CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021572Orig1s008

Trade Name:	CUBICIN
Generic or Proper Name:	daptomycin
Sponsor:	Cubist Pharmaceuticals, LLC
Approval Date:	May 25, 2006
Indication:	• Complicated skin and skin structure infections (cSSSI) caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillinresistant isolates), *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae* subsp. *equisimilis*, and *Enterococcus faecalis* (vancomycin-susceptible isolates only). Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram-negative or anaerobic organisms. • *Staphylococcus aureus* bloodstream infections (bacteremia), including those with right-sided infective endocarditis, caused by methicillin-susceptible and methicillin-resistant isolates. Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram-negative or anaerobic organisms.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021572Orig1s008

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-572/S-008

Cubist Pharmaceuticals, Inc.
Attention: Francis P. Tally, MD
Senior Vice President and Chief Scientific Officer
65 Hayden Avenue
Lexington, MA 02421

Dear Dr. Tally:

Please refer to your supplemental new drug application dated September 22, 2005, received September 26, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CUBICIN® (daptomycin for injection) Intravenous, 500 mg/vial.

We also acknowledge receipt of your submissions dated October 24, 2005, November 14, 2005, November 16, 2005, December 22, 2005, December 28, 2005, January 3, 2006, January 19, 2006, January 23, 2006, January 24, 2006 (2), January 25, 2006 (2), January 26, 2006 (2), January 31, 2006, February 3, 2006, February 10, 2006, February 21, 2006, February 22, 2006 (2), February 24, 2006 (2), February 28, 2006, March 1, 2006, March 3, 2006, March 13, 2006 (2), March 15, 2006, March 22, 2006, and March 27, 2006.

Your submissions of April 14, 2006, April 18, 2006, April 19, 2006, April 20, 2006, May 18, 2006, May 22, 2006 and May 24, 2006 constituted a complete response to our March 24, 2006 action letter.

This supplemental new drug application provides for the use of CUBICIN® (daptomycin for injection) Intravenous, 500 mg/vial, for the treatment of *Staphylococcus aureus* bloodstream infections (bacteremia), including those with right-sided infective endocarditis, caused by methicillin-susceptible and methicillin-resistant isolates.

We completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA.* Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-572/S-008**." Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your pediatric studies for ages 0 to 18 years until December 31, 2011.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed as follows:

1. Deferred pediatric study under PREA for the treatment of *Staphylococcus aureus* bloodstream infections (bacteremia), including those with right-sided infective endocarditis, caused by methicillin-susceptible and methicillin-resistant isolates.

   Final Report Submission: December 31, 2011

Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated "**Required Pediatric Study Commitments**".

We also remind you of your postmarketing study commitments, in your submission dated May 25, 2006. These commitments are listed below:

Clinical:

1. Description of Commitment: Conduct a study to evaluate the potential impact of daptomycin used in combination therapy in the treatment of *S.aureus* infective endocarditis.

Protocol Submission:	by	November, 2006
Study Start	by	April, 2007
Final Report Submission	by	June, 2010

Microbiology:

2. Description of Commitment: Perform studies to assess penetration of daptomycin into vegetations using simulated endocarditis vegetations *in vitro* and in animals.

Protocol Submission:	by	September, 2006
Study Start	by	October, 2006
Final Report Submission	by	December, 2007

3. Description of Commitment: Perform *in vitro* studies to evaluate potential factors affecting daptomycin potency including vancomycin exposure and the susceptibility of vancomycin intermediate *S. aureus* (VISA) strains to daptomycin.

Protocol Submission:	by	July, 2006
Study Start	by	August, 2006
Final Report Submission	by	December, 2006

4. Description of Commitment: Perform studies of the activity and penetration of daptomycin in biofilms.

Protocol Submission:	by	September, 2006
Study Start	by	December, 2006
Final Report Submission	by	April, 2007

5. Description of Commitment: Evaluate the efficacy of daptomycin in combination with other antibiotics *in vitro* and in animal models of bacterial endocarditis.

