (1.72-fold) from Phase 1 studies in which healthy volunteers received a single 4 mg/kg dose of daptomycin. The inter-subject variability of C_{max} and $AUC_{0-\infty}$ within a study was generally <20%. The source of variability between studies is unknown.

In the geriatric study (Study DAP-GER-01-11), the mean $AUC_{0-\infty}$ from healthy elderly subjects was within the range of values for healthy subjects from previous Phase 1 studies, although the $AUC_{0-\infty}$ from the control group (healthy young subjects) was less than previously observed from healthy subjects. The mean $AUC_{0-\infty}$ for elderly subjects was 58% greater than the control group of young subjects. Based on these findings and safety data from Phase 3 clinical studies, no dosage adjustment of daptomycin is warranted for elderly subjects with normal (for their age) renal function.

In skin blister study (DAP-00-04), the sponsor used a microbiological assay validated with serum to determine the concentration of daptomycin from plasma. No data were submitted to demonstrate the cross-validation of the microbiological assay in serum and plasma. It is known that anticoagulants can alter the *in vitro* protein binding of highly protein bound drugs (M. Klassen, S.C. Edberg. 1996. Measurement of antibiotics in human body fluids: Techniques and significance, p. 230-294. *In* V. Lorian (ed.), Antibiotics in laboratory medicine, Fourth edition, Williams and Wilkins, Baltimore) and thus, impact the results of a microbiological assay. Since the plasma concentrations of daptomycin from study DAP-00-04 were greater than any previous Phase 1 study in which healthy subjects received the same dose, the results of this study were deemed unacceptable for labeling purposes.

COMMENTS:

1. Although the sponsor used cryopreserved hepatocytes to assess the potential of daptomycin to act as an inhibitor and inducer of cytochrome P450 isoforms, the sponsor has not assessed the potential of daptomycin to act as a substrate. The sponsor is encouraged to evaluate the potential of daptomycin to act as a substrate of the predominant cytochrome P450 isoforms.

2. The reviewer recommends a dosage adjustment for patients with renal impairment, beginning at moderate renal impairment (CL_{CR} 30-50 mL/min). However, there was only one subject with a CL_{CR} of 30-50 mL/min in the renal impairment study (Study DAP-00-01) based on measured creatinine clearance. Although the relationship between CL_{CR} and CL_T is linear with increasing renal impairment, additional data are necessary to characterize the pharmacokinetics of daptomycin in subjects with moderate renal impairment.

A. RECOMMENDATIONS:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation III (OCPB/DPE-III) has reviewed NDA . The submission is acceptable from a Clinical Pharmacology point of view provided that the sponsor agrees with the Agency's label recommendations.

The Phase IV Commitment recommendations and labeling comments outlined in the annotated label should be conveyed to the sponsor.

B. PHASE IV COMMITMENTS:

1. [redacted]

2. It is recommended that the sponsor perform a clinical study to assess the safety, efficacy, and pharmacokinetics of daptomycin in renal impairment patients with complicated skin and skin structure infections. The sponsor is encouraged to include patients with foot and decubitus ulcers complicated by diabetes. Enrollment into the study should be limited to patients with an estimated (via the Cockcroft and Gault equation using ABW) creatinine clearance ≤50 mL/min and an attempt should be made to enroll an equal number of patients into the following categories: CL_{CR} 30-50 mL/min, CL_{CR} <30 mL/min, hemodialysis patients, and CAPD patients.

/S/

Charles R. Bonapace, Pharm.D.
Office of Clinical Pharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Philip M. Colangelo, Pharm.D., Ph.D., /S/
Team Leader

cc:
Division File: NDA 21-572
HFD-520 (CSO/Peat)
HFD-520 (MO/Ross, Thompson, Nambiar, Sorbello)
HFD-520 (Microbiology/Sheldon, Coderre)
HFD-880 (Division File, Lazor, Selen, Colangelo, Bonapace)
CDR (Clin. Pharm./Biopharm.)

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III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Eli Lilly and Company initiated the original development of daptomycin. Cubist licensed worldwide rights for daptomycin from Eli Lilly and Company on November 7, 1997 and submitted its Investigational New Drug Application (IND 57,693) on December 31, 1998 to begin clinical trials for daptomycin. The pre-clinical and clinical data previously generated by Eli Lilly and Company were used to support Cubist's initial clinical trials. Concurrently with conducting Phase 2 and 3 studies, Cubist initiated a full Phase 1 clinical pharmacology program with daptomycin to investigate daptomycin's pharmacokinetic profile in healthy subjects, special populations (renal impairment, hepatic impairment, elderly, and obesity), drug-drug interactions (probenecid, aztreonam, warfarin, and simvastatin), effects on nerve conduction and cardiac repolarization, and penetration of daptomycin into cantharides-induced skin blister fluid.

Cubist modified Eli Lilly's clinical strategy of administering divided daily doses to once-daily dosing since previous preclinical studies, data analysis, and modeling that showed that once-daily dosing may maximize the antibacterial efficacy while minimizing adverse effects.

Many of the Phase 1 clinical pharmacology studies performed by Eli Lilly and Company were not included in this review due to missing analytical validation data, illegible study reports, and/or assessment of pharmacokinetics with sub-clinical doses.

Pharmacokinetics in healthy subjects

The pharmacokinetics of daptomycin were assessed in 18 healthy subjects who received 4 mg/kg IV q24h for 7 days, 6 mg/kg IV q24h for 7 days, and 8 mg/kg IV q24h for 14 days. After the first dose of daptomycin, the pharmacokinetics were approximately linear based on total and unbound concentrations from 4 mg/kg to 6 mg/kg, whereas the total and unbound C_{max} and $AUC_{0-\infty}$ increased modestly greater than-dose proportional for the 8 mg/kg dose. After administration of 7 doses, the C_{max} and AUC_{0-24} based on total concentrations increased similar to the predicted accumulation for all three doses. Based on unbound concentrations, the C_{max} also increased similar to the predicted accumulation.

Distribution

After intravenous administration, the mean steady-state apparent volume of distribution ranged from 0.0875 to 0.0925 L/kg for 4 mg/kg to 6 mg/kg. The plasma concentration-time profiles were adequately fit using a 2-compartment model for doses ranging from 4 mg/kg to 8 mg/kg. The mean protein binding of daptomycin was approximately 92% and was independent of the plasma concentration. Daptomycin is primarily bound to human serum albumin in a concentration-independent manner, and to a lesser extent, human alpha-1-acid glycoprotein in a concentration-dependent manner (ranging from 40% to 25% over daptomycin concentration from 2.5 to 80 µg/mL, respectively).

The pharmacokinetics of daptomycin were assessed in four healthy adults with cantharides-induced skin blisters following a single 4 mg/kg IV dose of daptomycin. The mean plasma C_{max} and AUC_{0-24} were 80.1 µg/mL and 473 µg*hr/mL, respectively. The mean skin blister fluid C_{max}, AUC_{0-24}, and T_{max} were 22.7 µg/mL, 287 µg*hr/mL, and 3.5 hrs. The mean percent penetration in skin blister fluid was 61.0%. However, the results are unacceptable since the sponsor used a microbiological assay validated with serum to determine the concentration of daptomycin in plasma.

Metabolism
The sponsor has not assessed the potential of daptomycin to act as a substrate of cytochrome P450 isoforms using *in vitro* methods. A mass balance study demonstrated the presence of inactive metabolites of daptomycin in urine since the concentration of daptomycin determined by microbiological assay was less than the concentration based on total radioactivity. It is unknown if active metabolites of daptomycin are present in serum and/or urine.

Excretion
Based on the results of the mass balance study, approximately 78% of the administered dose was excreted in urine based on total radioactivity and 5.7% of the administered dose was excreted in feces collected for up to nine days. Only 52% of the administered dose was recovered from urine using microbiological assay.

Pharmacokinetics in Special Populations
Renal impairment
The effect of renal impairment on the pharmacokinetics of daptomycin were assessed after a single intravenous 4 mg/kg dose to 29 subjects with varying degrees of renal impairment. The mean $AUC_{0-\infty}$ was 50%, 92%, and 128% higher in subjects with CL_{CR} 50-80 mL/min, 30-50 mL/min, and CL_{CR} <30 mL/min, respectively compared to subjects with normal renal function. The mean $AUC_{0-\infty}$ was 120% higher in hemodialysis patients not receiving hemodialysis and 165% higher in CAPD patients compared to subjects with normal renal function. The CL_T was associated with measured creatinine clearance (r^2 = 0.688) and the mean CL_T progressively decreased as the degree of renal impairment increased. The mean CL_T was 32%, 49%, and 56% lower in subjects with CL_{CR} 50-80 mL/min, 30-50 mL/min, and CL_{CR} <30 mL/min, respectively compared to subjects with normal renal function. The mean CL_T was 55% lower in hemodialysis patients not receiving hemodialysis and 63% in CAPD patients compared to subjects with normal renal function. The unbound fraction of daptomycin was similar among subjects with creatinine clearance ranging from >80 mL/min to <30 mL/min, whereas the unbound fraction increased in hemodialysis and CAPD patients. The reviewer recommends a dosage adjustment for patients with creatinine clearance <30 mL/min.

Hepatic impairment
The effect of hepatic impairment on the pharmacokinetics of a single 4 mg/kg dose of daptomycin were assessed in 10 subjects with hepatic impairment (Child-Pugh Class B) and 9 matched healthy controls. Compared to healthy subjects, the mean C_{max} and $AUC_{0-\infty}$ values were similar between subjects with hepatic impairment and healthy subjects. The mean CL_T was 8% greater in subjects with hepatic impairment compared to healthy subjects and the mean terminal elimination half-life was shorter in subjects with hepatic impairment compared to healthy volunteers (8.97 hrs vs. 9.44 hrs, respectively). No dosage adjustment is warranted for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment was not assessed.

Elderly
The effect of age on the pharmacokinetics of a single 4 mg/kg dose of daptomycin were assessed in 12 healthy elderly subjects (≥75 years of age) and 11 matched young controls (18 to 30 years of age). The mean C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 4%, 46%, and 58% greater, respectively in healthy elderly subjects compared to young subjects. The mean CL_T, CL_R, and Ae were 35%, 41%, and 19% lower in elderly subjects compared to young subjects whereas the terminal elimination half-life was 74% greater in elderly subjects. However, the mean AUC_{0-24}, $AUC_{0-\infty}$, C_{24}, and CL_T were similar between healthy elderly subjects and healthy subjects from study DAP-00-02. Based on the findings of this study and safety data from the Phase 3 clinical studies, no dosage adjustment is warranted for elderly patients with normal (for their age) renal function.

Obesity
The pharmacokinetics of daptomycin were assessed in six moderately obese subjects (BMI 25-39.9 kg/m^2), six extremely obese subjects (BMI ≥40 kg/m^2), and 12 matched control subjects matched for gender, age, and renal function following the administration of a single 4 mg/kg IV dose (based on total body weight). In moderately obese subjects, the mean C_{max} and $AUC_{0-\infty}$ were 25% and 30% greater, respectively in obese subjects than matched controls. The mean CL_T and CL_R (not corrected by body weight) were 18% and 16% greater, respectively in moderately obese subjects compared to matched controls. In extremely obese subjects, the mean C_{max} and $AUC_{0-\infty}$ were 26% and 31% greater, respectively in obese subjects than matched controls. The mean CL_T and CL_R (not corrected by body weight) were 46% and 34% greater, respectively in extremely obese subjects compared to matched controls. Correction of CL_T and CL_R by actual body weight resulted in values that were less than weight-corrected clearance terms for matched controls, whereas correction of CL_T and CL_R by ideal body weight resulted in values that were greater than weight-corrected clearance terms for matched controls. The reviewer identified a dosage correction factor for moderately obese and extremely obese subjects (see page 149). However, the increase in exposure among obese subjects was less than other special populations and the dosage adjustment is not recommended for obese patients.

Drug-Drug Interactions
Based on the *in vitro* results, daptomycin IV 4 mg/kg is unlikely to inhibit or induce the metabolism of drugs dependent on cytochrome P450 isoforms CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4. However, it is unknown if daptomycin is a substrate of cytochrome P450 isoforms. The sponsor conducted clinical pharmacology studies to assess the interaction between daptomycin and aztreonam, probenecid, warfarin, simvastatin, and tobramycin.

Aztreonam
The pharmacokinetics of daptomycin and aztreonam were assessed in 15 healthy subjects following the administration of a singe dose of both daptomycin IV 6 mg/kg and aztreonam IV 1,000 mg. When daptomycin was administered with aztreonam, the mean C_{max}, $AUC_{0-\infty}$, CL_T, CL_R of either daptomycin or aztreonam were not substantially altered. The 90% confidence intervals of the geometric mean ratios for $AUC_{0-\infty}$ and C_{max} were within the predetermined limits of 0.80 to 1.25 for daptomycin and aztreonam and were not statistically significantly different. No dosage adjustment of either daptomycin or aztreonam is warranted when co-administered to patients.

Probenecid
The pharmacokinetics of a single daptomycin IV 4 mg/kg dose co-administered with probenecid 500 mg q6h for 10 doses were assessed in five healthy subjects. When daptomycin was administered with probenecid, the mean daptomycin C_{max}, $AUC_{0-\infty}$, CL_T, and CL_R of daptomycin was essentially unchanged. The 90% confidence intervals of the geometric mean ratios for $AUC_{0-\infty}$ and C_{max} for daptomycin were within the predetermined limits of 0.80 to 1.25 and were not statistically significantly different. No dosage adjustment of daptomycin is warranted in patients receiving probenecid 500 mg QID.

Warfarin
In a study to assess the pharmacokinetics of daptomycin and warfarin as well as the pharmacodynamics of warfarin, 16 healthy adult subjects received daptomycin IV 6 mg/kg q24h or placebo for 9 days with a single oral dose of warfarin 25 mg on Day 5. The mean C_{max}, $AUC_{0-\tau}$, and CL_T of daptomycin were similar when co-administered with warfarin. The mean C_{max}, $AUC_{0-\infty}$, and CL_T/F of R-warfarin and S-warfarin were not appreciably altered when co-administered with daptomycin. No pharmacodynamic interaction between warfarin and daptomycin was observed when warfarin was administered with daptomycin at steady-state. No dosage adjustment of either daptomycin or warfarin is recommended when co-administered to patients.

Simvastatin
In a study to assess the safety of daptomycin in subjects on a stable daily dose of simvastatin, 20 adult (≥30 years of age) subjects received daptomycin IV 4 mg/kg q24h or placebo for 14 days with simvastatin 40 mg daily. The mean trough concentration of daptomycin co-administered with simvastatin was similar to values reported in other studies. The mean plasma trough concentrations of simvastatin between subjects receiving daptomycin or placebo (NS) were similar. CPK concentrations remained below the upper limit of normal (60 to 400 U/L for males, 40 to 150 U/L for females) over 14 days of daptomycin or placebo administration. Although no dosage adjustment of daptomycin or simvastatin is warranted when co-administered to patients, concomitant administration of daptomycin and simvastatin is not recommended since inhibitors of HMG-CoA reductase may cause myopathy.

Tobramycin
Based on the results from a published study, the mean C_{max} and $AUC_{0-\infty}$ of daptomycin increased 12.7% and 8.7%, respectively when administered with tobramycin, whereas the mean C_{max} and $AUC_{0-\infty}$ of tobramycin decreased 10.7% and 6.6%, respectively when administered with daptomycin. No significant differences in any of the pharmacokinetic parameters were detected between the individual and combination treatments of the two agents. However, the dose of daptomycin assessed in the study (2 mg/kg) is less than the proposed therapeutic dose (4 mg/kg) for the treatment of complicated skin and skin-structure infections and the dose of tobramycin (1 mg/kg) is the minimal customary dose (3-5 mg/kg in divided doses or 7 mg/kg as a single dose). Caution is warranted when daptomycin is co-administered with tobramycin.

Cardiac Repolarization
In a randomized, placebo-controlled, double-blind study of 120 healthy adult subject, peripheral nerve function and cardiac repolarization were compared in subjects administered either IV daptomycin 6 mg/kg q24h or placebo for 14 consecutive days. Peripheral nerve function was assessed by electrophysiological measurement of the median nerve motor function, vibratory perception thresholds, and a neurological questionnaire (total, neuropathy, and myopathy components) on the day prior to dosing, Day 14, and two weeks after the end of treatment (Day 28). No statistically significant differences were observed in a comparison of change from baseline for electrophysiological measurement of the median nerve motor function or vibratory perception threshold. A statistically significant difference was observed between groups at Day 28 based on total score ($p=0.024$) and neuropathy specific questions ($p=0.048$) of the neurological questionnaire.

QT values from all subjects on Day 1 and Day 8 (pre-dose, 0.5, 1, 1.5, 2, 6, and 12 hrs) were corrected using Bazett's correction formula. The range in QTc values were similar between subjects receiving daptomycin and placebo and there were no statistically significant differences in the mean QTc values at any time point. QTc values corrected for baseline were not statistically significantly different between the treatment groups with respect to mean change from baseline. In addition, QT values corrected using Fridericia's correction formula were similar to those corrected using Bazett's.

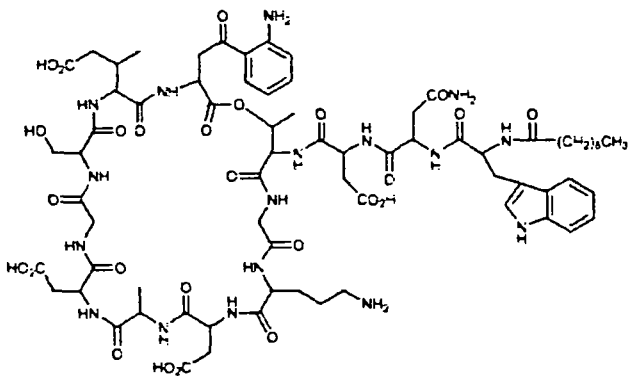
IV. QUESTION-BASED REVIEW

A. General Attributes

1. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product? What is the proposed mechanism of drug action and therapeutic indications? What is the proposed dosage and route of administration?

Daptomycin is a cyclic lipopeptide antibiotic derived from the fermentation of a strain of *Streptomyces roseosporus*.

The chemical name of daptomycin is N-decanoyl-L-tryptophyl-L-asparaginyl-L-aspartyl-L-threonylglycyl-L-ornithyl-L-aspartyl-D-alanyl-L-aspartylglycyl-D-seryl-*threo*-3-methyl-L-glutamyl-3-anthraniloyl-L-alanine ε_1-lactone. The chemical formula is $C_{72}H_{101}N_{17}O_{26}$ and the molecular weight is 1620.67. The chemical structure of daptomycin is shown below:



Daptomycin for injection is supplied as a sterile, preservative-free, pale yellow to light brown, lyophilized cake containing approximately 900 mg/g of daptomycin for intravenous use following reconstitution with 0.9% sodium chloride injection, USP. The only inactive ingredient is sodium hydroxide, which is used for pH adjustment. The formulation components of daptomycin for injection are shown in Table 1.

Table 1. Components and quantitative formulation of the unit dosage form - drug product

Component	Function	Quantity/250 mg vial	Quantity/500 mg vial
Daptomycin	Active ingredient	250 mg ± 10%	500 mg ± 10%
Sodium hydroxide, NF	pH adjustment		

The proposed mechanism of action for daptomycin is shown below in Figure 1. Daptomycin inserts directly into the cytoplasmic membrane of Gram-positive bacteria via a calcium-dependent process (Step 1). An ion-conduction structure is formed by the oligomerization of the inserted drug (Step 2). Finally, the ion structure disrupts the functional integrity of the membrane, resulting in release of intracellular potassium ions and dissipation of the membrane potential (Step 3). Depolarization of the membrane is followed by the arrest of bacterial DNA, RNA, and protein synthesis, and cell death. A secondary effect of daptomycin on Gram-positive bacteria may be the inhibition of lipoteichoic acid synthesis.

The antibacterial activity of daptomycin requires the presence of free (ionized) calcium. The effect of calcium over a range of 0-200 mg/L on the *in vitro* MIC of daptomycin using *S. aureus* ATCC 25923 and *E. faecalis* ATCC 29212 demonstrated that as the calcium concentration increased over this range, the MIC of daptomycin decreased 8 $\log_2$ (8-fold) for *E. faecalis* and 7 $\log_2$ (7-fold) for *S. aureus*. Broth supplemented with 50 mg/L calcium has a free (ionized) calcium concentration of 1.10 mmol/L and is similar to the normal range found in human serum (1.15-1.31 mmol/L).

Figure 1. Model for the mechanism of action of daptomycin

Daptomycin demonstrates *in vitro* activity against Gram-positive aerobes and Gram-positive anaerobes. Daptomycin demonstrates poor *in vitro* activity (MIC values 8 to >128 µg/mL) against Gram-negative aerobes and Gram-negative anaerobes.

The sponsor is seeking an indication for the treatment of complicated skin and skin structure infections ; caused by susceptible strains of the following Gram-positive organisms: *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subsp. *equisimilis*, *Enterococcus faecalis* (vancomycin-susceptible strains only). The proposed dosing regimen of daptomycin is 4 mg/kg administered intravenous (IV) over 30 min q24h for 7 to 14 days.

2. What efficacy and safety information contribute to the assessment of clinical pharmacology and biopharmaceutics study data?

The sponsor performed two Phase 3 clinical studies evaluating the safety and efficacy of daptomycin for the treatment of complicated bacterial skin and soft tissue infections (DAP-SST-98-01 and DAP-SST-99-01). Two additional Phase 3 clinical studies (DAP-CAP-00-05 and DAP-CAP-00-08) were submitted to provide supportive safety data of daptomycin in the treatment of community acquired pneumoniae. The Phase 3 clinical studies supporting the treatment of complicated bacterial skin and soft tissue infections are summarized below.

DAP-SST-98-01: This study was a multicenter, investigator blinded, randomized trial comparing the safety and efficacy of IV daptomycin to that of IV vancomycin or selected IV semi-synthetic penicillins in the treatment of complicated bacterial skin and soft tissue infections known or suspected to be due to Gram-positive organisms. Subjects were randomized to receive either IV daptomycin 4 mg/kg q24h (n=264 randomized) or comparator drug (n=266 randomized) for 7 to 14 days. Comparators consisted of vancomycin and antistaphylococcal penicillins (nafcillin, oxacillin, cloxacillin, and flucloxacillin). Subjects with a CL_{CR} of 70 to 30 mL/min were to receive a modified dosing regimen for daptomycin (4 mg/kg loading dose, followed by 3 mg/kg q36 hr); subjects with CL_{CR} <30 mL/min were excluded from the trial.

DAP-SST-99-01: This study was a multicenter, investigator blinded, randomized trial comparing the safety and efficacy of IV daptomycin to that of IV vancomycin or selected IV semi-synthetic penicillins in the treatment of complicated bacterial skin and soft tissue infections known or suspected to be due to Gram-positive organisms. Subjects were randomized to receive either IV daptomycin 4 mg/kg q24h (n=277 randomized) or comparator drug (n=294 randomized) for 7 to 14 days. Comparators consisted of vancomycin and antistaphylococcal penicillins (nafcillin, oxacillin, cloxacillin, and flucloxacillin). Subjects with a CL_{CR} of 70 to 30 mL/min were to receive a modified dosing regimen for daptomycin (4 mg/kg loading dose, followed by 3 mg/kg q36 hr); subjects with CL_{CR} <30 mL/min were excluded from the trial.

The sponsor also performed two Phase 3 clinical studies, DAP-CAP-00-05 and DAP-CAP-00-08, in the treatment of moderate to severe community-acquired acute bacterial pneumonia due to *S. pneumoniae*, including penicillin-resistant strains. Each study was a randomized, multicenter, double-blind, parallel group trial to evaluate daptomycin IV 4 mg/kg q24h compared to active treatment. Analysis of the results from study DAP-CAP-00-05 indicated that daptomycin did not meet the predetermined criteria for non-inferiority (which specified that the upper bound of the 95% CI for the difference in clinical success between the comparator, ceftriaxone, and daptomycin be <10%) in any of the populations analyzed. In light of these of these findings, Cubist decided to suspend enrollment in Study DAP-CAP-00-08. The Agency has agreed to use the data from studies DAP-CAP-00-05 and DAP-CAP-00-08 to support the safety of daptomycin.

The primary organ toxicity of daptomycin appears to be related to skeletal muscle, peripheral nerve, kidney, and the gastrointestinal tract. Skeletal myopathy was observed in both rats and dogs after repeated IV injections of daptomycin for 14 days to 6 months duration and appears microscopically as degenerative and regenerative changes in myocytes. No evidence of fibrosis or rhabdomyolysis was evident in repeat dose studies up to 150 mg/kg q24h in rats (human equivalent dose 24 mg/kg) and 100 mg/kg q24h in dogs (human equivalent dose 56 mg/kg). The precise mechanism of daptomycin's effect on skeletal muscle is not completely understood, but is likely to be mediated via perturbations of the muscle plasma membrane.

Serum CPK concentrations ≤1,000 U/L provided an imperfect marker of the extent of muscle damage in dogs due to false positives. Elevations of CPK >1,000 U/L correlated well with microscopic damage. Across the range of doses tested, mean CPK values corresponded to the degree of microscopic myofiber degeneration and the number of myofibers involved. No toxicologically significant microscopic changes were evident in muscle tissue in the absence of CPK elevations. Daptomycin-related skeletal muscle effects are reversible. Daptomycin's adverse effect on muscle was specific to skeletal muscle and was not observed in cardiac or smooth muscle.

The degree of skeletal myopathy in dogs appears to be primarily related to the dosing frequency (time between doses) and, secondarily, AUC, but not to peak plasma concentrations (C_{max}). Therefore, once-daily administration of daptomycin is expected to minimize skeletal muscle myopathy in patients as compared to fractionated daily dosing (q8h or q12h administration) as it relates to skeletal muscle effects.

Across animal species, the adverse effects on peripheral nerve of daptomycin were associated with doses 4- to 6-fold greater than those associated with skeletal myopathy. The peripheral neuropathy was characterized by axonal degeneration without demyelination. The degree of neuropathy correlated with daptomycin peak plasma concentrations (C_{max}). Peripheral nerve effects appear to be reversible, consistent with the absence of a microscopic effect on the neuronal cell body. However, the majority of dogs still had axonal degeneration present and reductions in the patellar reflex with 3 months recovery

after receiving 75 mg/kg once daily for 6 months. One quarter of dogs still had evidence of neuronal damage, although diminished in severity, with 3 months recovery after receiving 40 mg/kg.

Peripheral Nerve Function/Cardiac Repolarization:
The sponsor assessed the impact of daptomycin on peripheral nerve function and cardiac repolarization in a Phase 1 study of 120 healthy subjects. Subjects received either daptomycin IV 6 mg/kg or placebo once daily for 14 days. Peripheral nerve function was assessed by electrophysiological measurement of the median nerve motor function, vibratory perception thresholds, and a neurological questionnaire (total, neuropathy, and myopathy components) on the day prior to dosing, Day 14, and two weeks after the end of treatment (Day 28). No statistically significant differences were observed in a comparison of change from baseline for electrophysiological measurement of the median nerve motor function or vibratory perception threshold. A statistically significant difference was observed between groups at Day 28 based on total score ($p=0.024$) and neuropathy specific questions ($p=0.048$) of the neurological questionnaire. An additional blinded evaluation with a more conservative post hoc scoring system identified all subjects with a total score elevation of 4 or more. The results demonstrate that subjects in the daptomycin group had more abnormal findings (myopathy and neuropathy) than subjects in the NS group.

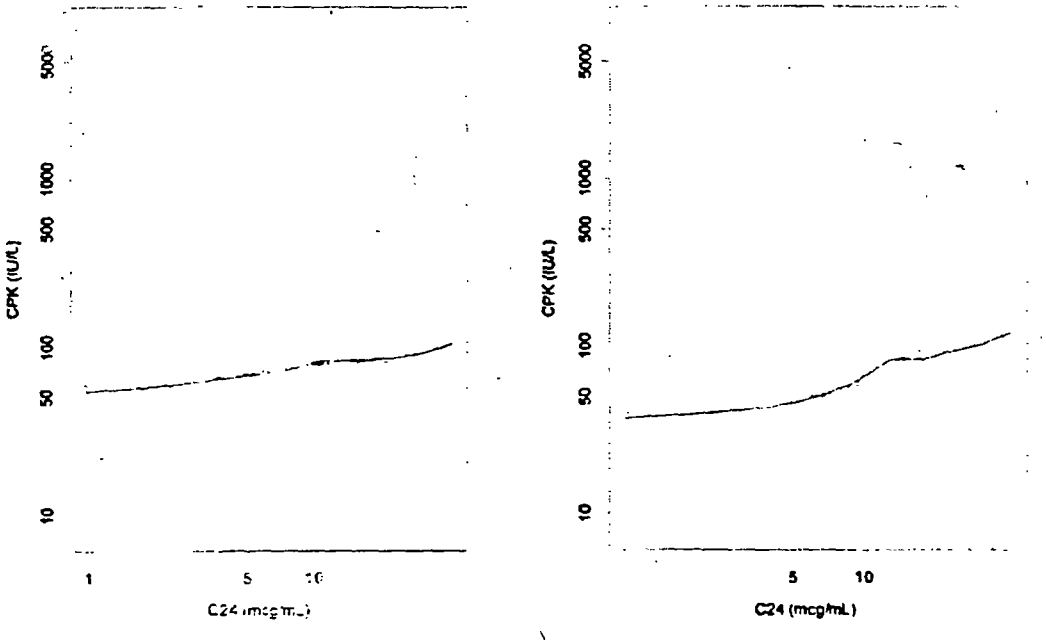
QT values from all subjects on Day 1 and Day 8 (pre-dose, 0.5, 1, 1.5, 2, 6, and 12 hrs) were corrected using Bazett's formula. The range in QTc values were similar between subjects receiving daptomycin and placebo and there were no statistically significant differences in the mean QTc values at any time point. QTc values corrected for baseline were not statistically significantly different between the treatment groups with respect to mean change from baseline. In addition, QT values corrected using Fridericia's formula were similar to those corrected using Bazett's formula.

There were no instances in which the QTc interval exceeded 500 msec (corrected using Bazett's or Fridericia's correction formulas) for subjects receiving daptomycin or placebo. When the QTc interval was corrected using the pre-dose baseline, the Δ QTc exceeded 60 msec once for daptomycin (subject 100) and twice for placebo (subject 47) with Bazett's formula, whereas the Δ QTc exceeded 60 msec five times for daptomycin (subjects 3, 7, 48, and 71) and four times for placebo (subjects 1, 24, 25, and 42) with Fridericia's formula.

Creatinine Phosphokinase (CPK):
In a previous Phase 1 study (Study B8B-MC-AVAP), 10 healthy male volunteers received either 3 mg/kg q12h or 4 mg/kg q12h for 14 days. None of the subjects receiving 3 mg/kg experienced an elevation of CPK, although two of five subjects in the 4 mg/kg group experienced an elevation of CPK associated with muscle weakness and myalgia involving both forearms. In one subject, CPK concentrations were elevated beginning on Day 9 and reached 20,812 U/L on Day 13. In the other subject, CPK concentrations were elevated beginning on Day 5 and exceeded 10,000 U/L on Day 10. No neurologic abnormalities were noted in neurologic examination or by quantitative neurologic testing.

The sponsor performed an exploratory analysis to evaluate the relationship between trough plasma concentrations (C_{24}) of daptomycin and CPK concentrations using data from Phase 1, Phase 2, and Phase 3 studies. The relationship between CPK and C_{24} for all observations and for a subset of observations collected after a minimum of 5 consecutive doses of daptomycin to approximate steady-state was explored graphically using scatter plots and is shown in Figure 2. Two subjects (subjects 115 and 146) had CPK concentrations of 4490 U/L and 8107 U/L, respectively and corresponding daptomycin trough plasma concentrations of 28.3 and 8.1 µg/mL, respectively. The majority of the CPK measurements (98.4%) were less than twice the upper limit of normal. In this range, there was a trend toward greater CPK concentrations with greater daptomycin trough plasma concentrations.

Figure 2. Relationship between trough concentration (C_{24}) and CPK for all observations (left, single and multiple dose) and collected after a minimum of 5 consecutive daptomycin doses (right)



B. General Clinical Pharmacology

1. What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers and how are they measured in clinical pharmacology and clinical studies?

In study DAP-SST-98-01, patients were evaluated for efficacy and safety at the end-of-therapy (within 3 days post-treatment), test-of-cure (7 to 12 days post-treatment), and post-study (12 to 28 days post-treatment). The clinical response at the test-of-cure was defined as cure, improved, failure, or unable to evaluate. The microbiological response at the test-of-cure evaluation was defined as eradicated (documented eradicated or presumed eradicated), persistent, or missing data.

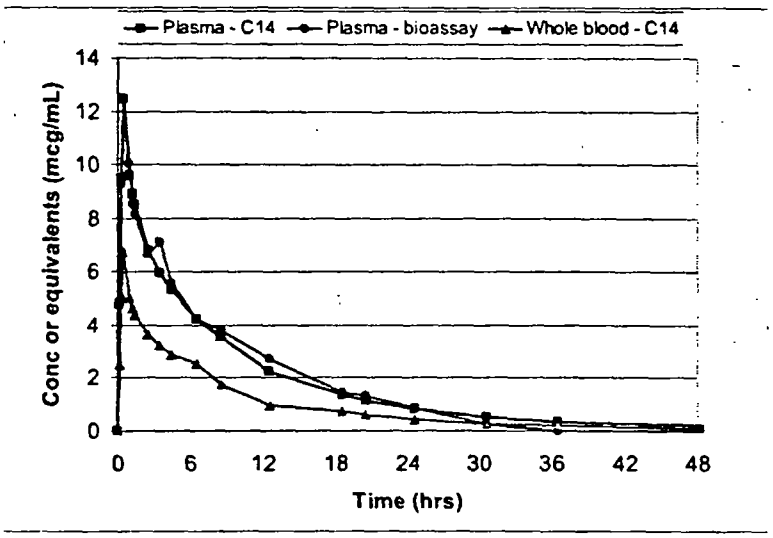
In study DAP-SST-99-01, patients were evaluated for efficacy at the end-of-therapy (within three days of the last dose of study drug), test-of-cure (7 to 12 days post-treatment), and post-study (12 to 28 days post-treatment). The clinical response at the test-of-cure was defined as cure, improved, failure, or unable to evaluate. The microbiological response at the test-of-cure evaluation was defined as satisfactory (documented eradicated or presumed eradicated), unsatisfactory (documented persistence or presumed persistence), or unknown.

2. Are the active moieties in plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The sponsor has not performed *in vitro* drug metabolism studies using human microsomes to determine if daptomycin is a substrate of cytochrome P450 isoforms and identify potential metabolites of daptomycin. In a mass balance study, daptomycin concentrations were determined by total ^{14}C (daptomycin equivalents) as well as microbiological assay. The sponsor stated that the presence of radiocarbon labeled drug and metabolites in urine was examined using [redacted], although the results from these analyses were not included in the study report and are unavailable from the sponsor. Plasma concentrations of daptomycin determined by bioassay (parent + active metabolites) were similar to

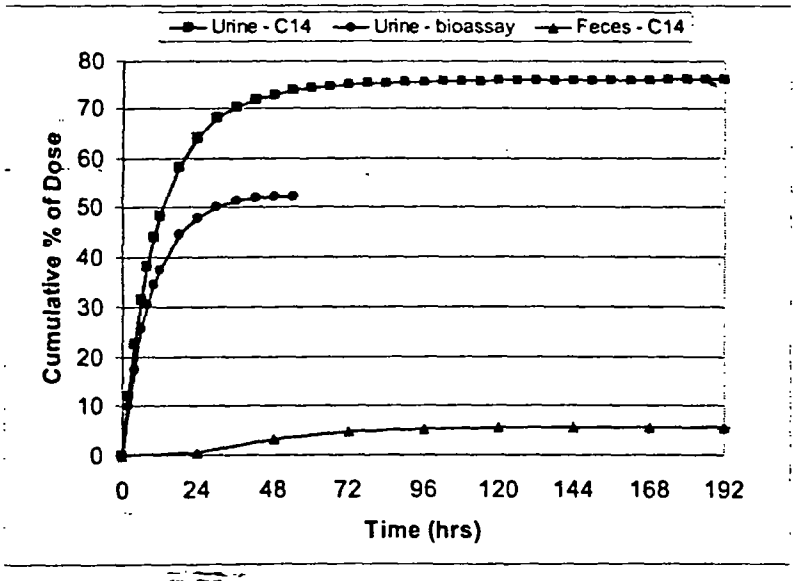
plasma concentrations determined by total ^{14}C (see Figure 3). However, it is unknown if active metabolites of daptomycin were present in plasma since no attempt was made to identify metabolites.

Figure 3. Mean daptomycin concentration-time profiles in plasma (bioassay and ^{14}C-equivalents) and whole blood (^{14}C-equivalents)



The mean cumulative excretion profiles of daptomycin in urine determined by bioassay and total ^{14}C are shown in Figure 4. Approximately 78% of the administered dose was recovered from urine based on total ^{14}C, whereas approximately 52% of the administered dose was recovered from urine using microbiologic assay. Less than 10% of total ^{14}C was recovered from feces collected for up to nine days. The decreased recovery of daptomycin with microbiological assay compared to the recovery based on total ^{14}C supports the presence of inactive metabolites in urine.

Figure 4. Mean cumulative excretion (%) of daptomycin in urine (bioassay and ^{14}C-equivalents) and feces (^{14}C-equivalents)

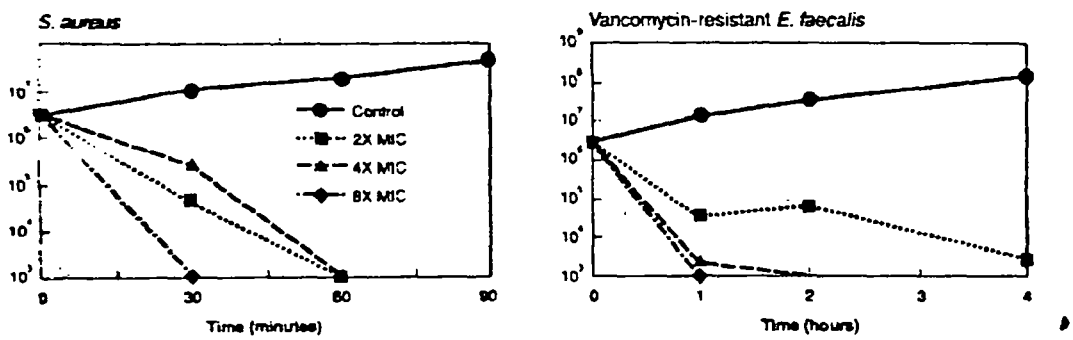


The concentration of daptomycin in plasma and urine was determined using [redacted] in the majority of study reports and represents the concentration of parent compound. Due to the similarity of plasma concentrations determined using the microbiologic assay and [redacted] it appears that daptomycin exists primarily as the parent compound in plasma. The sponsor has not attempted to identify the inactive metabolite(s) of daptomycin in urine. However, the concentration of the active moiety in plasma and urine were appropriately identified and determined to assess pharmacokinetic parameters.

3. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

The exposure-response relationship of daptomycin has been evaluated using *in vitro* time-kill studies and in vivo animal models of infection. Time-kill studies were used to assess the *in vitro* bactericidal activity of daptomycin over time. As shown in Figure 5, the rate of bacterial killing increased with increasing drug concentration against a strain of *Staphylococcus aureus* and a strain of vancomycin-resistant *Enterococcus faecalis*. Based on summary microbiology data, daptomycin appears to exhibit concentration-dependent bactericidal activity.

Figure 5. Bactericidal activity of daptomycin



Reference: Thorne GM and Alder J. Clinical Microbiology Newsletter. 2002;24(5):33-40.

Pharmacodynamic investigations have been conducted using various animal models. The results using thigh infections in neutropenic mice and renal infections in immunocompetent mice are presented below. In these studies, the PK/PD parameters that were most associated with efficacy were the AUC/MIC and C_{max}/MIC, whereas the percentage of the dosing interval that plasma concentrations exceeded the MIC (T>MIC) was associated with efficacy but not to the extent of the AUC/MIC and C_{max}/MIC. These findings are consistent with the concentration-dependent bactericidal activity of daptomycin demonstrated with *in vitro* time-kill studies.