Protocol Submission:	by	September, 2006
Study Start	by	October, 2006
Final Report Submission	by	December, 2007

We also remind you that you have agreed to collect the following information:

Clinical:

1. Monitor outcomes of patients with *S. aureus* bacteremia and infective endocarditis from the ongoing Cubicin Outcome Registry and Experience (CORE) database. Summarize data in annual report for 2 years.

Microbiology:

1. Monitor reports of resistance and collect isolates for determination of daptomycin and vancomycin minimum inhibitory concentration (MIC) when possible. Submit findings in periodic safety update reports (PSUR).
2. Perform surveillance studies to monitor the activity of daptomycin for a period of no less than 2 years. A summary of findings are to be included in each year's annual report.
3. Collect organisms that become resistant to daptomycin and perform studies to characterize the mode(s) of resistance, including genetic changes.
4. Determine cross-resistance of daptomycin resistant bacteria to other antimicrobials.
5. Evaluate the impact of sub-inhibitory concentrations of daptomycin on the development of resistance and the results of serial passage experiments.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence**."

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call J. Christopher Davi, Regulatory Project Manager at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Janice M. Soreth, MD
Director,
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Approved labeling dated May 25, 2006

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Janice Soreth

5/25/2006 06:45:10 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021572Orig1s008

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-572/S-008

Cubist Pharmaceuticals, Inc.
Attention: David Mantus, PhD
Director, Regulatory Affairs
65 Hayden Avenue
Lexington, MA 02421

Dear Dr. Mantus:

Please refer to your new drug application (NDA) dated September 22, 2005, received September 26, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CUBICIN® (daptomycin for injection) Intravenous, 500 mg/vial.

We also acknowledge receipt of your submissions dated October 11, 2005, October 24, 2005, November 14, 2005, November 16, 2005, December 22, 2005, December 28, 2005, January 3, 2006, January 19, 2006, January 23, 2006, January 24, 2006, January 25, 2006, January 26, 2006, January 31, 2006, February 3, 2006, February 10, 2006, February 21, 2006, February 22, 2006, February 24, 2006, February 28, 2006, March 1, 2006, March 3, 2006, March 13, 2006, March 15, 2006, and March 16, 2006.

This supplemental new drug application provides for the use of CUBICIN® (daptomycin for injection) Intravenous, 500 mg/vial, for the treatment of Complicated Skin and Skin Structure Infections (cSSSI) and *Staphylococcus aureus* Bacteremia/Endocarditis.

We have completed our review of this application, and it is approvable. Before the application may be approved, however, it will be necessary for you to revise your proposed labeling, submitted to the Agency on March 12, 2006. Please address issues raised by the review team in their proposed label of March 14, 2006 and in the meetings of March 20, 21, 22, and 24, 2006 concerning the following sections of the label:

1. Indications and Usage
2. Clinical Studies Section
3. Dosage and Administration
4. Clinical Pharmacology

In addition, please address how data regarding patients with persisting or relapsing *Staphylococcus aureus* (PRSA) bacteremia, increasing MICs, and patient outcomes should be included in product labeling. Approval is contingent upon agreement on content of labeling.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Anti-Infective and Ophthalmology Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call J. Christopher Davi, Regulatory Project Manager (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Janice M. Soreth, MD, Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Janice Soreth

3/24/2006 05:26:06 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021572Orig1s008