Animal Infection Models:

1) Safdar N, Andes D, Craig WA. In-vivo Pharmacodynamic activity of daptomycin. Not Published.
A neutropenic murine thigh infection model was used to characterize the PK/PD parameters and magnitude of the parameters with antimicrobial effect. Female ICR/Swiss mice were rendered neutropenic with cyclophosphamide and thigh muscles were infected ($\approx 10^{5-6}$ CFUs/thigh) with nine isolates of *S. pneumoniae* (intermediate susceptibility to penicillin, n=2; penicillin resistant, n=7), four isolates of *S. aureus* (MRSA, n=1), and two isolates of vancomycin-resistant *E. faecium*. Animals were treated for 24 hrs with subcutaneous daptomycin doses of 0.20 to 400 mg/kg/day divided into 1, 2, 4, or 8 doses. Protein binding in mouse plasma was 90%. The results were analyzed using the sigmoid dose-effect model. Non-linear regression analysis was used to determine which PK/PD parameter was best associated with efficacy.

The relationship between total and unbound daptomycin T>MIC and total daptomycin peak/MIC and AUC_{0-24}/MIC and the number of viable organisms in the thigh of neutropenic mice after 24 hrs of therapy are shown in Figures 6 and 7. The peak/MIC and AUC_{0-24}/MIC were the PK/PD parameters that were best associated with in vivo efficacy (r^2=83% for peak/MIC and 86% for AUC_{0-24}/MIC for total daptomycin) compared with 17% T>MIC for total daptomycin and 50% for T>MIC for unbound daptomycin. The relationship between the unbound daptomycin AUC_{0-24}/MIC and the static dose or doses producing one and two log_{10} reductions in viable *S. aureus* are shown in Figure 8. The daily dose (mg/kg/day) required for a static effect was similar or less with the q24h dosing regimen when compared to those of more frequent dosing regimens (see Table 2).

Figure 6. Relationship between total (left) and unbound (right) T>MIC and the number of viable *S. aureus* in the thigh of neutropenic mice after 24 hrs of therapy

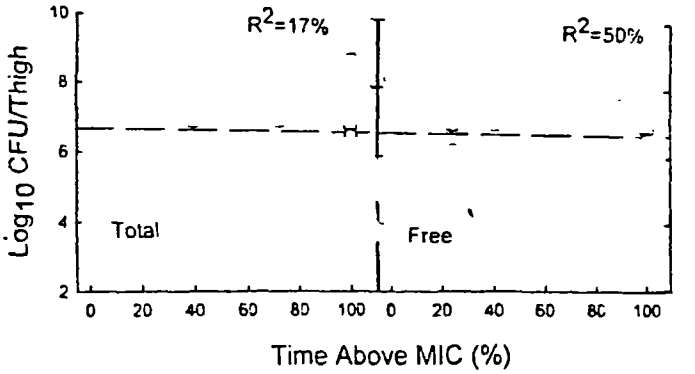


Figure 7. Relationship between total peak/MIC and AUC_{0-24}/MIC and the number of viable *S. aureus* in the thigh of neutropenic mice after 24 hrs of therapy

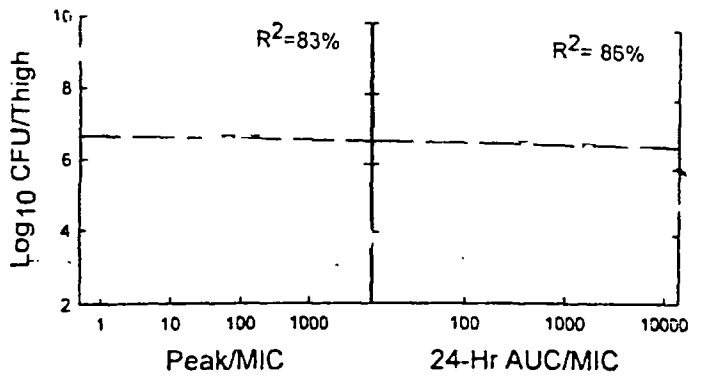
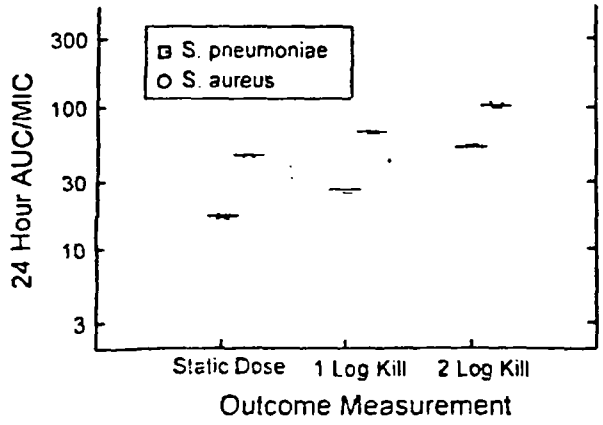


Table 2. Comparison of static doses (mg/kg/day) necessary to produce a static effect when administered q3h, q6h, q12h, and q24h

	Static dose of daptomycin (mg/kg/day)			
Organism	q3h	q6h	q12h	q24h
S. aureus	53.3	18.5	26.0	23.0
S. pneumoniae	1.88	1.77	2.04	1.35

Unlike time-dependent antimicrobials, the dose necessary to product a static effect increased when the daily dose was fractionated. Thus, AUC_{0-24}/MIC and peak/MIC appear to be the most important PK/PD parameters in determining in vivo efficacy of daptomycin against *S. aureus and S. pneumoniae*. It also appears that once-daily administration of daptomycin may maintain in vivo antimicrobial activity while minimize the incidence of myopathy observed with q12h dosing during Phase 1 study B8B-MC-AVAP.

Figure 8. Relationship between unbound AUC_{0-24}/MIC and the static dose or doses producing one and two log_{10} reduction in viable organisms with *S. pneumoniae* and *S. aureus*



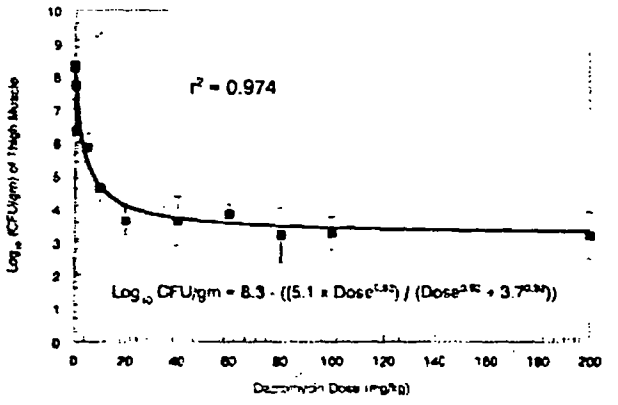
2) Louie A, Kaw P, Liu W, Jumbe N, Miller MH, Drusano GL. Pharmacodynamics of daptomycin in a murine thigh model of *Staphylococcus aureus* infection. Antimicrob. Agents Chemother. 2001;45(3):845-851.

Female ICR/Swiss mice were rendered neutropenic with cyclophosphamide and each thigh muscle was infected with *S. aureus* ATCC 29213 and two clinical isolates of *S. aureus* ($\approx 10^5$ CFUs/thigh). In part 1 of the study, animals received a single dose of intraperitoneal daptomycin two hrs after inoculation to determine the ED_{40}, ED_{50}, ED_{60}, and ED_{80} and were sacrificed 24 hrs later. Daptomycin doses consisted of 0 (control), 0.1, 1, 5, 10, 20, 40, 60, 80, 100, and 200 mg/kg.

In part 2 of the study, animals received intraperitoneal daptomycin dosages corresponding to the ED_{40}, ED_{60}, and ED_{80} over 24 hrs and were administered as a single dose, two divided doses (q12h), or four divided doses (q6h). Protein binding in mouse plasma was 90%. The relationship between the dosage of daptomycin and the bacterial density in thigh muscles was evaluated by an inhibitory sigmoid E_{max} dose-response model.

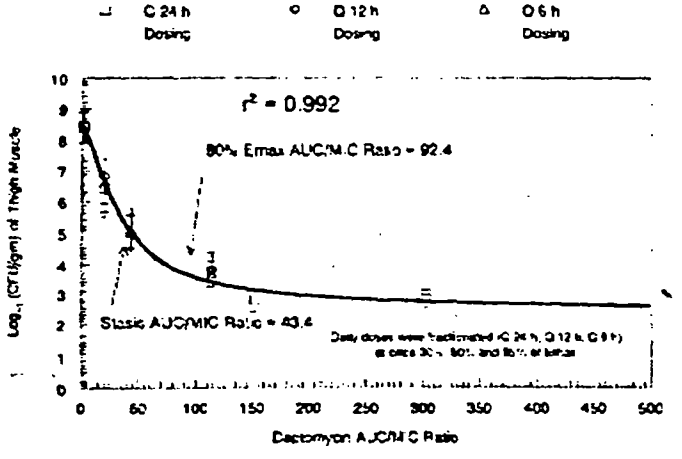
The static dose (same bacterial density at 24 hrs as time zero) was 7.1 mg/kg. The ED_{40}, ED_{50}, ED_{60}, ED_{80}, and ED_{90} were 2.5, 3.7, 5.6, 15.0, and 33.7 mg/kg, respectively. The results are shown in Figure 9.

Figure 9. Relationship between dose of daptomycin (mg/kg) and *S. aureus* density in thigh muscles from dose ranging study



Once-daily administration of the total dose of daptomycin produced the greatest C_{max}/MIC and the lowest T>MIC, whereas the q6h schedule resulted in the greatest T>MIC. However, the bacterial densities were similar for groups that received the same total dose of daptomycin in one, two, or four equally divided doses over 24 hrs (see Figure 10). These results support the findings that daptomycin may exhibit concentration-dependent antimicrobial activity and the AUC_{0-24}/MIC was the PK/PD parameter best associated with efficacy.

Figure 10. Relationship between unbound AUC/MIC of daptomycin and *S. aureus* density in thigh muscles from dose ranging study



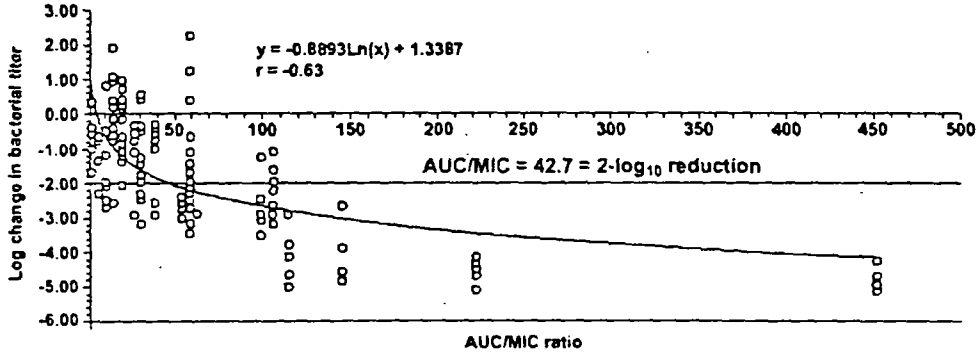
3) Alder J, Li T, Yu D, Morton L, Silverman J, Zhang X, Critchley I, Thorne G. Analysis of daptomycin efficacy and breakpoint standards in a murine model of *Enterococcus faecalis* and *Enterococcus faecium* renal infection. Presented at the American College of Clinical Pharmacy Annual Meeting, 2002.

Due to the difficulty in obtaining an active enterococcal infection in thigh tissue, female CD-1 immunocompetent mice were injected with nine clinical isolates of *Enterococcus faecalis* (vancomycin resistant, n=5) or a single isolate of *Enterococcus faecium* (≈10^8 CFUs/mouse) through the tail vein. Four hrs after inoculation, mice were treated subcutaneously with 5, 10, 25, or 50 mg/kg of daptomycin once daily for three consecutive doses. On Day 3, the kidneys were removed and the viable organisms

enumerated. The dose required to achieve a 2-$\log_{10}$ reduction in bacterial titer (ED_{2log}) as well as the correlation between $\log_{10}$ reduction in bacterial count vs. AUC/MIC were calculated by regression analysis.

Mean reductions of ≥2 $\log_{10}$ (ED_{2log}) in bacterial burden were obtained at calculated ED_{2log} values of 1.7 to 32.4 mg/kg/day for all enterococcal isolates. As shown in Figure 11, there was a relationship between the AUC/MIC ratio and the reduction in bacterial burden against enterococcus. The ED_{2log} was achieved at an AUC/MIC ratio ≥42.7.

Figure 11. Correlation between AUC/MIC and $\log_{10}$ reduction in bacterial titer in renal tissue



Based on in vivo animal models of infection, it appears that the optimal dosage regimen of daptomycin may be once-daily administration to optimize antimicrobial activity as well as minimize the incidence of myopathy. Overall, the magnitude of the unbound AUC/MIC ratio associated with a static effect was 16 for *S. pneumoniae* and approximately 44 for *S. aureus*. The magnitude of the total AUC/MIC ratio associated with a static effect was 1.7 for *E. faecium* (33.8 for a 2-$\log_{10}$ reduction), whereas the total AUC/MIC ratio associated with a mean reduction of ≥2 $\log_{10}$ was ≥42.7 for *E. faecalis*. However, only two isolates of *E. faecium* were assessed. Thus, the maximum MIC values that are likely to be associated with efficacy in humans (based on phase 1 pharmacokinetic data) are 1.0 µg/mL for *S. aureus*, 2.0 µg/mL for *S. pneumoniae*, and 8.0 µg/mL for *E. faecalis*. Based on the administration of 4 mg/kg IV q24h and the maximum MIC values that are likely to be associated with efficacy from above, the estimated unbound AUC/MIC ratio is approximately 49 for *S. aureus*, 25 for *S. pneumoniae*, and 6 for *E. faecalis*.

Monte-Carlo Analysis:

Monte-Carlo analysis was performed by the sponsor to calculate probabilities of daptomycin achieving AUC/MIC criteria determined from in vivo animal models of infection. The MIC values were obtained from the SECURE-US study for *S. aureus* (mean MIC 0.27 ± 0.11 µg/mL), *Streptococcus* spp. (mean MIC 0.21 ± 0.22 µg/mL), and *E. faecalis* (mean MIC 1.0 ± 0.88 µg/mL). The AUC_{0-24} values on day 7 were obtained from Phase 1 study DAP-00-02 (mean AUC_{0-24} 493 ± 75.4 µg*hr/mL) after subjects received 4 mg/kg q24h for 7 days. A total of 10,000 simulations were done for each pathogen group. The MIC distributions were defined by uniform distributions, while AUC distributions were defined with log-normal distributive assumptions.

The AUC/MIC pharmacodynamic criteria established by the sponsor *for S. aureus*, *Streptococcus* spp., and *E. faecalis* were 180, 160, and 132. These criteria were obtained from neutropenic thigh infection models for *S. aureus* and *Streptococcus* spp., and *E. faecalis*). Although the sponsor based calculations on total daptomycin concentrations rather than unbound concentrations, the protein binding of daptomycin in mice is similar to that in humans (approximately 90%); thus, the use of total concentrations

is acceptable provided that comparisons (between human and animal) are based only on either total or unbound concentrations.

Based on the results of the Monte Carlo analysis, the sponsor states that the probability of achieving an AUC/MIC criteria of 180 for *S. aureus* is 99.9%. The reviewer disagrees with the AUC/MIC criteria used by the sponsor (animal study #1 supports 438 and study #2 supports 434). Thus, the probability of achieving an AUC/MIC criteria of approximately 436 would decrease.

The sponsor states that the probability of achieving an AUC/MIC criteria of 160 for Streptococcus spp. is 99.9%. However, the AUC/MIC criteria for *S. pneumoniae* was determined to be 160 (animal study #1) and it is unknown if this value applies to *Streptococcus* spp. Thus, the use of 160 as an AUC/MIC criteria for *Streptococcus* spp. is inappropriate unless supported by additional data.

The sponsor states that the probability of achieving an AUC/MIC criteria of 132 for *E. faecalis* is 96.9%. The sponsor also performed forecasting based on theoretically higher MIC distributions for organisms with MIC values beyond those observed clinically. The probability of achieving an AUC/MIC criteria of 48 (a value of 42.7 was obtained from animal study #3 using an immunocompetent renal infection model with *E. faecalis*) for *E. faecalis* with a MIC value of 8.0 µg/mL was 96.2%. The probability declines to 4.1% with a MIC value of 16 µg/mL. The reviewer agrees with the values predicted by the sponsor for *E. faecalis*, although the analysis is limited since the organism does not produce an adequate infection in neutropenic thigh models, the renal infection animal model was immunocompetent, and drug concentrations at the site of infection may be greater in the renal infection model compared to the thigh infection model. Thus, the AUC/MIC criteria may be substantially greater than the proposed value of 48.

Human efficacy:
The most common Gram-positive pathogens encountered in the daptomycin group during Phase 3 clinical studies (Studies DAP-SST-98-01 and DAP-SST-99-01) were *S. aureus* (70.9%), of which 76% were known to be methicillin-susceptible, *S. pyogenes* (21.8%), and *E. faecalis* (10.7%, vancomycin susceptibility not specified). The rates of clinical success and pathogen eradication by daptomycin MIC per organism isolated at baseline for comparative complicated skin and skin structure infections are shown in Table 3.

There was no apparent association between the clinical success or pathogen eradication rate and MIC value for *S. aureus*, *S. pyogenes*, *Streptococcus* spp., and *E. faecalis*. The MIC values did not exceed 2.0 µg/mL for any organism in the daptomycin group in the ME population.

Table 3. MIC values by pathogen obtained in Phase 3 clinical studies (DAP-SST-98-01 and DAP-SST-99-01) and the clinical and microbiological outcome (ME population)

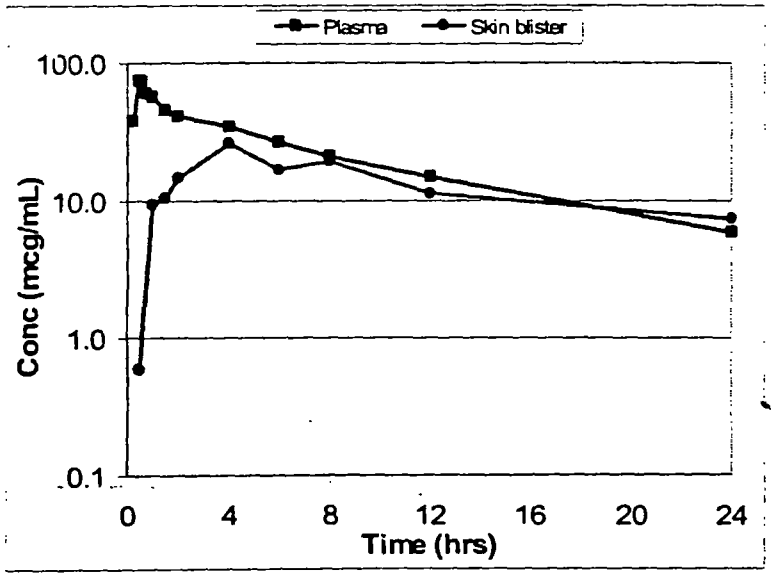
		Clinical success		Pathogen eradication	
Baseline pathogen	Daptomycin MIC (µg/mL)	N	(%)	N	(%)
S. aureus (MSSA)	0.12	4/5	80.0%	2/5	40.0%
	0.25	14/22	63.6%	11/22	50.0%
	0.5	3/3	100.0%	2/3	66.7%
S. aureus (Total)	0.12	30/39	76.9%	25/39	64.1%
	0.25	150/181	82.9%	124/181	68.5%
	0.5	17/18	94.4%	14/18	77.8%
S. pyogenes	≤0.03	59/64	92.2%	57/64	89.1%
	0.06	14/15	93.3%	13/15	86.7%

Table 3 (continued). MIC values by pathogen obtained in Phase 3 clinical studies (DAP-SST-98-01 and DAP-SST-99-01) and the clinical and microbiological outcome (ME population)

		Clinical success		Pathogen eradication	
Baseline pathogen	Daptomycin MIC (µg/mL)	N	(%)	N	(%)
Streptococcus spp.	≤0.03	63/68	92.6%	61/68	89.7%
	0.06	19/20	95.0%	18/20	90.0%
	0.12	11/15	73.3%	10/15	66.7%
	0.25	14/18	77.8%	14/19	73.7%
	0.5	7/10	70.0%	8/11	72.7%
	1	3/3	100.0%	3/3	100.0%
E. faecalis (Vancomycin susceptible)	0.5	7/11	63.6%	7/11	63.6%
	1	7/12	58.3%	7/12	58.3%
	2	11/13	84.6%	9/13	69.2%

Tissue Penetration:
The sponsor assessed the penetration of daptomycin into cantharides-induced skin blisters in six healthy subjects following the administration of a single dose of daptomycin IV 4 mg/kg. The plasma concentration-time profiles of daptomycin in plasma and skin blister fluid are shown in Figure 12.