LABELING

Cubicin®

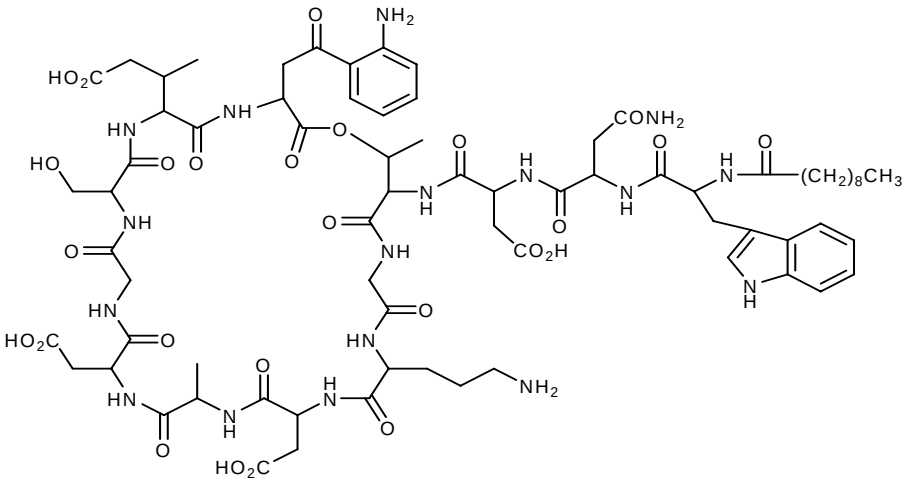
(daptomycin for injection)

Rx only

To reduce the development of drug-resistant bacteria and maintain the effectiveness of CUBICIN and other antibacterial drugs, CUBICIN should be used only to treat or prevent infections caused by bacteria.

DESCRIPTION

CUBICIN contains daptomycin, a cyclic lipopeptide antibacterial agent derived from the fermentation of *Streptomyces roseosporus*. The chemical name is *N*-decanoyl-L-tryptophyl-D-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 structure is:



The empirical formula is $C_{72}H_{101}N_{17}O_{26}$; the molecular weight is 1620.67. CUBICIN is supplied as a sterile, preservative-free, pale yellow to light brown, lyophilized cake containing approximately 900 mg/g of daptomycin for intravenous (IV) use following reconstitution with 0.9% sodium chloride injection. The only inactive ingredient is sodium hydroxide which is used in minimal quantities for pH adjustment. Freshly reconstituted solutions of CUBICIN range in color from pale yellow to light brown.

CLINICAL PHARMACOLOGY

Pharmacokinetics

The mean (SD) pharmacokinetic parameters of daptomycin at steady-state following IV administration of 4 to 12 mg/kg q24h to healthy young adults are summarized in Table 1.

Daptomycin pharmacokinetics were generally linear and time-independent at doses of 4 to 12 mg/kg q24h. Steady-state trough concentrations were achieved by the third daily dose. The mean (SD) steady-state trough concentrations attained following administration of 4, 6, 8, 10 and 12 mg/kg q24h were 5.9 (1.6), 6.7 (1.6), 10.3 (5.5), 12.9 (2.9) and 13.7 (5.2) µg/mL, respectively.

Table 1. Mean (SD) CUBICIN Pharmacokinetic Parameters in Healthy Volunteers at Steady-State

Dose[b] (mg/kg)	Pharmacokinetic Parameters[a]				
	AUC_{0-24} (µg*h/mL)	$t_{1/2}$ (h)	V_{ss} (L/kg)	CL_T (mL/h/kg)	C_{max} (µg/mL)
4 (N=6)	494 (75)	8.1 (1.0)	0.096 (0.009)	8.3 (1.3)	57.8 (3.0)
6 (N=6)	632 (78)	7.9 (1.0)	0.101 (0.007)	9.1 (1.5)	93.9 (6.0)
8 (N=6)	858 (213)	8.3 (2.2)	0.101 (0.013)	9.0 (3.0)	123.3 (16.0)
10 (N=9)	1039 (178)	7.9 (0.6)	0.098 (0.017)	8.8 (2.2)	141.1 (24.0)
12 (N=9)	1277 (253)	7.7 (1.1)	0.097 (0.018)	9.0 (2.8)	183.7 (25.0)

a. AUC_{0-24}, area under the concentration time-curve from 0 to 24 hours; $t_{½}$, terminal elimination half-life; V_{ss}, volume of distribution at steady-state; CL_T, plasma clearance; C_{max}, maximum plasma concentration.

b. Doses of CUBICIN in excess of 6 mg/kg have not been approved.

Distribution

Daptomycin is reversibly bound to human plasma proteins, primarily to serum albumin, in a concentration-independent manner. The overall mean binding ranged from 90 to 93%.

In clinical studies, mean serum protein binding in subjects with $CL_{CR} \geq 30$ mL/min was comparable to that observed in healthy subjects with normal renal function. However, there was a trend toward decreasing serum protein binding among subjects with $CL_{CR} < 30$ mL/min (87.6%), including those receiving hemodialysis (85.9%) and continuous ambulatory peritoneal dialysis (CAPD) (83.5%). The protein binding of daptomycin in subjects with hepatic impairment (Child-Pugh B) was similar to healthy adult subjects.

The volume of distribution at steady-state (V_{ss}) of daptomycin in healthy adult subjects was approximately 0.10 L/kg and was independent of dose.

Metabolism

In vitro studies with human hepatocytes indicate that daptomycin does not inhibit or induce the activities of the following human cytochrome P450 isoforms: 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4. In *in vitro* studies, daptomycin was not metabolized by human liver microsomes. It is unlikely that daptomycin will inhibit or induce the metabolism of drugs metabolized by the P450 system.

In five healthy young adults after infusion of radiolabeled ^{14}C-daptomycin, the plasma total radioactivity was similar to the concentration determined by microbiological assay.

In a separate study, no metabolites were observed in plasma on Day 1 following administration of CUBICIN at 6 mg/kg to subjects. Inactive metabolites have been detected in urine, as determined by the difference in total radioactive concentrations and microbiologically active concentrations. Minor amounts of three oxidative metabolites and one unidentified compound were detected in urine. The site of metabolism has not been identified.

Excretion

Daptomycin is excreted primarily by the kidney. In a mass balance study of five healthy subjects using radiolabeled daptomycin, approximately 78% of the administered dose was recovered from urine based on total radioactivity (approximately 52% of the dose based on microbiologically active concentrations) and 5.7% of the dose was recovered from feces (collected for up to nine days) based on total radioactivity.

Because renal excretion is the primary route of elimination, dosage adjustment is necessary in patients with severe renal insufficiency (CL_{CR} <30 mL/min) (see **DOSAGE AND ADMINISTRATION**).

Special Populations

Renal Insufficiency

Population derived pharmacokinetic parameters were determined for infected patients (complicated skin and skin structure infections and *S. aureus* bacteremia) and non-infected subjects with varying degrees of renal function (Table 2). Plasma clearance (CL_T), elimination half-life ($t_{1/2}$), and volume of distribution (V_{SS}) were similar in patients with complicated skin and skin structure infections compared with those with *S. aureus* bacteremia. Following the administration of CUBICIN 4 mg/kg q24h, the mean CL_T was 9%, 22%, and 46% lower among subjects and patients with mild (CL_{CR} 50-80 mL/min), moderate (CL_{CR} 30-50 mL/min), and severe (CL_{CR} <30 mL/min) renal impairment, respectively, than those with normal renal function (CL_{CR} >80 mL/min). The mean steady-state systemic exposure (AUC), $t_{1/2}$, and V_{SS} increased with decreasing renal function, although the mean AUC was not markedly different for patients with CL_{CR} 30-80 mL/min compared with those with normal renal function. The mean AUC for patients with CL_{CR} <30 mL/min and for patients on hemodialysis (dosed post-dialysis) were approximately 2- and 3-times higher, respectively, than for patients with normal renal function. Following the administration of CUBICIN 4 mg/kg q24h, the mean C_{max} ranged from 60 to 70 µg/mL in patients with CL_{CR} ≥30 mL/min, while the mean C_{max} for patients with CL_{CR} <30 mL/min ranged from 41 to 58 µg/mL. The mean C_{max} ranged from 80 to 114 µg/mL in patients with mild to moderate renal impairment and was similar to that of patients with normal renal function after the administration of CUBICIN 6 mg/kg 24h. In patients with renal insufficiency, both renal function and creatine phosphokinase (CPK) should be monitored more frequently. CUBICIN should be administered following the completion of hemodialysis on hemodialysis days (see **DOSAGE AND ADMINISTRATION** for recommended dosage regimens).