Figure 12. Mean daptomycin plasma concentrations in plasma and skin blister fluid following the administration of a single 4 mg/kg dose



The pharmacokinetic parameters calculated by the sponsor following administration of daptomycin IV 4 mg/kg to healthy male subjects are shown in Table 4. The mean skin blister fluid AUC_{0-24} was 318 µg*hr/mL and represents 68.4% of the mean plasma AUC_{0-24} (468 µg*hr/mL).

Table 4. Mean (CV%) pharmacokinetic parameters for daptomycin in plasma and skin blister fluid

	Sponsor's results		Reviewer's results
Parameter	**Plasma (n=6)**	**Skin blister fluid (n=6)**	**Skin blister fluid (n=4)**
C_{max} (µg/mL)	77.5 (11%)	27.6 (34%)	22.7 (31%)
T_{max} (hrs)	0.54 (8%)	3.7 (22%)	3.5 (29%)
AUC_{0-24} (µg*hr/mL)	468 (3%)	318 (27%)	287 (26%)
$AUC_{0-\infty}$ (µg*hr/mL)	530 (2%)	---	---
V_{SS} (L/kg)	0.082 (15%)	---	---
Vz (L/kg)	0.078 (12%)	---	---
CL_T (mL/min)	9.84 (3%)	---	---
CL_T (mL/hr/kg)	7.60 (12%)	---	---
Half-life (hrs)	7.74 (8%)	16.9 (64%)	ND
Ae (%)	59.7 (17%)	---	---
Penetration (%)	---	68.4 (29%)	61.0 (28%)

ND - the reviewer was unable to characterize the terminal elimination phase

Although the sponsor stated that skin blister samples were not collected at 15, 35, and 45 min after daptomycin administration, the concentration of daptomycin in skin blister fluid was missing from various other time points for several subjects. Subject 001 was missing skin blister concentrations at 0.5, 1, 1.5, 2, and 8 hrs; subject 003 was missing skin blister concentrations at 0.5, 1.5, 2, and 12 hrs; subject 004 was missing a skin blister concentration at 6 hrs. Thus, the reviewer calculated the AUC_{0-24} and percent penetration of daptomycin into skin blister fluid using the data from subjects 004, 005, 006, and 007 (shown as the right column in Table 1). The mean C_{max}, T_{max}, AUC_{0-24}, and % penetration were 22.7 µg/mL, 3.5 hrs, 287 µg*hr/mL, and 61.0%, respectively. Thus, daptomycin penetrates into extracellular fluid.

The sponsor used a microbiological assay validated with serum to determine the concentration of daptomycin from plasma. No data were submitted to demonstrate the cross-validation of the microbiological assay in serum and plasma. It is known that anticoagulants can alter the *in vitro* protein binding of highly protein bound drugs and thus, impact the results of a microbiological assay. Since the concentration of daptomycin from study DAP-00-04 was greater than any previous Phase 1 study in which healthy subjects received the same dose, the results of this study were deemed unacceptable for labeling purposes.

Based on pharmacokinetic parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship? Do pharmacokinetic parameters change with time following chronic dosing?

Protein Binding:
Daptomycin is approximately 92% bound to plasma proteins in healthy subjects, primarily to human serum albumin in a concentration-independent manner while binding to human alpha-1-acid glycoprotein in a concentration-dependent manner (ranging from 40% to 25% over daptomycin concentration from 2.5 to 80 µg/mL, respectively). The binding of daptomycin to plasma proteins is relatively weak (K_d of 90.3 µM) and reversible.

Serum protein binding in subjects with CL_{CR} ≥30 mL/min is comparable to that observed in healthy subjects with normal renal function. However, there was a trend of decreasing serum protein binding

among subjects with CL_{CR} <30 mL/min (87.6%) as well as hemodialysis patients (85.9%) and CAPD patients (83.5%).

The protein binding of daptomycin in subjects with hepatic impairment (Child-Pugh B) were similar to healthy adult subjects. The mean protein binding of daptomycin in subjects with hepatic impairment was 91.3%.

Pharmacokinetics in Healthy Subjects:
The sponsor assessed the pharmacokinetics of daptomycin in 32 healthy subjects following the administration of daptomycin IV 4 mg/kg q24h × 7 days, 6 mg/kg q24h × 7 days, and 8 mg/kg q24h × 14 days. The plasma concentration-time profiles on Day 1 and Day 7 for the dosage regimens are shown in Figure 13. The pharmacokinetic parameter estimates based on total and unbound concentrations are shown in Tables 5 and 6. The mean total clearance values based on total daptomycin concentrations were 5.55, 8.57, and 7.23 mL/hr/kg (11.0, 9.8, and 8.5 mL/min), respectively after the first dose. The renal clearance values based on total daptomycin concentrations were 6.06, 4.57, 4.38 mL/hr/kg (6.9, 5.3, and 5.1 mL/min), respectively after the first dose and represents 54% to 64% of the total drug clearance. Thus, daptomycin is a low extraction ratio drug.

The mean total clearance values based on unbound daptomycin concentrations were 135, 126, and 81 mL/hr/kg (154, 147, and 95 mL/min), respectively after the first dose. The renal clearance values based on unbound daptomycin concentrations were 84.6, 59.6, 50.1 mL/hr/kg (99.5, 69.4, and 58.6 mL/min), respectively after the first dose.

Figure 13. Median daptomycin plasma concentrations on Day 1 (left) and Day 7 (right) following a 30 min infusion of 4 mg/kg for 7 days, 6 mg/kg for 7 days, or 8 mg/kg for 14 days

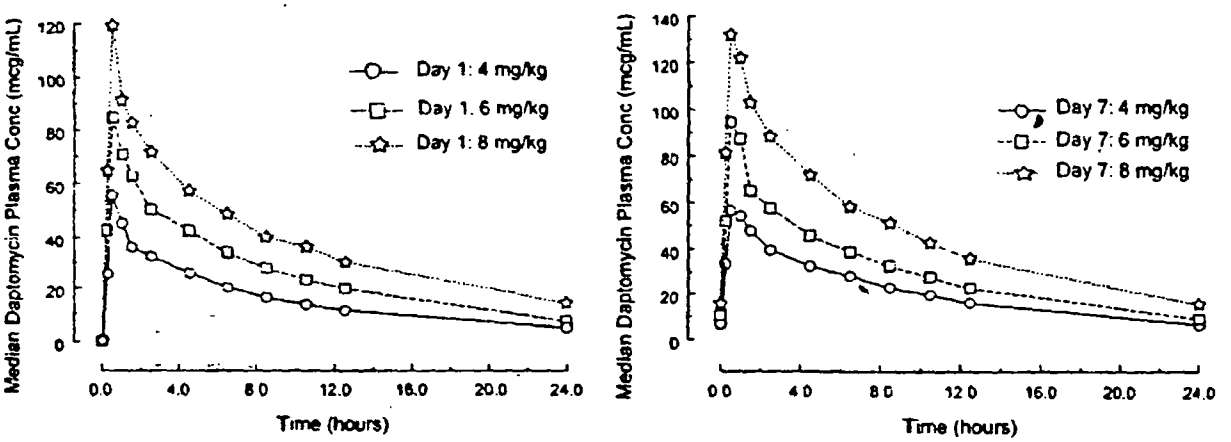


Table 5. Mean (CV%) pharmacokinetic parameters for <u>total</u> daptomycin 4 mg/kg q24h, 6 mg/kg q24h, and 8 mg/kg q24h on Days 1, 7, and 14

Parameter	4 mg/kg		6 mg/kg		8 mg/kg		
	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7	Day 14
C_{max} (µg/mL)	54.6 (10%)	57.8 (5%)	86.4 (8%)	98.6 (12%)	116.3 (9%)	133.0 (10%)	129.5 (11%)
T_{max} (hrs)	0.5 (0%)	0.8 (37%)	0.5 (0%)	0.6 (35%)	0.5 (0%)	0.6 (35%)	1.0 (0%)
AUC_{0-24} (µg*hr/mL)	354 (18%)	494 (15%)	622 (7%)	747 (12%)	932 (13%)	1,130 (10%)	1,090 (10%)
$AUC_{0-\infty}$ (µg*hr/mL)	425 (14%)	ND	705 (9%)	ND	1,127 (14%)	ND	ND
Vss (L/kg)	0.0925 (12%)	ND	0.0876 (8%)	ND	0.0907 (14%)	ND	ND
Vz (L/kg)	0.1042 (15%)	0.0960 (9%)	0.0962 (10%)	0.1038 (13%)	0.0994 (14%)	0.0922 (12%)	0.0946 (13%)
CL_T (mL/hr/kg)	9.55 (13%)	8.28 (16%)	8.57 (9%)	8.13 (12%)	7.23 (15%)	7.15 (11%)	7.41 (10%)
CL_R (mL/hr/kg)	6.06 (20%)	4.82 (27%)	4.57 (23%)	4.42 (6%)	4.38 (6%)	3.73 (15%)	3.99 (20%)
Half-life (hrs)	7.39 (12%)	8.15 (12%)	7.83 (12%)	8.94 (15%)	9.59 (11%)	8.99 (13%)	8.86 (9%)
Fu (%)	7.85 (25%)	8.41 (20%)	7.04 (23%)	7.74 (19%)	8.95 (16%)	8.90 (10%)	9.44 (10%)
Ae_{0-24} (%)	53.0 (20%)	59.1 (10%)	47.4 (24%)	55.0 (13%)	52.1 (10%)	52.7 (18%)	54.0 (16%)

ND - only performed on Day 1

The linearity of daptomycin was also assessed following the administration of daptomycin IV 4 mg/kg, 6 mg/kg, and 8 mg/kg. As shown in Table 7, the mean C_{max} and $AUC_{0-\infty}$ of total and unbound daptomycin increased greater-than proportional to dose, whereas the mean CL_T and CL_R decreased modestly with increasing dose, especially with unbound concentrations. The decrease in mean CL_T was greatest with the 8 mg/kg dose. The mean V_{SS} and Vz remained nearly constant with increasing dose for total daptomycin, whereas both parameters decreased with increasing dose for unbound daptomycin. The mean half-life was greatest with the 8 mg/kg regimen and corresponded to a decrease in total clearance.

Table 6. Mean (CV%) pharmacokinetic parameters for <u>unbound</u> daptomycin 4 mg/kg q24h, 6 mg/kg q24h, and 8 mg/kg q24h on Days 1, 7, and 14

	4 mg/kg		6 mg/kg		8 mg/kg		
Parameter	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7	Day 14
C_{max} (µg/mL)	4.24 (30%)	4.78 (16%)	5.89 (11%)	7.57 (22%)	10.33 (8%)	12.18 (12%)	11.63 (11%)
AUC_{0-24} (µg*hr/mL)	28.2 (41%)	40.7 (20%)	42.3 (8%)	56.9 (18%)	82.6 (10%)	103.4 (12%)	98.2 (14%)
$AUC_{0-\infty}$ (µg*hr/mL)	33.4 (34%)	ND	47.9 (9%)	ND	99.8 (11%)	ND	ND
Vss (L/kg)	1.27 (25%)	ND	1.10 (40%)	ND	1.02 (12%)	ND	ND
Vz (L/kg)	1.38 (24%)	1.18 (11%)	1.20 (41%)	1.41 (27%)	1.12 (12%)	1.01 (14%)	1.06 (15%)

Table 6 (continued). Mean (CV%) pharmacokinetic parameters for unbound daptomycin 4 mg/kg q24h, 6 mg/kg q24h, and 8 mg/kg q24h on Days 1, 7, and 14

	4 mg/kg		6 mg/kg		8 mg/kg		
Parameter	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7	Day 14
CL_T (mL/hr/kg)	131.5 (29%)	101.8 (21%)	126.0 (9%)	108.8 (21%)	81.0 (11%)	78.2 (11%)	82.7 (13%)
CL_R (mL/hr/kg)	84.6 (40%)	59.1 (30%)	59.6 (28%)	59.8 (23%)	50.1 (12%)	40.9 (15%)	44.6 (22%)
CL_{NR} (mL/hr/kg)	46.9 (53%)	39.0 (16%)	66.4 (15%)	49.0 (29%)	31.1 (26%)	37.3 (26%)	38.1 (24%)

The mean plasma concentration-time profiles comparing Day 1 and Day 7 (and Day 14 for 8 mg/kg) for all three dosage regimens are shown in Figure 14. Thus, the pharmacokinetics of daptomycin are nearly linear and time-independent at doses up to 6 mg/kg administered once daily for 7 days.

With repeat administration, the mean C_{max} and AUC_{0-24} of total and unbound daptomycin increased similar to the predicted accumulation ratio of 1.14 (once daily administration with a half-life of 8 hrs). The mean CL_T and CL_R were similar on Day 7 compared to Day 1 and Day 14 compared to Day 1 (8 mg/kg dose). The mean V_{SS} and Vz were similar with repeat administration for total daptomycin as well as unbound daptomycin.

Figure 14. Mean daptomycin plasma concentrations on Day 1 and Day 7 following a 30 min infusion of 4 mg/kg for 7 days, 6 mg/kg for 7 days, or 8 mg/kg for 14 days

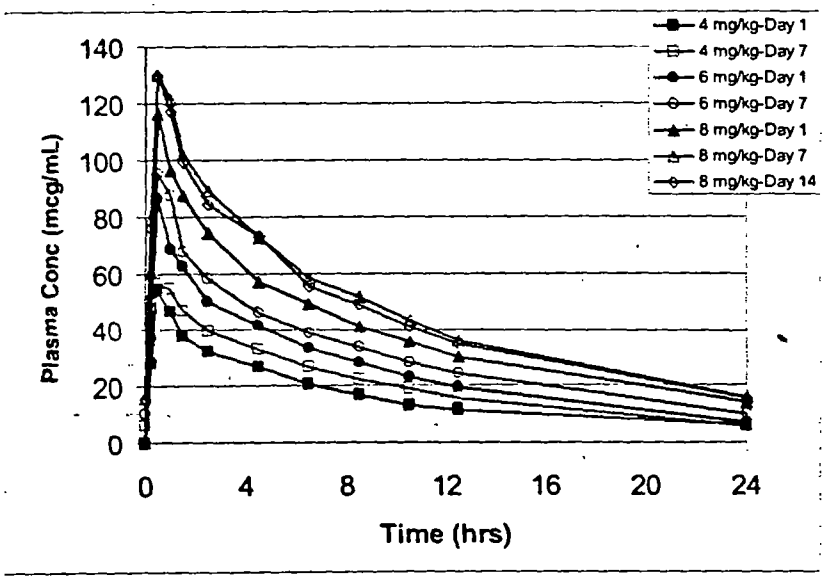


Table 7. Ratios of mean pharmacokinetic parameters for total and unbound daptomycin assessing linearity and accumulation

Parameter	1st Dose (normalized by 4 mg/kg)		7th Dose (normalized by 4 mg/kg)		Ratio Day 7/Day 1			
Total	6 mg/kg	8 mg/kg	6 mg/kg	8 mg/kg	4 mg/kg	6 mg/kg	8 mg/kg	8 mg/kg*
C_{max}	1.58	2.13	1.71	2.30	1.06	1.14	1.14	1.11
AUC_{0-24}	1.76	2.63	1.51	2.29	1.39	1.20	1.21	1.17
V_Z	0.92	0.95	1.08	0.95	0.92	1.08	0.93	0.95
CL_T	0.90	0.76	0.98	0.86	0.87	0.95	0.99	1.02
CL_R	0.75	0.72	0.92	0.77	0.80	0.97	0.85	0.91
t1/2	1.06	1.30	1.10	1.10	1.10	1.14	0.94	0.92
Unbound								
C_{max}	1.39	2.44	1.58	2.55	1.13	1.28	1.18	1.13
CL_T	0.96	0.62	1.07	0.77	0.77	0.86	0.97	1.02
CL_R	0.70	0.59	1.01	0.69	0.70	1.00	0.82	0.89
CL_{NR}	1.42	0.66	1.26	0.96	0.83	0.74	1.20	1.22
V_Z	0.87	0.81	1.20	0.86	0.85	1.17	0.91	0.95
Ae_{0-24}	0.89	0.98	0.93	0.89	1.12	1.16	1.01	1.04
Ac_{0-}	0.83	0.97	0.93	0.89	0.92	1.03	0.85	0.87

*8 mg/kg - Day 14/Day 1; ND = not performed

4. How does the pharmacokinetics of the drug and its major active metabolites in healthy volunteers compared to that in patients?

The sponsor performed a population pharmacokinetic analysis to describe the pharmacokinetics of daptomycin in healthy subjects and patients with acute bacterial infections as well as identify sources of inter-individual variability in the pharmacokinetics of daptomycin. Data for the analysis were obtained from 282 adult subjects in nine Phase 1 studies and six Phase 2/3 studies. Of the 282 subjects included in the analysis, 153 were from Phase 1 studies. The remaining 129 subjects included in the analysis were patients with Gram-positive bacterial infections enrolled in the Phase 2/3 studies. Each Phase 2/3 subject provided sparse (up to 6) blood samples for measurement of daptomycin plasma concentrations.

The final population pharmacokinetic model was a two-compartment linear model with first order elimination and included four parameters: systemic clearance (CL), volume of central compartment (V1), inter-compartmental clearance (Q), and volume of the peripheral compartment (V2).

Among healthy subjects with varying degrees of renal function and patients with complicated skin and skin structure infections, the clearance of daptomycin was primarily influenced by renal function, and to a lesser extent, sex and body temperature. Compared to healthy subjects, the presence of infection resulted in approximately a 100% increase in the apparent volume of distribution of the peripheral compartment. The median volume of the peripheral compartment in healthy subjects was estimated to be 3.1 L and the median volume of peripheral compartment for patients with an acute bacterial infection was estimated to be 6.0 L. Please consult the pharmacometric review for more information on the pharmacokinetics of daptomycin in patients (see Appendix D. Pharmacometric Consult).

5. What is the inter- and intra-subject variability of pharmacokinetic parameters in volunteers and patients, and what are the major causes of variability?

The inter-subject variability (CV%) for daptomycin was ≤30% for most pharmacokinetic parameters in healthy subjects from Phase 1 clinical studies. The greatest inter-subject variability (≤49%) was observed with CL_R. The degree of inter-subject variability appeared to be similar for pharmacokinetic parameters

based on total and unbound daptomycin concentrations. However, a large degree of inter-study variability was observed among studies with healthy volunteers. The cause of the inter-study variability is unknown.

C. Intrinsic factors

1. What intrinsic factors (age, gender, weight, height, disease, genetic polymorphism, pregnancy, organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

The sponsor performed a population pharmacokinetic analysis to describe the pharmacokinetics of daptomycin in healthy subjects and patients with acute bacterial infections to identify sources of inter-individual variability in the pharmacokinetics of daptomycin. The clearance of daptomycin was primarily dependent on renal function, and to a lesser extent by sex and elevated body temperature (>37°C). The systemic clearance in females was estimated to be approximately 80% that of male subjects with similar renal function.

The rate and extent of daptomycin distribution into extravascular fluid was determined to be influenced by body weight. The presence of acute infection resulted in an approximately 2-fold increase in the volume of the peripheral compartment. The median volume of the peripheral compartment in a healthy subject was estimated to be 3.1 L and the median volume of peripheral compartment for a subject with an acute bacterial infection was estimated to be 6.0 L.

The sponsor performed clinical pharmacology studies to assess the impact of renal impairment, hepatic impairment, age, and obesity on the pharmacokinetics of daptomycin. Each intrinsic factor is addressed below.

Renal impairment:
The pharmacokinetics of daptomycin were assessed in 29 subjects with normal renal function and various degrees of renal impairment following the administration of a single 4 mg/kg dose. Subjects were assigned to groups (CL_{CR} ≥80 mL/min, CL_{CR} 50 to <80 mL/min, CL_{CR} 30 to <50 mL/min, CL_{CR} <30 mL/min, hemodialysis [HD], and continuous ambulatory peritoneal dialysis [CAPD]) based on their measured creatinine clearance or mode of dialysis. The mean plasma concentration-time profiles for all subjects are shown in Figure 15.