Table 2. Mean (SD) Daptomycin Population Pharmacokinetic Parameters Following Infusion of 4 mg/kg or 6 mg/kg to Infected Patients and Non-Infected Subjects with Varying Degrees of Renal Function

Renal Function	$t_{1/2}$[a] (h) 4 mg/kg	V_{ss}[a] (L/kg) 4 mg/kg	CL_T[a] (mL/h/kg) 4 mg/kg	$AUC_{0-\infty}$[a] (µg*h/mL) 4 mg/kg	AUC_{ss}[b] (µg*h/mL) 6 mg/kg	$C_{min,ss}$[b] (µg*h/mL) 6 mg/kg
Normal (CL_{CR} >80 mL/min)	9.39 (4.74) N=165	0.13 (0.05) N=165	10.9 (4.0) N=165	417 (155) N=165	545 (296) N=62	6.9 (3.5) N= 61
Mild Renal Impairment (CL_{CR} 50-80 mL/min)	10.75 (8.36) N=64	0.12 (0.05) N=64	9.9 (4.0) N=64	466 (177) N=64	637 (215) N=29	12.4 (5.6) N=29
Moderate Renal Impairment (CL_{CR} 30-<50 mL/min)	14.70 (10.50) N=24	0.15 (0.06) N=24	8.5 (3.4) N=24	560 (258) N=24	868 (349) N=15	19.0 (9.0) N=14
Severe Renal Impairment (CL_{CR} <30 mL/min)	27.83 (14.85) N=8	0.20 (0.15) N=8	5.9 (3.9) N=8	925 (467) N=8	1050, 892 N=2	24.4, 21.4 N=2
Hemodialysis	29.81 (6.13) N=21	0.15 (0.04) N=21	3.7 (1.9) N=21	1244 (374) N=21	NA	NA

Note: CL_{CR}, creatinine clearance estimated using the Cockcroft-Gault equation with actual body weight; $AUC_{0-\infty}$, area under the concentration time-curve extrapolated to infinity; AUC_{ss}, area under the concentration time-curve calculated over the 24-hour dosing interval at steady-state; $C_{min,ss}$, trough concentration at steady-state; NA, not applicable.

a. Parameters obtained following a single dose from patients with complicated skin and skin structure infections and healthy subjects.

b. Parameters obtained at steady-state from patients with *S. aureus* bacteremia.

Hepatic Insufficiency

The pharmacokinetics of daptomycin were evaluated in 10 subjects with moderate hepatic impairment (Child-Pugh Class B) and compared with healthy volunteers (N=9) matched for gender, age, and weight. The pharmacokinetics of daptomycin were not altered in subjects with moderate hepatic impairment. No dosage adjustment is warranted when administering CUBICIN to patients with mild to moderate hepatic impairment. The pharmacokinetics of daptomycin in patients with severe hepatic insufficiency have not been evaluated.

Gender

No clinically significant gender-related differences in daptomycin pharmacokinetics have been observed. No dosage adjustment is warranted based on gender when administering CUBICIN.

Geriatric

The pharmacokinetics of daptomycin were evaluated in 12 healthy elderly subjects (≥75 years of age) and 11 healthy young controls (18 to 30 years of age). Following administration of a single 4 mg/kg IV dose, the mean total clearance of daptomycin was reduced approximately 35% and the mean $AUC_{0-\infty}$ increased approximately 58% in elderly subjects compared with young healthy

subjects. There were no differences in C_{max}. No dosage adjustment is warranted for elderly patients with normal renal function.