The mean pharmacokinetic parameters following the administration of daptomycin IV 4 mg/kg to subjects with normal renal function and renal impairment are shown in Table 8 and the geometric mean ratios and 90% confidence intervals are shown in Table 9. The mean $AUC_{0-\infty}$ increased 50%, 92%, and 128% in subjects with CL_{CR} 50-80 mL/min, 30-50 mL/min, and CL_{CR} <30 mL/min, respectively compared to subjects with normal renal function. In dialysis patients, the mean $AUC_{0-\infty}$ increased 120% in hemodialysis patients not receiving hemodialysis and 165% in CAPD patients compared to subjects with normal renal function.

The mean CL_T progressively decreased as the degree of renal impairment increased. The mean CL_T decreased 32%, 49%, and 56% in subjects with CL_{CR} 50-80 mL/min, 30-50 mL/min, and CL_{CR} <30 mL/min, respectively compared to subjects with normal renal function. The mean CL_T decreased 55% in hemodialysis patients not receiving hemodialysis and 63% in CAPD patients compared to subjects with normal renal function.

Figure 15. Mean daptomycin plasma concentrations following a single 4 mg/kg dose of daptomycin to subjects with varying degrees of renal impairment

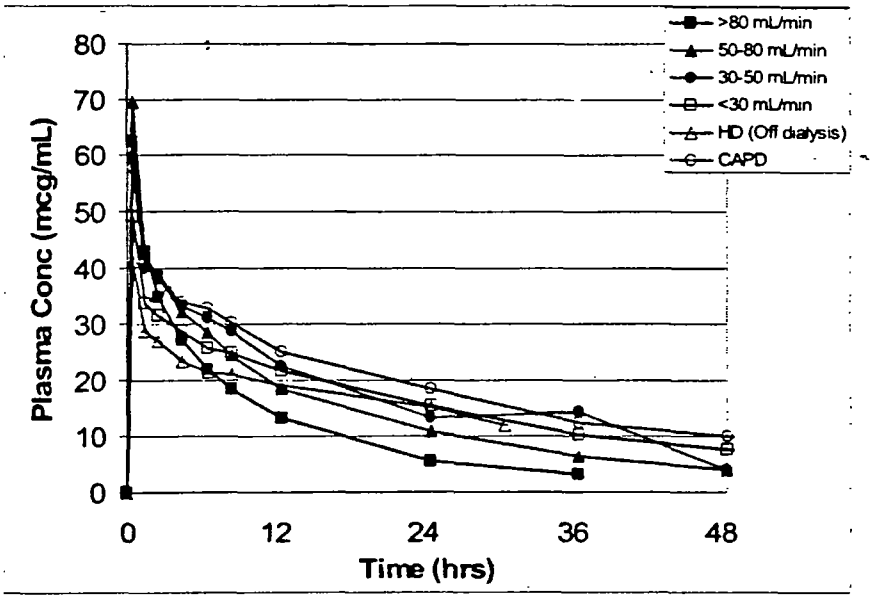


Table 8. Mean (CV%) pharmacokinetic parameters by renal function (based on measured creatinine clearance) following a single dose of daptomycin IV 4 mg/kg

	Creatinine Clearance (mL/min)					
Parameter	>80 mL/min (n=7)	50-80 mL/min (n=4)	30-<50 mL/min (n=1)	<30 mL/min (n=6)	HD* (n=6)	CAPD (n=5)
C_{max} (µg/mL)	62.4 (28%)	69.6 (24%)	59.6	49.0 (19%)	41.1 (16%)	57.7 (19%)
C_{24} (µg/mL)	5.5 (20%)	10.9 (31%)	13.2	15.4 (22%)	15.3 (18%)	18.3 (5%)
AUC_{0-24} (µg*hr/mL)	437 (15%)	560 (15%)	618	568 (14%)	497 (14%)	676 (9%)
AUC_{0-t} (µg*hr/mL)	445 (15%)	647 (21%)	895	983 (23%)	717 (24%)	1,209 (8%)
$AUC_{0-\infty}$ (µg*hr/mL)	517 (13%)	778 (20%)	993	1,176 (21%)	1,138 (30%)	1,368 (7%)
V_{SS} (L/kg)	0.0999 (22%)	0.0952 (13%)	0.0908	0.1334 (19%)	0.1469 (24%)	0.1053 (10%)
CL_T (L/hr/kg)	0.0079 (13%)	0.0054 (25%)	0.0040	0.0035 (19%)	0.0036 (27%)	0.0029 (8%)
CL_R (L/hr/kg)	0.0049 (24%)	0.0032 (32%)	0.0016	0.0010 (48%)	—	—
$t_{1/2}$ (hrs)	9.6 (21%)	13.9 (18%)	16.64	28.2 (19%)	30.0 (53%)	26.3 (13%)
Ae (% dose)	55.4 (24%)	50.0 (12%)	35.4	22.3 (38%)	—	—

* HD = hemodialysis patients not receiving hemodialysis

When dialysis patients received hemodialysis for 3 hrs, the mean CL_T increased by 19.4%. Approximately 15% of the administered dose was removed by 3 hrs of hemodialysis, whereas approximately 11% of the administered dose was removed by CAPD over 48 hrs.

Table 9. Geometric mean ratios (renal impairment/normal renal function) and 90% CIs for pharmacokinetic parameters by renal function (based on measured creatinine clearance)

	Creatinine Clearance (mL/min)				
Parameter	**50-80 mL/min (n=4)**	**30-<50 mL/min (n=1)**	**<30 mL/min (n=6)**	**HD (n=6)**	**CAPD (n=5)**
C_{max} (µg/mL)	1.12 (0.83 to 1.52)	0.99*	0.80 (0.63 to 1.01)	0.67 (0.54 to 0.84)	0.94 (0.73 to 1.21)
C_{24} (µg/mL)	1.92 (1.40 to 2.65)	2.45*	2.80 (2.27 to 3.46)	2.79 (2.28 to 3.41)	3.40 (2.85 to 4.06)
AUC_{0-24} (µg*hr/mL)	1.28 (1.09 to 1.50)	1.43*	1.30 (1.13 to 1.49)	1.14 (0.99 to 1.31)	1.55 (1.37 to 1.76)
AUC_{0-t} (µg*hr/mL)	1.44 (1.18 to 1.76)	2.03*	2.18 (1.83 to 2.60)	1.59 (1.33 to 1.91)	2.73 (2.40 to 3.11)
$AUC_{0-\infty}$ (µg*hr/mL)	1.49 (1.23 to 1.80)	1.93*	2.25 (1.92 to 2.65)	2.14 (1.74 to 2.64)	2.66 (2.37 to 2.98)
V_{SS} (L/kg)	0.97 (0.76 to 1.24)	0.93*	1.35 (1.08 to 1.68)	1.48 (1.16 to 1.87)	1.08 (0.87 to 1.34)
CL_T (L/hr/kg)	0.67 (0.55 to 0.81)	0.51*	0.44 (0.37 to 0.52)	0.44 (0.35 to 0.55)	0.37 (0.33 to 0.42)
CL_R (L/hr/kg)	0.65 (0.47 to 0.91)	0.33*	0.18 (0.12 to 0.27)	—	—
$t_{1/2}$ (hrs)	1.46 (1.15 to 1.85)	1.77*	2.95 (2.40 to 3.64)	2.93 (2.11 to 4.06)	2.78 (2.29 to 3.38)
Ae (% dose)	0.92 (0.71 to 1.21)	0.66*	0.39 (0.27 to 0.55)	—	—

*90% CIs were not calculated for the 30-50 mL/min group (n=1)

The plasma protein binding of daptomycin at the end of infusion (0.5 hrs) and two hrs later (2 hrs) following the administration of a single dose of daptomycin 4 mg/kg is shown in Table 10. The mean protein binding for subjects with normal renal function was 89.2%. The unbound fraction of daptomycin was similar among subjects with creatinine clearance ranging from >80 mL/min to <30 mL/min, whereas the unbound fraction of daptomycin increased in HD and CAPD patients.

Table 10. Mean (SD) percentage of unbound daptomycin based on measured creatinine clearance

	Sample Time		
Category	**0.5 hrs**	**2.5 hrs**	**Overall**
>80 mL/min	11.6% (2.5)	9.9% (1.8)	10.8% (2.3)
50-80 mL/min	10.1% (2.3)	12.2% (3.7)	11.2% (3.1)
30-<50 mL/min	9.4%*	10.2%*	9.8% (0.5)
<30 mL/min	12.9% (2.5)	11.9% (1.5)	12.4% (2.0)
HD-Off dialysis	14.6% (3.9)	13.6% (4.6)	14.1% (4.1)
HD-On dialysis	15.4% (5.4)	16.3% (3.1)	15.9% (4.2)
CAPD	15.7% (2.4)	17.3% (3.6)	16.5% (2.9)

* n=1 for CL_{CR} 30-50 mL/min

Dosage Adjustment:
In the Phase 3 clinical efficacy studies supporting complicated skin and skin structure infections (DAP-SST-98-01 and DAP-SST-99-01), the protocols stated that patients with a CL_{CR} >70 mL/min should receive daptomycin IV 4 mg/kg q24h, whereas patients with a CL_{CR} of 70 to 30 mL/min should receive a modified dosing regimen of daptomycin (4 mg/kg loading dose, followed by 3 mg/kg q36 hr). Patients with a CL_{CR} <30 mL/min were to be excluded from the study. A comparison of the clinical success (cure + clinical improvement) and clinical failure rates for daptomycin and comparator based on the clinically evaluable population for patients with CL_{CR} >70 mL/min and 30-70 mL/min are shown in Table 11.

Table 11. Clinical outcome at the test-of-cure evaluation for clinically evaluable patients with CL_{CR} >70 mL/min and 30 to 70 mL/min

Clinical Response	CL_{CR} (mL/min)	DAP-SST-98-01		DAP-SST-99-01	
		Daptomycin	Comparator	Daptomycin	Comparator
Clinical success	>70 mL/min	76.9% (n=133)	76.2% (n=125)	90.9% (n=189)	91.2% (n=208)
Clinical success	30-70 mL/min	63.2% (n=24)	72.7% (n=32)	72.4% (n=21)	76.0% (n=19)
Clinical failure	>70 mL/min	23.1% (n=40)	23.8% (n=39)	9.1% (n=19)	8.8% (n=20)
Clinical failure	30-70 mL/min	36.8% (n=14)	27.3% (n=12)	27.6% (n=8)	24.0% (n=6)

Among the two studies, 32% and 68% of clinically evaluable patients had a CL_{CR} of 30-<50 mL/min and CL_{CR} 50-70 mL/min, respectively. Two patients had a CL_{CR} <30 mL/min (20 and 27 mL/min). Although the protocol stated that patients with a CL_{CR} of 30-70 mL/min were supposed to receive a reduced dosage, only 45.2% of patients in the CL_{CR} 30-<50 mL/min group and 30.9% of patients in the 50-70 mL/min group actually received a reduced dosage. The rates of clinical success among patients who received the dosage adjustment and those who didn't receive the dosage adjustment are shown in Table 12. In general, patients who received the reduced dosage regimen had a lower clinical success rate compared to those who received 4 mg/kg q24h. However, the incidence of serious adverse events were similar among patients who didn't receive the dosage adjustment vs. those who did receive the dosage adjustment, regardless of creatinine clearance

Table 12. Clinical success with and without a dosage adjustment among clinically evaluable patients with CL_{CR} 30 to 70 mL/min

Renal Function	No dose adjustment	Dose adjustment	Comparator
30 to 70 mL/min			
Success (n)	73% (32)	57% (13)	74% (51)
95% CI	1% (-16% to 18%)	17% (-5% to 40%)	
30 to <50 mL/min			
Success (n)	58% (7)	44% (4)	70% (21)
95% CI	12% (-21% to 44%)	26% (-11% to 62%)	
50 to 70 mL/min			
Success (n)	78% (25)	64% (9)	77% (30)
95% CI	-1% (-21% to 18%)	13% (-16% to 41%)	

Based on the results of Tables 11 and 12, it appears that the clinical efficacy rate was similar among daptomycin and comparator for patients with CL_{CR} >70 mL/min, whereas the clinical efficacy rate was reduced to a greater extent among patients with CL_{CR} 30-70 mL/min receiving daptomycin compared to comparator. The rate of clinical success was further reduced among patients receiving the reduced daptomycin regimen. Thus, the reduced dosing regimen of daptomycin (4 mg/kg loading dose, followed by 3 mg/kg q36 hr) may be inadequate to maintain the clinical efficacy rates observed among patients with CL_{CR} >70 mL/min receiving daptomycin IV 4 mg/kg q24h. In addition, daptomycin IV 4 mg/kg

q24h may be necessary in patients with CL_{CR} 30-70 mL/min to achieve the clinical efficacy observed in patients with CL_{CR} >70 mL/min.

In order to compare doses not evaluated in this study, the reviewer fit daptomycin plasma concentration-time data from subjects with normal renal function and various degrees of renal impairment using a two-compartment pharmacokinetic model with zero-order input and first-order output and micro-constants as primary parameters with WinNonlin Professional, Version 4.0. A weighting factor of 1/Y was used for all subjects. Parameter estimates were obtained for V_1, K_{10}, K_{12}, and K_{21}. Daptomycin plasma concentration-time profiles were simulated using a two-compartment model and the pharmacokinetic parameter estimates previously obtained. Simulated dosing regimens consisted of 4 mg/kg q24h for subjects with CL_{CR} >80 mL/min and CL_{CR} 50-80 mL/min, 4 mg/kg q36h for subjects with CL_{CR} 30-50 mL/min, 4 mg/kg q48h for subjects with CL_{CR} 30-50 mL/min, <30 mL/min, HD patients, and CAPD patients, and 5 mg/kg q48h for CL_{CR} <30 mL/min and HD patients. Daptomycin was administered as a 30 minute infusion and all subjects received seven doses. HD patients received hemodialysis from approximately 30.5 to 34.5 hrs after the start of the infusion.

A pharmacokinetic analysis was performed to asses the C_{max}, C_{min} (C_{24}, C_{36}, or C_{48}), and $AUC_{0-\tau}$ based on total plasma concentrations and a PK/PD analysis was performed to determine the absolute time unbound plasma concentrations remained below the MIC based on simulated plasma concentration-time data for each subject. MIC values of 1 and 2 µg/mL were chosen since they represent potential "susceptible" interpretive criteria for *Staphylococcus aureus* and *Streptococcus* spp.

The mean (range) C_{max}, C_{min}, and $AUC_{0-\tau}$ for the seventh dose as well as the mean (range) time below the MIC for all seven doses are shown in Table 13. Since daptomycin's antimicrobial activity appears to exhibit concentration-dependent killing (based on summarized microbiology data) and the occurrence of myopathy may be related to the time between doses in which the plasma concentration remains above a threshold concentration, dosage regimens proposed by the reviewer were selected for subjects with renal impairment based on matching the C_{max}, C_{min}, $AUC_{0-\tau}$, and time in which the plasma concentrations remains below the MIC to subjects with normal renal function. **The dosage regimens proposed by the reviewer are bolded.**

Table 13. Mean (range) C_{max}, C_{min}, $AUC_{0-\tau}$, and absolute time below the MIC per dosing interval (Time <MIC)

Renal Function	C_{max} (µg/mL)	C_{min} (µg/mL)	$AUC_{0-\tau}$ (µg*hr/mL)	Time <MIC (hrs)	
				MIC = 1 µg/mL	MIC = 2 µg/mL
>80 mL/min					
4 mg/kg q24	68.8	6.8	500	4.7	13.9
50-80 mL/min					
3 mg/kg q36h	55.6	6.6	558	11.6	23.9
4 mg/kg q24h	83.5	14.4	744	2.3	5.4
30-<50 mL/min					
3 mg/kg q36h	53.1*	8.6*	730*	5.3*	21.8*
4 mg/kg q24h	**82.3***	**23.2***	**973***	**0.0***	**1.2***
4 mg/kg q36h	70.8*	11.4*	973*	0.5*	15.0*
4 mg/kg q48h	65.7*	6.08*	975*	12.5*	29.0*
5 mg/kg q48h	83.3*	7.8*	1,244*	6.6*	23.1*
<30 mL/min					
4 mg/kg q36h	66.1	17.7	1,110	0.0	5.5
4 mg/kg q48h	59.3	10.6	1,115	1.7	17.6
5 mg/kg q48h	74.4	13.2	1.394	0.2	11.3

Table 13 (continued). Mean (range) C_{max}, C_{min}, $AUC_{0-\tau}$, and absolute time below the MIC per dosing interval (Time <MIC)

Renal Function	C_{max} (μg/mL)	C_{min} (μg/mL)	$AUC_{0-\tau}$ (μg*hr/mL)	Time <MIC (hrs)	
				MIC = 1 μg/mL	MIC = 2 μg/mL
HD					
4 mg/kg q48h	51.9	10.9	1,045	5.0	17.4
5 mg/kg q48h	64.9	13.7	1,306	2.8	12.4
CAPD					
4 mg/kg q48h	70.3	15.2	1,449	0.0	2.7

*n=1 for CL_{CR} 30-<50 mL/min; $AUC_{0-\tau}$ represents q24h, q36h, and q48 h dosing intervals

The sponsor proposes 4 mg/kg q24 for subjects with CL_{CR} >40 mL/min and 4 mg/kg q48h for patients with CL_{CR} ≤40 mL/min for complicated skin and skin structure infections. The reviewer proposes 4 mg/kg q24 for subjects with CL_{CR} ≥30 mL/min and 4 mg/kg q48h for patients with CL_{CR} <30 mL/min, including hemodialysis and CAPD patients (see Table 14). Daptomycin should be administered immediately following hemodialysis on hemodialysis days.

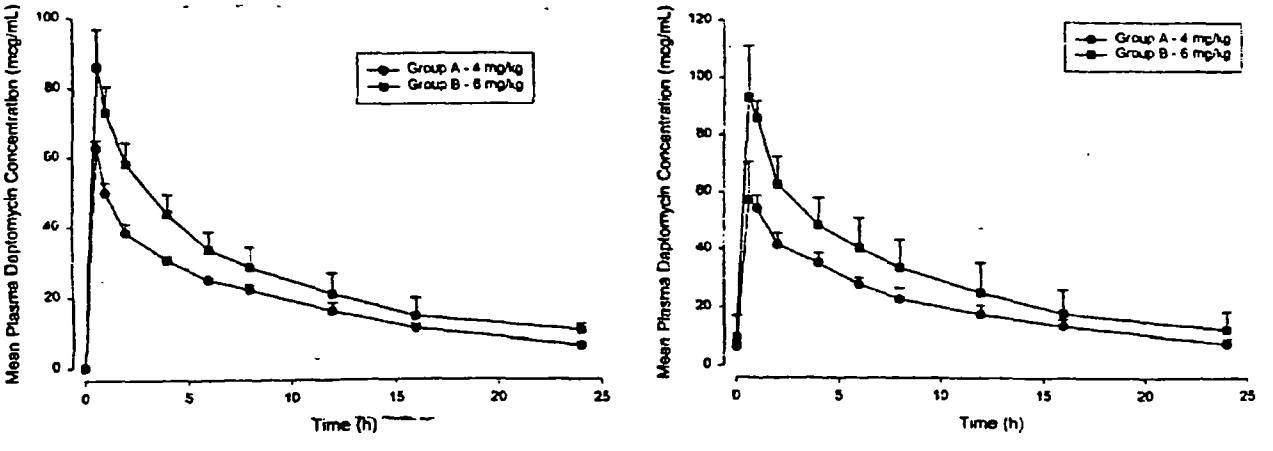
Table 14. Proposed dosage regimens for subjects with varying degrees of renal function

Creatinine Clearance (mL/min)	Dosage Regimen
≥30 mL/min	4 mg/kg q24h
<30 mL/min, including hemodialysis* and CAPD	4 mg/kg q48h

*Daptomycin should be administered following hemodialysis on hemodialysis days

In a second renal impairment study (Study DAP-MDRI-01-09), the sponsor enrolled eight subjects with moderate renal impairment (CL_{CR} 30-50 mL/min). The sponsor did not enroll a control group. Four subjects received daptomycin IV 4 mg/kg q24h for 14 days and four subjects received daptomycin IV 6 mg/kg IV for 11 days. All subjects had an estimated CL_{CR} of 30-50 mL/min using IBW, three subjects had an estimated CL_{CR} of 30-50 mL/min using actual body weight, and one subject had a measured CL_{CR} of 30-50 mL/min. The mean plasma concentration-time profiles of daptomycin IV 4 mg/kg or 6 mg/kg for all eight subjects after the first dose (left) and last dose (14th or 11th dose, right) are shown in Figure 16.