Obesity

The pharmacokinetics of daptomycin were evaluated in six moderately obese (Body Mass Index [BMI] 25 to 39.9 kg/m^2) and six extremely obese (BMI ≥40 kg/m^2) subjects and controls matched for age, sex, and renal function. Following administration of a single 4 mg/kg IV dose based on total body weight, the plasma clearance of daptomycin normalized to total body weight was approximately 15% lower in moderately obese subjects and 23% lower in extremely obese subjects compared with non-obese controls. The $AUC_{0-\infty}$ of daptomycin increased approximately 30% in moderately obese and 31% in extremely obese subjects compared with non-obese controls. The differences were most likely due to differences in the renal clearance of daptomycin. No dosage adjustment of CUBICIN is warranted in obese subjects.

Pediatric

The pharmacokinetics of daptomycin in pediatric populations (<18 years of age) have not been established.

Drug-Drug Interactions

Drug-drug interaction studies were performed with CUBICIN and other drugs that are likely to either be co-administered or associated with overlapping toxicity.

Aztreonam

In a study in which 15 healthy adult subjects received a single dose of CUBICIN 6 mg/kg IV, aztreonam 1 g IV, and both in combination, the C_{max} and $AUC_{0-\infty}$ of daptomycin were not significantly altered by aztreonam; the C_{max} and $AUC_{0-\infty}$ of aztreonam were also not significantly altered by daptomycin. No dosage adjustment of either antibiotic is warranted when co-administered.

Tobramycin

In a study in which 6 healthy adult males received a single dose of CUBICIN 2 mg/kg IV, tobramycin 1 mg/kg IV, and both in combination, the mean C_{max} and $AUC_{0-\infty}$ of daptomycin increased 12.7% and 8.7%, respectively, when administered with tobramycin. The mean C_{max} and $AUC_{0-\infty}$ of tobramycin decreased 10.7% and 6.6%, respectively, when administered with CUBICIN. These differences were not statistically significant. The interaction between daptomycin and tobramycin with a clinical dose of CUBICIN is unknown. Caution is warranted when CUBICIN is co-administered with tobramycin.

Warfarin

In 16 healthy subjects, concomitant administration of CUBICIN 6 mg/kg q24h for 5 days followed by a single oral dose of warfarin (25 mg) had no significant effect on the pharmacokinetics of either drug and did not significantly alter the INR (International Normalized Ratio) (see **PRECAUTIONS, Drug Interactions**).

Simvastatin

In 20 healthy subjects on a stable daily dose of simvastatin 40 mg, administration of CUBICIN 4 mg/kg IV q24h for 14 days (N=10) was not associated with a higher incidence of adverse events than subjects receiving placebo once daily (N=10) (see **PRECAUTIONS, Drug Interactions**).

Probenecid

Concomitant administration of probenecid (500 mg four times daily) and a single dose of CUBICIN 4 mg/kg IV did not significantly alter the C_{max} and $AUC_{0-\infty}$ of daptomycin. No dosage adjustment of CUBICIN is warranted when CUBICIN is co-administered with probenecid.

MICROBIOLOGY

Daptomycin is an antibacterial agent of a new class of antibiotics, the cyclic lipopeptides. Daptomycin is a natural product which has clinical utility in the treatment of infections caused by aerobic Gram-positive bacteria. The *in vitro* spectrum of activity of daptomycin encompasses most clinically relevant Gram-positive pathogenic bacteria. Daptomycin retains potency against antibiotic resistant Gram-positive bacteria including isolates resistant to methicillin, vancomycin, and linezolid.

Daptomycin exhibits rapid, concentration-dependent bactericidal activity against Gram-positive organisms *in vitro*. This has been demonstrated both by time-kill curves and by MBC/MIC ratios (minimum bactericidal concentration/minimum inhibitory concentration) using broth dilution methodology. Daptomycin maintained bactericidal activity *in vitro* against stationary phase *S. aureus* in simulated endocardial vegetations. The clinical significance of this is not known.