Figure 16. Mean daptomycin plasma concentration-time profiles after the first dose (left) and last dose (right) following infusion of 4 mg/kg or 6 mg/kg



The reviewer analyzed the data from the seven subjects with a measured creatinine clearance of 50-80 mL/min. The pharmacokinetic parameters for subjects with a measured CL_{CR} 50-80 mL/min are shown in Table 15. When compared to the mean pharmacokinetic parameters from the control group (CL_{CR} >80 mL/min) of Study DAP-00-01, the mean C_{max}, $AUC_{0-\infty}$, and CL_T from subjects with mild renal impairment were similar, whereas the mean half-life decreased 11%.

Table 15. Mean (CV%) pharmacokinetic parameters for daptomycin 4 mg/kg q24h and 6 mg/kg q24h for subjects with measured CL_{CR} of 50-80 mL/min

	4 mg/kg (n=4)		6 mg/kg (n=3)	
Parameter	Day 1	Day 14	Day 1	Day 11
C_{max} (µg/mL)	62.6 (4%)	59.3 (18%)	91.2 (22%)	94.9 (6%)
C_{24} (µg/mL)	6.03 (17%)	7.74 (22%)	9.29 (0%)	8.75 (8%)
AUC_{0-1} (µg*hr/mL)	448 (5%)	---	588 (25%)	---
$AUC_{0-\infty}$ (µg*hr/mL)	522 (7%)	---	683 (27%)	---
$AUC_{0-\tau}$ (µg*hr/mL)	---	511 (13%)	---	641 (21%)
V_{SS} (L/kg)	0.094 (7%)	---	0.086 (4%)	---
Varea (L/kg)	0.101 (14%)	0.113 (6%)	0.094 (4%)	0.096 (9%)
CL_T (mL/hr/kg)	8.21 (8%)	8.25 (9%)	9.16 (30%)	9.61 (26%)
Half-life (hrs)	8.48 (11%)	9.55 (15%)	7.50 (27%)	7.13 (22%)

The relationship between creatinine clearance and $AUC_{0-\infty}$ values after the first dose from Study DAP-MDRI-01-09 and Study DAP-00-01 is shown in Figure 17. In this figure, the $AUC_{0-\infty}$ was corrected to a dose of 4 mg/kg in study DAP-MDRI-01-09. The $AUC_{0-\infty}$ values in Study DAP-MDRI-01-09 were similar to the control group (CL_{CR} >80 mL/min) in Study DAP-00-01. Based on the results of this study, no dosage adjustment of daptomycin is warranted for subjects with mild renal impairment.

The reviewer also compared the pharmacokinetic parameters from subjects with mild renal impairment (Study DAP-MDRI-01-09) to subjects with normal renal function (Study DAP-00-02). In Study DAP-00-02, six healthy adult subjects received daptomycin 4 mg/kg q24h for 7 days and six healthy adult subjects received daptomycin 6 mg/kg q24h for 7 days. The geometric mean ratios (mild renal impairment/normal renal function) after the first dose and the last dose are shown in Table 16.

Figure 17. Relationship between creatinine clearance and $AUC_{0-\infty}$ after a single dose of daptomycin in studies DAP-MDRI-01-09 and DAP-00-01

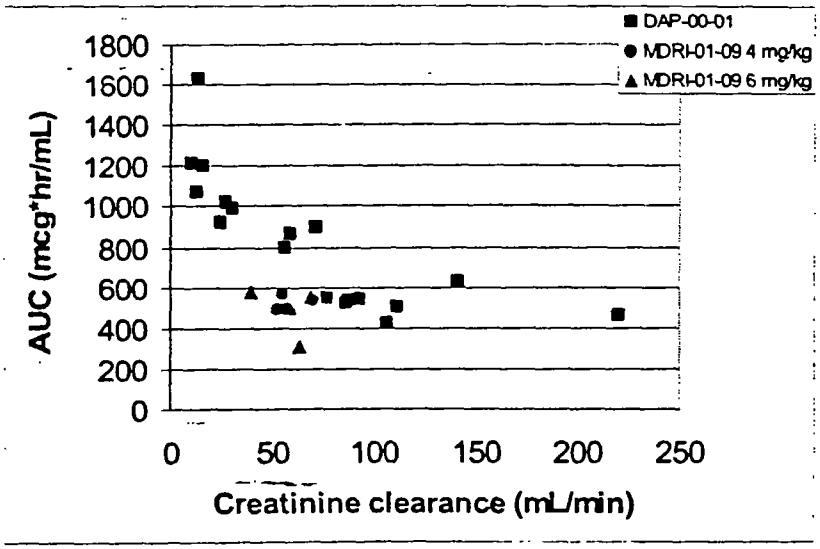


Table 16. Geometric mean ratios (mild renal impairment/normal renal function) for daptomycin 4 mg/kg q24h and 6 mg/kg q24h after the first and last dose

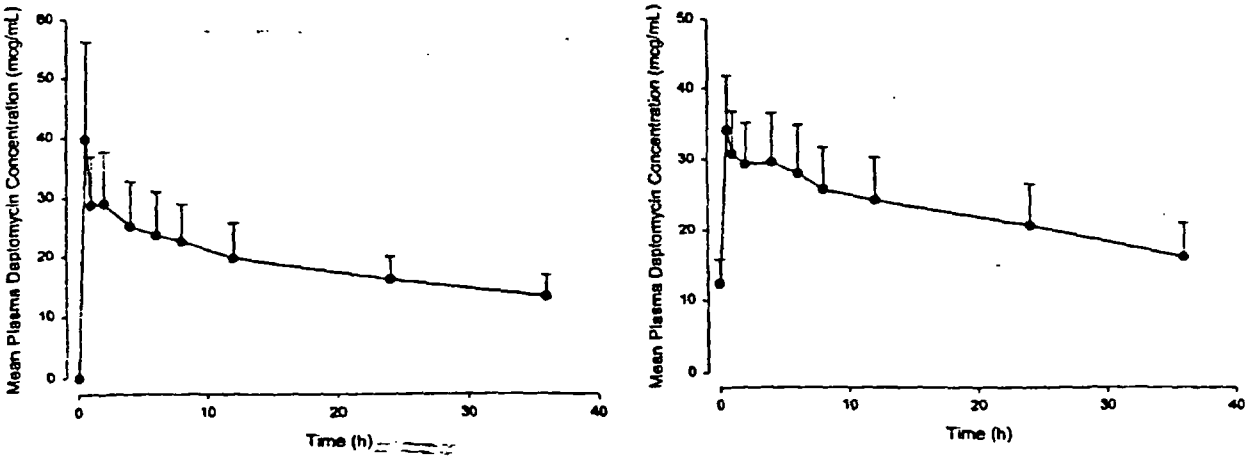
	4 mg/kg		6 mg/kg	
Parameter	First dose	Last dose	First dose	Last dose
C_{max} (µg/mL)	1.15	1.01	1.06	0.97
AUC_{0-T} (µg*hr/mL)	---	1.04	---	0.85
$AUC_{0-\infty}$ (µg*hr/mL)	1.23	---	0.94	---
V_{SS} (L/kg)	1.02	---	0.99	---
CL_T (L/hr/kg)	0.86	1.00	1.04	1.17

The pharmacokinetic parameters were similar between subjects with normal renal function (Study DAP-00-02) and subjects with mild renal impairment (Study DAP-MDRI-01-03). Although the geometric mean C_{max} and $AUC_{0-\infty}$ were greater in subjects with mild renal impairment after the first dose (4 mg/kg group), the parameters were similar after the last dose in the 4 mg/kg group and both doses in the 6 mg/kg group.

In the third renal impairment study, six hemodialysis patients received a single loading dose of IV daptomycin 4 mg/kg over 30 min followed by six doses of daptomycin 3 mg/kg q48h, whereas one subject received a single loading dose of IV daptomycin 6 mg/kg over 30 min followed by six additional doses of daptomycin 4 mg/kg q48h. Patients received hemodialysis on their usual days. The mean plasma concentration-time profiles for daptomycin after the first (left plot) and last dose (right plot) are shown in Figure 18.

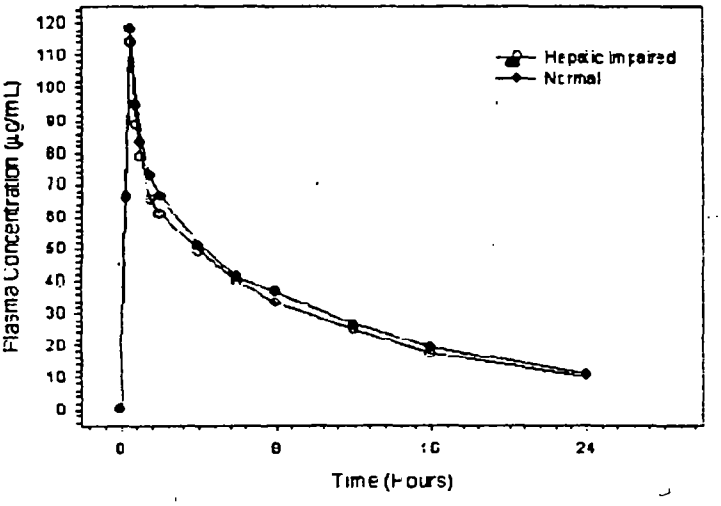
Since the sponsor did not enroll a control group of healthy volunteers, the reviewer compared the pharmacokinetic parameter estimates of hemodialysis patients from Study DAP-MDRI-01-03 to hemodialysis patients from Study DAP-00-01 (single dose of daptomycin 4 mg/kg). After the first dose of daptomycin, the mean C_{max} was similar among patients from both studies, whereas the mean $AUC_{0-\infty}$ was 30% greater in Study DAP-MDRI-01-03. After the last dose, the mean C_{max} was 50% lower in study DAP-MDRI-01-03 and the mean $AUC_{0-\infty}$ was 15% lower. The mean $AUC_{0-\infty}$ from Study DAP-MDRI-01-03 was greater than anticipated since the five patients received hemodialysis on their usual days and received a 25% reduction in dose.

Figure 18. Mean daptomycin plasma concentration-time profiles for Group A on Day 1 (left, 4 mg/kg) and Day 13 (right, 3 mg/kg)



Hepatic impairment:
The pharmacokinetics of daptomycin were assessed in ten subjects with moderate hepatic impairment (Child-Pugh B) and nine control subjects matched by weight, age, and gender following the administration of a single 6 mg/kg dose. The mean plasma concentration-time profiles for hepatic impairment and control subjects are shown in Figure 19.

Figure 19. Mean total daptomycin plasma concentration-time profiles following a single dose of IV daptomycin 6 mg/kg in subjects with hepatic impairment and healthy subjects



The total daptomycin pharmacokinetic parameter estimates are shown in Table 17. The mean C_{max} and AUC values were similar between subjects with hepatic impairment and healthy subjects. The mean CL_T was 8% greater in subjects with hepatic impairment compared to healthy subjects, whereas the mean V_{SS} was similar between the two groups of subjects. The mean terminal elimination half-life was shorter in subjects with hepatic impairment compared to healthy volunteers (8.97 hrs vs. 9.44 hrs, respectively).

The unbound mean AUC_{0-24} and $AUC_{0-\infty}$ were both 12% greater in subjects with hepatic impairment compared to healthy subjects. Although the mean CL_T was 11% lower in hepatic impairment subjects, the mean CL_R was 10% greater compared to healthy subjects.

Table 17. Mean (CV%) total and unbound daptomycin pharmacokinetic parameters

	Total daptomycin		Unbound daptomycin	
Parameter	**Hepatic impairment (n=10)**	**Healthy subjects (n=9)**	**Hepatic impairment (n=10)**	**Healthy subjects (n=9)**
AUC_{0-24} (µg*hr/mL)	727 (17%)	779 (11%)	60.7 (25%)	54.1 (22%)
AUC_{0-t} (µg*hr/mL)	790 (25%)	779 (11%)	65.1 (25%)	54.1 (22%)
$AUC_{0-\infty}$ (µg*hr/mL)	867 (23%)	928 (13%)	71.7 (25%)	64.3 (22%)
C_{max} (µg/mL)	113.7 (15%)	118.3 (13%)	9.59 (28%)	8.23 (24%)
T_{max} (hrs)	0.50 (0%)	0.53 (16%)	—	—
CL_T (mL/hr/kg)	7.10 (20%)	6.55 (13%)	86.4 (28%)	97.2 (20%)
CL_R (mL/hr/kg)	4.09 (49%)	3.05 (18%)	50.7 (46%)	46.2 (28%)
Vz (L/kg)	0.088 (16%)	0.090 (16%)	1.12 (34%)	1.33 (24%)
Vss (L/kg)	0.082 (17%)	0.081 (13%)	1.04 (35%)	1.21 (23%)
Half-life (hrs)	8.97 (19%)	9.44 (9%)	—	—
Ae_{24} (%)	49.3 (39%)	39.8 (22%)	—	—

The 90% confidence intervals of the geometric mean ratios for C_{max} and $AUC_{0-\infty}$ were within the 0.80 to 1.25 range based on total daptomycin concentrations but outside of the 0.80 to 1.25 range based on unbound daptomycin concentrations (see Table 18). The differences in the pharmacokinetic parameter estimates based on total and unbound concentrations were not statistically significantly different between subjects with impaired hepatic function and normal hepatic function.

Table 18. Geometric mean ratios (hepatic impairment/normal hepatic function) and 90% confidence intervals for subjects with hepatic impairment and normal hepatic function

	Total		Unbound	
Parameter	Point estimate	90% CI	Point estimate	90% CI
AUC_{0-24}	0.926	(0.830 to 1.035)	1.112	(0.918 to 1.347)
$AUC_{0-\infty}$	0.922	(0.803 to 1.058)	1.106	(0.917 to 1.336)
C_{max}	0.959	(0.856 to 1.074)	1.150	(0.927 to 1.428)

The mean percentage of unbound daptomycin was 8.13% and 9.20% at 0.5 hrs and 8 hrs after the start of the infusion, respectively in subjects with hepatic impairment. The mean percentage of unbound daptomycin was 6.72% and 7.38% at 0.5 hrs and 8 hrs after the start of the infusion, respectively in healthy subjects. Thus, the mean percent unbound of daptomycin increased 21.1% and 16.1% at 0.5 hrs and 8 hrs after the start of the infusion, respectively, in subjects with hepatic impairment compared to healthy subjects. Overall, no dosage adjustment is warranted for patients with mild to moderate hepatic impairment since the C_{max} and $AUC_{0-\infty}$ geometric mean ratios were within the no-effect boundaries. The effect of severe hepatic impairment was not studied.

Elderly:

The pharmacokinetics of daptomycin were assessed in 12 healthy elderly subjects and 11 healthy young subjects following the administration of a single 4 mg/kg dose. The mean plasma concentration-time profiles for healthy elderly and young subjects are shown in Figure 20.

The daptomycin pharmacokinetic parameter estimates are shown in Table 19. The mean C_{max} values were similar between healthy elderly and young subjects, whereas the mean AUC_{0-t} and $AUC_{0-\infty}$ were 46% and 58% greater, respectively in elderly subjects compared to young subjects. The mean CL_T, CL_R, and Ae were 35%, 41%, and 19% lower in elderly subjects compared to young subjects. The terminal elimination half-life was 74% greater in elderly subjects compared to young subjects.

Figure 20. Mean plasma concentration-time profiles of daptomycin following a single dose of 4 mg/kg IV to healthy elderly and young subjects

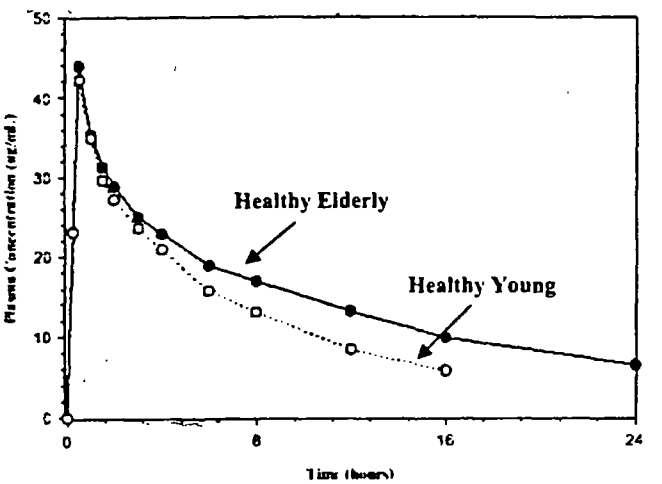


Table 19. Mean (CV%) daptomycin pharmacokinetic parameter estimates when administered to healthy elderly and healthy young subjects

Parameter	Healthy Elderly (n=12)	Healthy Young (n=11)
AUC_{0-t} (µg*hr/mL)	361 (18%)	248 (13%)
AUC_{0-24} (µg*hr/mL)	361 (18%)	268 (11%)
$AUC_{0-\infty}$ (µg*hr/mL)	474 (23%)	301 (12%)
C_{max} (µg/mL)	44.0 (17%)	42.3 (15%)
C_{24} (µg/mL)	6.4 (29%)	3.4*
T_{max} (hrs)	0.5 (7%)	0.5 (28%)
CL_T (mL/hr/kg)	9.86 (25%)	15.09 (16%)
CL_R (mL/hr/kg)	4.27 (40%)	7.20 (24%)
Vz (L/kg)	0.166 (29%)	0.147 (14%)
Vss (L/kg)	0.155 (27%)	0.136 (13%)
Half-life (hrs)	11.86 (19%)	6.80 (8%)
Ae (%)	34.3 (46%)	42.6 (16%)

* - n=1; the plasma concentration was below the LOQ ——→ µg/mL) by 24 hrs in 10 of 11 healthy young subjects

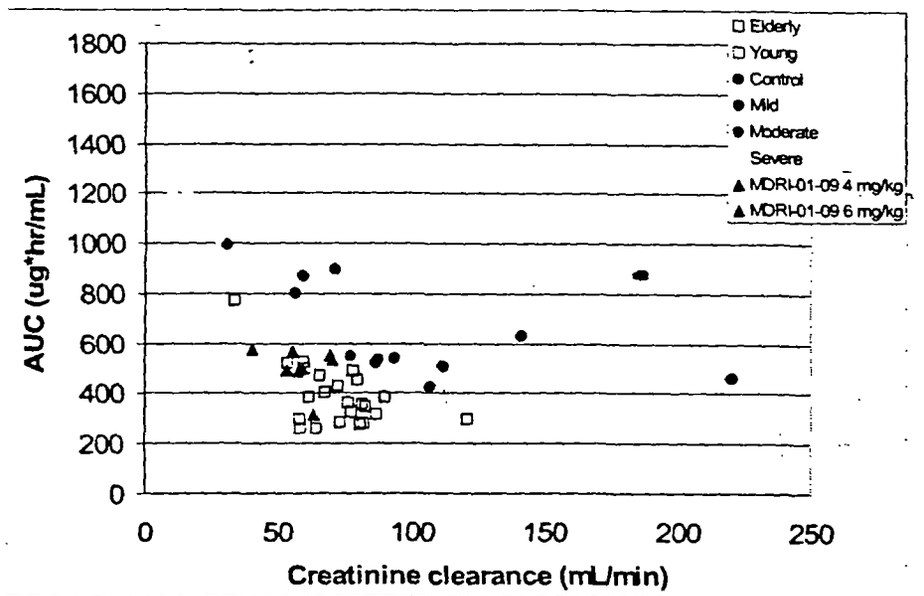
The 90% confidence intervals of the daptomycin geometric mean ratio for AUC_{0-t} and $AUC_{0-\infty}$ were outside of the predetermined limits of 0.80 to 1.25 and were statistically significantly greater in healthy elderly compared to young subjects (see Table 20). The 90% confidence interval of the daptomycin geometric mean ratio for C_{max} was within the predetermined limits of 0.80 to 1.25 and was not statistically significantly different between the two groups of subjects.

Table 20. Geometric mean ratios and 90% confidence intervals for daptomycin (healthy elderly/healthy young subjects)

Parameter	Point estimate	90% CI
AUC_{0-t}	1.4472	1.3046 - 1.6053
$AUC_{0-\infty}$	1.5517	1.3745 - 1.7518
C_{max}	1.0382	0.9257 - 1.1644

Although the mean $AUC_{0-\infty}$ was 58% greater in healthy geriatric subjects compared to healthy young subjects in the current study, the mean $AUC_{0-\infty}$ and CL_T were similar between healthy elderly subjects from the current study and healthy young subjects from Study DAP-00-02. The $AUC_{0-\infty}$ values from healthy young subjects in the current study were substantially less than the $AUC_{0-\infty}$ values from other Phase 1 studies (Studies DAP-00-01 and DAP-MDRI-0109) based on their measured creatinine clearance (see Figure 21). Doses were adjusted to 4 mg/kg. Based on the lower systemic exposure in the current study compared to other Phase 1 studies receiving similar doses, the decreased efficacy among patients >65 yrs of age from Phase 3 studies, and safety data from Phase 3 studies, no dosage adjustment is warranted for elderly patients with normal (for their age) renal function.

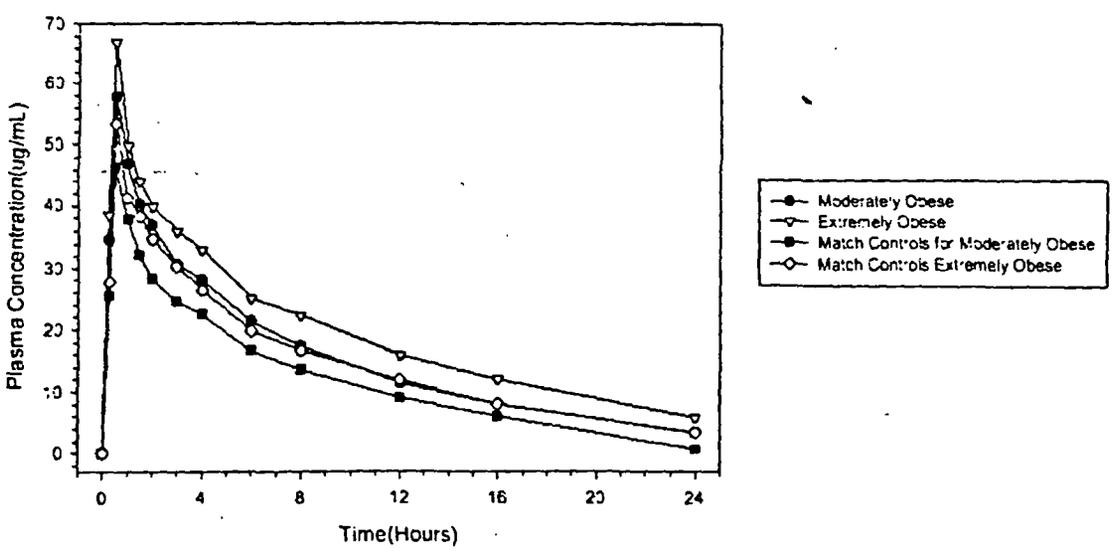
Figure 21. Mean plasma concentration-time profiles of daptomycin following a single dose of 4 mg/kg IV to healthy elderly and young subjects



Obesity:

The pharmacokinetics of daptomycin in obesity were assessed in six moderately obese subjects (BMI 25-39.9 kg/m^2). six extremely obese subjects (BMI ≥40 kg/m^2), and 12 matched control subjects matched for gender, age, and renal function following the administration of a single 4 mg/kg IV dose (based on total body weight). The mean plasma concentration-time profiles of daptomycin following a single 4 mg/kg dose to moderately or severely obese subjects and non-obese matched controls are shown in Figure 22.

Figure 22. Mean plasma concentration-time profiles of daptomycin following a single dose of 4 mg/kg IV to healthy elderly and young subjects



The mean daptomycin pharmacokinetic parameter estimates in obese subjects following the administration of a single dose of daptomycin IV 4 mg/kg are shown in Table 21.

Table 21. Mean (CV%) daptomycin pharmacokinetic parameter estimates in obese subjects and matched controls

	Moderately Obese		Extremely Obese	
Parameter	**Obese**	**Control**	**Obese**	**Control**
AUC_{0-t} (µg*hr/mL)	375 (16%)	269 (13%)	473 (17%)	353 (20%)
AUC_{0-24} (µg*hr/mL)	379 (15%)	288 (10%)	473 (17%)	361 (17%)
$AUC_{0-\infty}$ (µg*hr/mL)	421 (16%)	322 (10%)	548 (25%)	419 (25%)
C_{max} (µg/mL)	57.8 (13%)	46.3 (15%)	67.0 (10%)	53.2 (11)
C_{24} (µg/mL)	4.1 (17%)[a]	3.7[b]	5.9 (49)	5.1 (40%)[c]
T_{max} (hrs)	0.50 (0%)	0.50 (0%)	0.50 (0%)	0.50 (0%)
CL_T (mL/hr)	856 (8%)	724 (6%)	1,016 (29%)	696 (34%)
CL_R (mL/hr)	492 (15%)	422 (16%)	500 (32%)	373 (29%)
Vz (L)	9.00 (9%)	7.14 (13%)	11.33 (18%)	7.44 (17%)
Vss (L)	8.10 (12%)	6.60 (11%)	10.82 (15%)	6.78 (17%)
Half-life (hrs)	7.34 (13%)	6.83 (10%)	8.13 (21%)	8.04 (29%)
Ae (%)	51.8 (12%)	52.3 (16%)	42.7 (14%)	48.6 (17%)

a-plasma concentration below LLOQ in 1/6 subjects; b-plasma concentration below LLOQ in 5/6 subjects; c-plasma concentration below LLOQ in 2/6 subjects

In moderately obese subjects, the mean C_{max} and $AUC_{0-\infty}$ were 25% and 30% greater, respectively in obese subjects than matched controls. The mean CL_T and CL_R (not corrected by body weight) were 18% and 16% greater in moderately obese subjects compared to matched controls.

When corrected for actual body weight (ABW), the mean CL_T and CL_R were 15% and 16% lower in moderately obese subjects compared to matched controls. In contrast, the mean CL_T and CL_R were 10% and 9% greater in moderately obese subjects compared to matched controls when corrected for ideal body weight (IBW). The mean elimination half-life was 7% longer in obese subjects compared to matched controls.

The mean V_{SS} (not corrected for body weight) was 23% greater in moderately obese subjects compared to matched controls. When V_{SS} was corrected for actual body weight, it decreased 12% compared to matched controls. In contrast, the mean V_{SS} increased 15% in moderately obese subjects compared to matched controls when corrected for ideal body weight.

In extremely obese subjects, the mean C_{max} and $AUC_{0-\infty}$ were 26% and 31% greater, respectively in obese subjects than matched controls. When corrected for actual body weight (ABW), the mean CL_T and CL_R were 23% and 30% lower in extremely obese subjects compared to matched controls. In contrast, the mean CL_T and CL_R were 48% and 37% greater in moderately obese subjects compared to matched controls when corrected for ideal body weight (IBW).

The mean V_{SS} (not corrected for weight) was 60% greater in extremely obese subjects compared to matched controls. When V_{SS} was corrected for actual body weight, it decreased 15% compared to matched controls. In contrast, the mean V_{SS} was 62% greater in extremely obese subjects compared to matched controls when corrected for ideal body weight.

The differences in daptomycin clearance between obese and matched non-obese controls may be attributed to an increase in daptomycin clearance with increased body mass index. No dosage adjustment

of daptomycin is warranted for moderately obese (BMI 25-39.9 kg/m^2) and extremely obese (BMI ≥40 kg/m^2) patients.

Pediatrics:
The sponsor has not conducted clinical pharmacology studies to determine daptomycin pharmacokinetics in pediatric patients.

2. Based upon what is known about exposure-response relationships and their variability, and the groups studied (volunteers vs. patients), what dose regimen adjustments, if any, are recommended for each of these subgroups? If dosage regimen adjustments are not based on exposure-response relationships, describe the alternative basis for the recommendation.

Based on the information known about the exposure-response relationship and the intrinsic factors studied, dosage regimen adjustments are only recommended for patients with renal impairment. Please refer to section IV.C.1, Renal Impairment for a dosage recommendations.

D. Extrinsic factors

1. What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

The sponsor did not assess the impact of herbal products, diet, smoking, or alcohol use on the pharmacokinetics and exposure of daptomycin. Thus, the effect of these variables on the exposure/response relationship of daptomycin is unknown.

2. Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dose regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

Not applicable.

3. Drug-drug interactions

The sponsor evaluated the potential of daptomycin to inhibit human cytochrome (CYP) P450 isoforms using pooled human hepatocytes and daptomycin concentrations ranging from 2.5 to 40 µg/mL. Based on the *in vitro* results, daptomycin IV 4 mg/kg is unlikely to inhibit the metabolism of drugs via the following P450 isoforms: CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4.

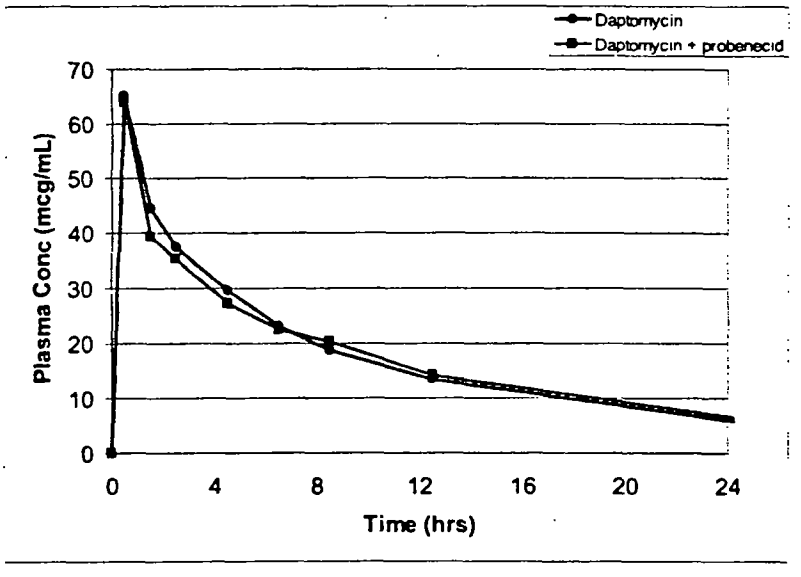
In addition, the sponsor also evaluated the potential of daptomycin to act as an inducer of human CYP P450 isoforms using fresh liver tissue (from 3 donors) and daptomycin concentrations ranging from 25 to 400 µg/mL. Based on the results, daptomycin IV 4 mg/kg is not anticipated to induce the metabolism of drugs cleared by isoforms CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4.

The sponsor performed clinical pharmacology studies to assess the drug-drug interaction between daptomycin and probenecid, aztreonam, warfarin, and simvastatin. The results of each of these studies are discussed below.

Probenecid:
The pharmacokinetics of daptomycin alone and in combination with probenecid were assessed in five healthy adult subjects with a measured CL_{CR} >80 mL/min/1.73 m^2 (subjects 1, 10, 15, 19, and 35). Each subject received a single dose of daptomycin IV 4 mg/kg with and without probenecid (500 mg QID on Days -2 and -1, 500 mg prior to the daptomycin infusion on Day 1, and six hours after the daptomycin infusion). However, the measured CL_{CR} of subject 10 was only 76.7 mL/min.

The mean plasma concentration-time profiles of daptomycin administered with and without probenecid for the five subjects are shown in Figure 23. The mean plasma concentration-time profiles of daptomycin were similar when administered alone and in combination with probenecid.

Figure 23. Mean daptomycin plasma concentration-time profiles following the administration of a single 4 mg/kg dose of daptomycin alone and with probenecid



The mean daptomycin pharmacokinetic parameter estimates following the administration of a single dose of daptomycin IV 4 mg/kg alone and in combination with probenecid are shown in Table 22. When daptomycin was administered with probenecid, the daptomycin mean C_{max}, $AUC_{0-\infty}$, CL_T, CL_R and elimination half-life were essentially unchanged.

Table 22. Mean (CV%) daptomycin pharmacokinetic parameter estimates alone and in combination with probenecid in subjects with normal renal function

Parameter	Daptomycin alone	Daptomycin + Probenecid
C_{max} (µg/mL)	65.1 (34%)	64.0 (31%)
C_{24} (µg/mL)	5.6 (12%)	6.3 (29%)
AUC_{0-t} (µg*hr/mL)	454 (16%)	479 (27%)
$AUC_{0-\infty}$ (µg*hr/mL)	534 (12%)	536 (23%)
V_{SS} (L/kg)	0.0975 (27%)	0.0967 (19%)
CL_T (L/hr/kg)	0.0077 (13%)	0.0078 (22%)
$t_{1/2}$ (hrs)	9.71 (19%)	9.17 (7%)
CL_R (L/hr/kg)	0.0042 (12%)	0.0046 (24%)
Ae (% dose)	55.3 (15%)	61.0 (42%)

The reviewer calculated the geometric mean ratios and 90% confidence intervals for daptomycin (daptomycin + probenecid/daptomycin) (see Table 23). The 90% confidence intervals of the geometric mean ratios for C_{max} and $AUC_{0-\infty}$ were within the predetermined limits of 0.80 to 1.25 for daptomycin and were not statistically significantly different. Although not statistically significantly different, the CL_T, CL_R, and V_{SS} of daptomycin were outside of the 0.80 to 1.25 range when administered in combination with probenecid. Thus, daptomycin and probenecid do not exhibit a significant drug-drug interaction when administered in combination. No dosage adjustment of daptomycin is warranted in patients receiving probenecid 500 mg QID.

Table 23. Geometric mean ratios and 90% confidence intervals (CV%) for daptomycin pharmacokinetic parameter estimates alone and in combination with probenecid

Parameter	Point estimate	90% CI
AUC_{0-t}	1.0374	0.8924 to 1.2060
$AUC_{0-\infty}$	0.9874	0.8813 to 1.1062
C_{max}	0.9977	0.8199 to 1.2140

The reviewer also assessed the impact of probenecid on the protein binding of daptomycin. The unbound fraction of daptomycin modestly increased at the end of the infusion for all five subjects (see Table 24) following the administration of probenecid (11.5% vs. 10.0%). At 2.5 hrs after the start of the infusion, the unbound fraction of daptomycin was independent of the administration of probenecid (10.0% for daptomycin alone vs. 10.5% for daptomycin + probenecid, respectively). The protein binding was not available for one subject at 2.5 hrs after receiving daptomycin and probenecid. Thus, the unbound fraction of daptomycin modestly increased at the end of infusion when administered with probenecid, although the unbound fraction was similar 2.5 hrs after the start of the infusion.

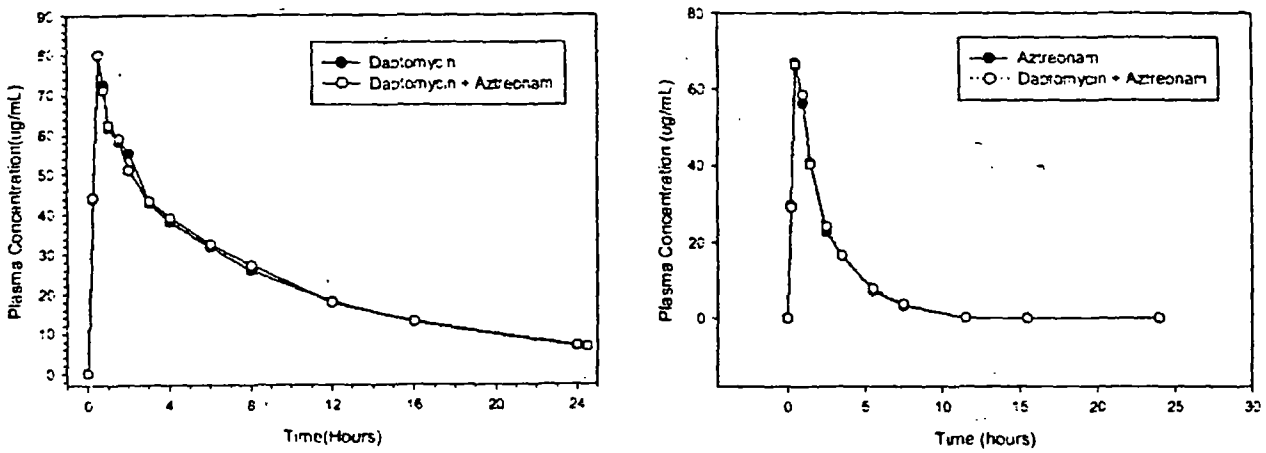
Table 24. Mean (SD) percentage of unbound daptomycin with and without probenecid at the end of the infusion (0.5 hrs) and two hrs later (2.5 hrs)

	Sample Time (After start of infusion)		
Category	0.5 hrs	2.5 hrs	Overall
Daptomycin alone	10.0% (2.2)	10.0% (1.8)	10.1% (1.9)
Daptomycin + Probenecid	11.5% (2.1)	10.5% (1.8)	11.0% (1.9)

Aztreonam:

The pharmacokinetics of daptomycin in combination with aztreonam and the pharmacokinetics of aztreonam in combination with daptomycin were assessed in 18 healthy adult subjects following the administration of a single dose of daptomycin 6 mg/kg IV alone, aztreonam 1,000 mg IV alone, or both. The mean plasma concentration-time profiles of daptomycin and aztreonam are shown in Figure 24.

Figure 24. Mean plasma concentration-time profiles of daptomycin (left) and aztreonam (right) alone and in combination



The mean plasma concentrations of daptomycin and aztreonam were similar when administered alone and in combination to healthy subjects.

The daptomycin and aztreonam pharmacokinetic parameter estimates following the administration of a single dose of daptomycin IV 6 mg/kg and aztreonam IV 1,000 mg alone and in combination are shown in Table 25.. When daptomycin was co-administered with aztreonam, the mean C_{max}, $AUC_{0-\infty}$, CL_T, and CL_R of either daptomycin or aztreonam were not substantially altered.

Table 25. Mean (CV%) daptomycin and aztreonam pharmacokinetic parameters alone and in combination

	Daptomycin 6 mg/kg IV		Aztreonam 1,000 mg IV	
Parameter	**Daptomcycin alone**	**Daptomycin + Aztreonam**	**Aztreonam alone**	**Aztreonam + Daptomycin**
AUC_{0-t} (µg*hr/mL)	561 (13%)	565 (10%)	156 (15%)	160 (16%)
$AUC_{0-\infty}$ (µg*hr/mL)	650 (16%)	648 (13%)	164 (15%)	169 (16%)
C_{max} (µg/mL)	82.1 (18%)	80.9 (13%)	66.9 (13%)	67.1 (16%)
T_{max} (hrs)	0.69 (54%)	0.59 (8%)	0.51 (10%)	0.57 (31%)
C_{24} (µg/mL)	6.65 (23%)	6.79 (22%)	—	—
CL_T (mL/hr/kg)	9.65 (16%)	9.66 (13%)	84.46 (14%)	82.00 (16%)
CL_R (mL/hr/kg)	6.26 (20%)	5.65 (24%)	61.70 (23%)	58.49 (25%)
Vz (L/kg)	0.121 (17%)	0.117 (13%)	0.208 (15%)	0.214 (14%)
Vss (L/kg)	0.109 (15%)	0.106 (11%)	0.189 (11%)	0.192 (13%)
Half-life (hrs)	8.77 (17%)	8.51 (15%)	1.71 (13%)	1.83 (8%)
Ae (%)	56.7 (18%)	51.2 (20%)	72.4 (17%)	70.3 (17%)

The geometric mean ratio and 90% confidence intervals for daptomycin (daptomycin + aztreonam/daptomycin) and aztreonam (aztreonam + daptomycin/aztreonam) are shown in Table 26. The 90% confidence intervals of the geometric mean ratios for $AUC_{0-\infty}$ and C_{max} were within the predetermined limits of 0.80 to 1.25 for daptomycin and aztreonam and were not statistically significantly different. Thus, daptomycin and aztreonam do not exhibit a significant drug-drug interaction when administered in combination. No dosage adjustment of either daptomycin or aztreonam is warranted when co-administered to patients.

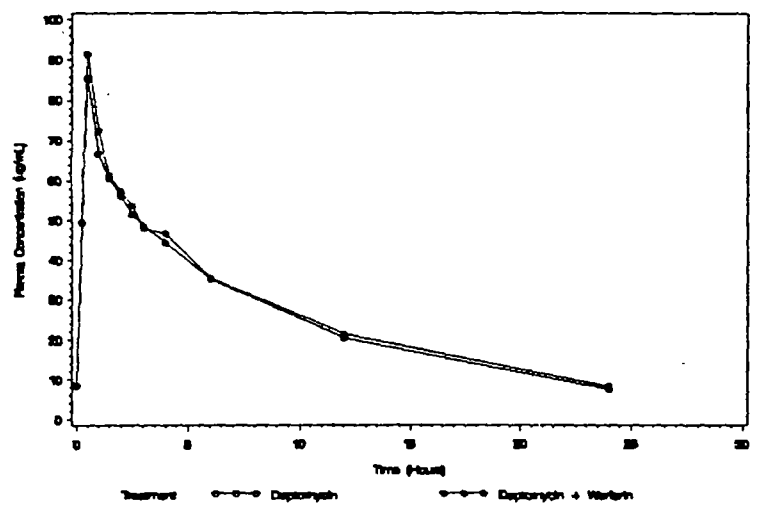
Table 26. Geometric mean ratios and 90% confidence intervals for daptomycin and aztreonam administered alone and in combination

	Daptomycin		Aztreonam	
Parameter	Point estimate	90% CI	Point estimate	90% CI
AUC_{0-t}	1.0107	0.9368 - 1.0904	1.0256	0.9219 - 1.1410
$AUC_{0-\infty}$	1.0017	0.9146 - 1.0971	1.0320	0.9262 - 1.1497
C_{max}	0.9923	0.8979 - 1.0966	1.0008	0.9097 - 1.1011

Warfarin:

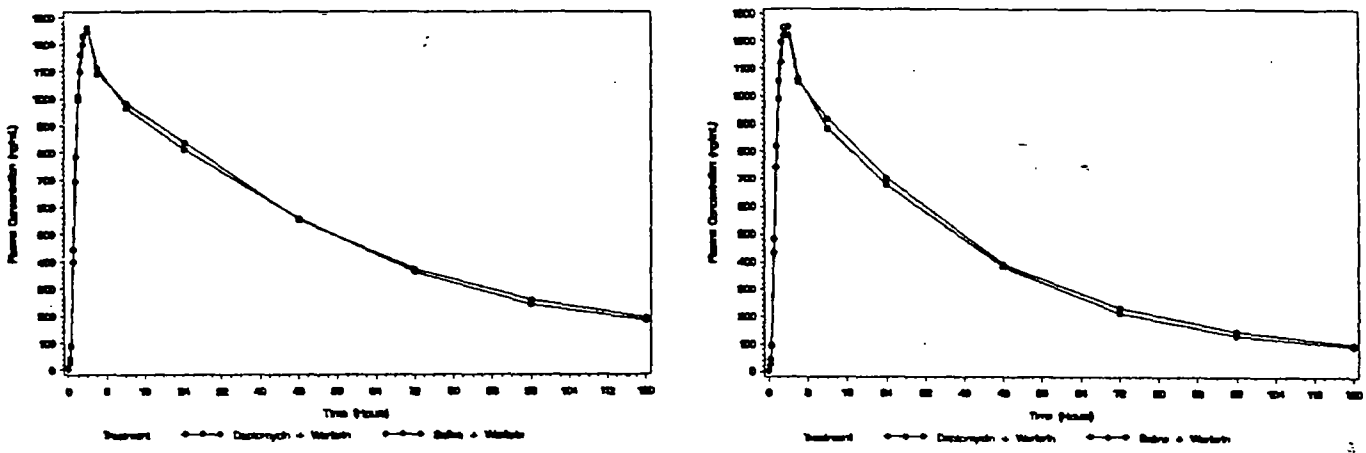
The pharmacokinetics of daptomycin in combination with warfarin and the pharmacokinetics of warfarin in combination with daptomycin were assessed in 16 healthy adult subjects following the administration of daptomycin 6 mg/kg IV q24h or normal saline (NS) and 25 mg of oral warfarin. The mean plasma concentration-time profiles of daptomycin are shown in Figure 25.

Figure 25. Mean plasma concentration-time profiles of daptomycin alone and in combination with warfarin



The mean plasma concentration-time profiles of R-warfarin and S-warfarin following a single oral dose of warfarin 25 mg (2 × 10 mg tablets + 1 × 5 mg tablet) alone or in combination with daptomycin IV 6 mg/kg at steady-state are shown in Figure 26. The mean plasma concentrations of R-warfarin and S-warfarin were both similar when administered alone and in combination with daptomycin to healthy subjects.

Figure 26. Mean plasma concentration-time profiles of R-warfarin (left) and S-warfarin (right) alone and in combination with daptomycin



The daptomycin, R-warfarin, and S-warfarin pharmacokinetic parameter estimates following the administration of NS or a single dose of warfarin 25 mg to subjects receiving daptomycin IV 6 mg/kg q24h are shown in Table 27. In general, the mean C_{max}, AUC_{0-t}, V_{SS}, CL_T, and half-life of daptomycin were similar when co-administered with warfarin.

Table 27. Mean (CV%) daptomycin and warfarin pharmacokinetic parameters alone and administered in combination

	Daptomycin		R-Warfarin		S-Warfarin	
Parameter	Daptomycin alone	Daptomycin + Warfarin	R-Warfarin alone	R-Warfarin + Daptomycin	S-Warfarin alone	S-Warfarin + Daptomycin
AUC_{0-t} (µg*hr/mL)	---	---	62.2 (18%)	63.5 (17%)	47.3 (26%)	49.3 (27%)
$AUC_{0-\tau}$ (µg*hr/mL)	658 (15%)	635 (16%)	---	---	---	---
$AUC_{0-\infty}$ (µg*hr/mL)	764 (18%)	727 (18%)	75.6 (23%)	78.6 (24%)	53.0 (31%)	55.4 (33%)
C_{max} (µg/mL)	91.5 (12%)	85.5 (12%)	1.39 (20%)	1.34 (17%)	1.38 (18%)	1.38 (17%)
T_{max} (hrs)	0.58 (2%)	0.54 (8%)	3.50 (38%)	3.81 (63%)	2.75 (39%)	2.91 (26%)
CL_T (mL/hr/kg)*	9.56 (17%)	9.85 (18%)	5.03 (32%)	4.86 (32%)	7.29 (31%)	7.02 (30%)
Vz (L/kg)	0.10 (10%)	0.10 (12%)	0.33 (17%)	0.33 (16%)	0.38 (16%)	0.36 (19%)
Vss (L/kg)*	0.10 (13%)	0.10 (11%)	0.31 (14%)	0.31 (12%)	0.33 (13%)	0.32 (11%)
Half-life (hrs)	8.56 (13%)	8.14 (14%)	48.2 (20%)	50.2 (24%)	38.1 (24%)	37.7 (22%)

The mean C_{max}, $AUC_{0-\infty}$, V_{SS}/F, CL_T/F, and half-life of R-warfarin and S-warfarin were not appreciably altered when co-administered with daptomycin.

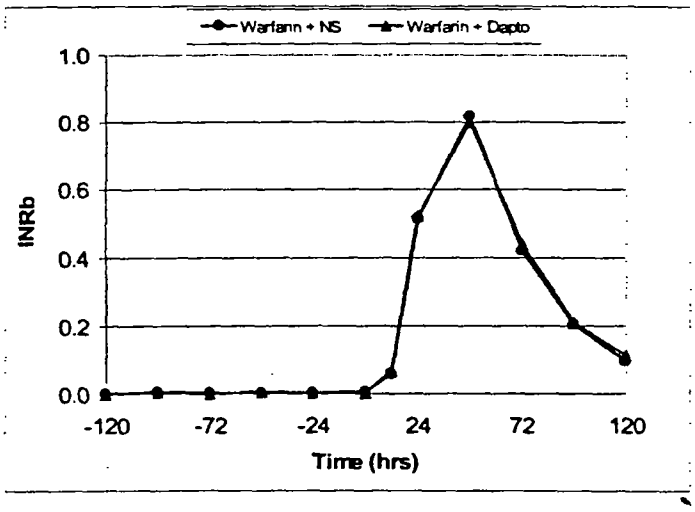
The geometric mean ratios and 90% confidence intervals for daptomycin (daptomycin + warfarin/daptomycin), R-warfarin (warfarin + daptomycin/warfarin), and S-warfarin (warfarin + daptomycin/warfarin) are shown in Table 28. The 90% confidence intervals of the geometric mean ratios for the AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were within the predetermined limits of 0.80 to 1.25 for daptomycin and warfarin (S-warfarin and R-warfarin) and were not statistically significantly different. Thus, co-administration of daptomycin and warfarin does not statistically significantly effect the pharmacokinetics of daptomycin, R-warfarin, or S-warfarin.

Table 28. Geometric mean ratios and 90% confidence intervals for daptomycin, R-warfarin, and S-warfarin administered alone and in combination

	Daptomycin		R-Warfarin		S-Warfarin	
Parameter	Ratio	90% CI	Ratio	90% CI	Ratio	90% CI
AUC_{0-t}	---	---	1.0227	1.0001 - 1.0459	1.0402	1.0184 - 1.0626
$AUC_{0-\tau}$	0.9629	0.9415 - 0.9847	---	---	---	---
$AUC_{0-\infty}$	---	---	1.0372	0.9985 - 1.0774	1.0421	1.0150 - 1.0699
C_{max}	0.9350	0.9103 - 0.9604	0.9669	0.8946 - 1.0451	0.9996	0.9469 - 1.0553

The mean baseline corrected INR (INR_b) vs. time profiles for warfarin + daptomycin and warfarin + placebo (NS) are shown in Figure 27. The results support the absence of a pharmacodynamic interaction between warfarin and daptomycin when a single dose of warfarin wass administered with daptomycin at steady-state (fifth IV dose). The reviewer found no substantial difference between INR vs. time when either the INR_b (INR corrected for baseline) or INR_t (INR not corrected for baseline) was used. No dosage adjustment of either daptomycin or warfarin is warranted when co-administered to patients.

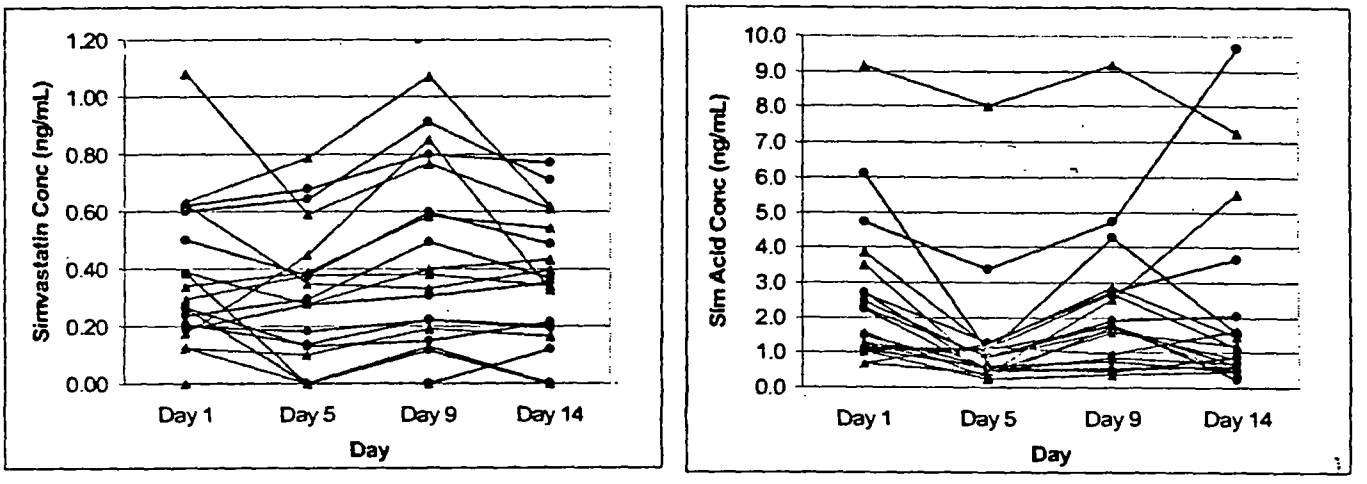
Figure 27. Mean baseline corrected INR (INR_b) vs. time profiles for subjects receiving warfarin + normal saline (NS) and warfarin + daptomycin



Simvastatin:

The safety of daptomycin 4 mg/kg IV q24h for 14 days administered in combination with simvastatin was assessed in 20 healthy adult subjects already on a stable daily dose of 40 mg once daily since both drugs can have an effect on skeletal muscle and CPK concentrations. The daily plasma trough concentrations of simvastatin and simvastatin acid are shown in Figure 28.

Figure 28. Stick plots of simvastatin (left) and simvastatin acid (right) plasma trough concentrations on Days 1, 5, 9, and 14 for subjects receiving daptomycin (circles) or NS (triangles)



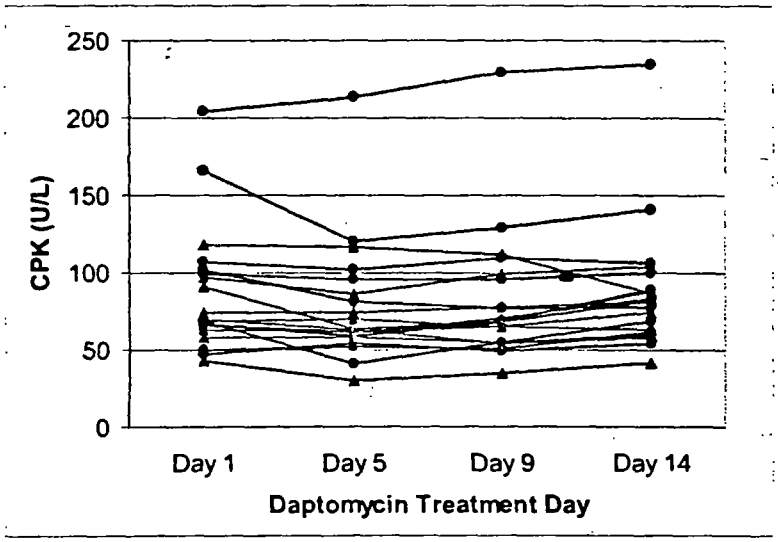
The mean simvastatin and simvastatin acid plasma trough concentration data are shown in Table 29 for subjects that received daptomycin IV 4 mg/kg q24h or placebo (NS) for 14 days. The mean plasma trough concentration of simvastatin between subjects receiving daptomycin or NS were similar. However, it appears that mean plasma trough concentrations of simvastatin acid decreased following administration of daptomycin or NS and remained below Day 1 concentrations in the daptomycin group to a greater extent than the NS group. Although these observations may represent a decreased production of the active metabolite (simvastatin acid) when simvastatin is administered with daptomycin, the observations are based on plasma trough concentrations only and may not reflect accurate changes in the 24 hr AUC.

Table 29. Mean (SD) plasma simvastatin and simvastatin acid trough concentration data on Days 1, 5, 9, and 14 for subjects receiving daptomycin and NS

Analyte	Concentration (ng/mL)			
	Day 1	Day 5	Day 9	Day 14
Simvastatin				
Daptomycin Group	0.35 (0.17)	0.34 (0.22)	0.42 (0.29)	0.38 (0.23)
NS Group	0.42 (0.31)	0.41 (0.20)	0.52 (0.32)	0.43 (0.16)
Simvastatin Acid				
Daptomycin Group	2.68 (1.60)	1.06 (0.85)	1.97 (1.52)	2.04 (2.86)
NS Group	2.42 (2.62)	1.42 (2.34)	2.40 (2.53)	2.05 (2.37)

As shown in Figure 29, CPK concentrations remained below the upper limit of normal (60 to 400 U/L for males, 40 to 150 U/L for females) over 14 days of daptomycin or placebo administration. The CPK values for subject 012 (daptomycin group) was 204 U/L on Day 1 and steadily increased to 235 U/L on Day 14. The CPK values for Subject 015 (daptomycin group) was 164 U/L on Day 1 and decreased to 120 U/L on Day 5. The CPK concentrations for the other subjects remained relatively constant over the course of the study. In addition, CPK concentrations on Days 5, 9, and 14 did not appear to be associated with plasma daptomycin trough concentrations in subject receiving simvastatin 40 mg daily. Although no dosage adjustment of daptomycin or simvastatin is warranted when co-administered to patients, concomitant administration of daptomycin and simvastatin is not recommended since inhibitors of HMG-CoA reductase may cause myopathy.

Figure 29. CPK concentrations Days 1, 5, 9, and 14 for subjects receiving daptomycin (circles) and NS (triangles)



4. What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

The dosage regimen recommended for Phase 3 studies DAP-SST-98-01 and DAP-SST-99-01 was 4 mg/kg q24h for patients with CL_{CR} >70 mL/min and 4 mg/kg loading dose followed by 3 mg/kg q36h for patients with CL_{CR} 30-70 mL/min. However, the proposed label recommends 4 mg/kg q48h for patients with CL_{CR} ≤40 mL/min, including hemodialysis and CAPD patients. The sponsor has not provided a rationale for the dosage recommendation used in Phase 3 clinical studies since it is inconsistent with the sponsor's renal impairment recommendations in the proposed label.

The relationship between the dosage regimen and the incidence of myopathy is unresolved. The sponsor found a trend between the plasma concentration at 24 hrs (C_{24}) and the CPK concentration. However, the incidence of myopathy does not appear to be consistently related to the C_{24}, C_{max}, or AUC. Since it does appear to be related to the dosing frequency (q12h vs. q24h), it is plausible that myopathy may develop when the plasma concentration of daptomycin remains above a threshold concentration and prevents adequate regeneration of myocytes from occurring between doses of daptomycin.

E. General Biopharmaceutics

1. Based on BCS principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

Not applicable.

2. What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

On September 14, 2000, Cubist submitted a CMC amendment describing a modified manufacturing process based on the use of [redacted] rather than [redacted] daptomycin (see Table 30). At this time, a site change to [redacted] for drug product manufacture was made and a 500

mg/vial configuration was added to the existing 250 mg/vial configuration. In this amendment, Cubist provided evidence of the comparability between the acetonitrile- and isopropyl alcohol (IPA)-based purification process. This material represents the current daptomycin formulation used to supply both non-clinical and clinical studies sponsored by Cubist in the current NDA submission.

Table 30. Daptomycin Process Development

Process Step	Stage of Development (Drug Substance-Drug Product)
[redacted]	

3. What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendations should be made, if any, regarding administration of the product in relation to meals or meal type?

Not applicable.

4. When would a fed BE study be appropriate and was on conducted?

Not applicable.

5. How does the dissolution conditions and specifications assure in vivo performance and quality of the product?

Not applicable.

6. If different-strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

Not applicable.

7. If the NDA is for a modified release formulation of an approved immediate release product without supportive safety/efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK/PD relationship?

Not applicable.

8. If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?

Not applicable.

9. What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

Not applicable.

10. If replicate design studies were conducted and individual BE was analyzed, what were the outcomes with respect to variability and subject-by-formulation interactions?

Not applicable.

F. Analytical Section

1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

In the majority of studies, the concentration of daptomycin from plasma and urine were determined using a validated — assay. In Study DAP-00-01, the concentration of daptomycin from plasma was initially determined with a validated — method. However, during the pharmacokinetic analysis of the plasma concentration data by the sponsor, it was observed that the plasma concentrations in this study were greater than those in other phase 1 studies with the same once-daily dose. The concentration of daptomycin in plasma from several subjects in Study DAP-00-01 was determined using a validated — assay and compared to concentrations determined with the — assay. It was determined that the — method overestimated the plasma concentrations of daptomycin by an average of 46% (range — compared to the — method. Plasma concentrations determined using a microbiologic assay and the — assay were similar from Phase 1 studies in which subjects received the same dose. The sponsor was requested to re-assay all plasma samples from this study using the validated — assay. In Study DAP-00-04, plasma and urine concentrations of daptomycin were determined using a validated microbiological assay with *Staphylococcus aureus* F1445 as the indicator organism.

2. Which metabolites have been selected for analysis and why?

No metabolites have been selected for analysis from plasma and urine. Although it is unknown if metabolites of daptomycin are present in plasma, inactive metabolites of daptomycin are known to be present in urine. However, the sponsor has not attempted to identify metabolites of daptomycin in plasma or urine.

3. For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

All moieties measured in plasma, urine, and dialysate represent total concentrations. The protein binding of daptomycin in plasma was determined using equilibrium dialysis against 0.2 M phosphate buffer at 37°C for 3 ± 0.5 hrs. The percent unbound (% free) daptomycin concentration was calculated from the ratio of free drug concentration (phosphate buffer side) to total drug concentration (serum side) multiplied by 100. Pharmacokinetic parameters of unbound daptomycin were calculated using the concentration of daptomycin corrected for protein binding.