Mechanism of Action

The mechanism of action of daptomycin is distinct from any other antibiotic. Daptomycin binds to bacterial membranes and causes a rapid depolarization of membrane potential. This loss of membrane potential causes inhibition of protein, DNA, and RNA synthesis, which results in bacterial cell death.

Mechanism of Resistance

At this time, no mechanism of resistance to daptomycin has been identified. Currently, there are no known transferable elements that confer resistance to daptomycin.

Cross-Resistance

Cross-resistance has not been observed with any other antibiotic class.

Interactions with Other Antibiotics

In vitro studies have investigated daptomycin interactions with other antibiotics. Antagonism, as determined by kill curve studies, has not been observed. *In vitro* synergistic interactions of daptomycin with aminoglycosides, β-lactam antibiotics, and rifampin have been shown against

some isolates of staphylococci (including some methicillin-resistant isolates) and enterococci (including some vancomycin-resistant isolates).

Complicated Skin and Skin Structure Infection (cSSSI) Studies

The emergence of daptomycin non-susceptible isolates occurred in 2 infected patients across the set of Phase 2 and pivotal Phase 3 clinical trials. In one case, a non-susceptible *S. aureus* was isolated from a patient in a Phase 2 study who received CUBICIN at a less than the protocol-specified dose for the initial 5 days of therapy. In the second case, a non-susceptible *Enterococcus faecalis* was isolated from a patient with an infected chronic decubitus ulcer enrolled in a salvage trial.

S. aureus Bacteremia/Endocarditis and Other Post-Approval Studies

In subsequent clinical trials, non-susceptible isolates were recovered. *S. aureus* was isolated from a patient in a compassionate use study and from 7 patients in the *S. aureus* bacteremia/endocarditis study (see **PRECAUTIONS**). An *E. faecium* was isolated from a patient in a VRE study.

Daptomycin has been shown to be active against most isolates of the following microorganisms both *in vitro* and in clinical infections, as described in the **INDICATIONS AND USAGE** section.

Aerobic and facultative Gram-positive microorganisms:

Enterococcus faecalis (vancomycin-susceptible isolates only)
Staphylococcus aureus (including methicillin-resistant isolates)
Streptococcus agalactiae
Streptococcus dysgalactiae subsp. *equisimilis*
Streptococcus pyogenes

The following *in vitro* data are available, but their clinical significance is unknown. Greater than 90% of the following microorganisms demonstrate an *in vitro* MIC less than or equal to the susceptible breakpoint for daptomycin versus the bacterial genus. The efficacy of daptomycin in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials.

Aerobic and facultative Gram-positive microorganisms:

Corynebacterium jeikeium
Enterococcus faecalis (vancomycin-resistant isolates)
Enterococcus faecium (including vancomycin-resistant isolates)
Staphylococcus epidermidis (including methicillin-resistant isolates)
Staphylococcus haemolyticus

Susceptibility Testing Methods

Susceptibility testing by dilution methods requires the use of daptomycin susceptibility powder. The testing of daptomycin also requires the presence of physiological levels of free calcium ions (50 mg/L of calcium, using calcium chloride) in Mueller-Hinton broth medium.

Dilution Technique

Quantitative methods are used to determine antimicrobial MICs. These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure[1, 2] based on a broth dilution method or equivalent using standardized inoculum and concentrations of daptomycin. The use of the agar dilution method is not recommended with daptomycin[2]. The MICs should be interpreted according to the criteria in Table 3.

Diffusion Technique

Quantitative methods that require measurement of zone diameters have not been shown to provide reproducible estimates of the susceptibility of bacteria to daptomycin. The use of the disk diffusion method is not recommended with daptomycin[2, 3].

Table 3. Susceptibility Interpretive Criteria for Daptomycin

	Broth Dilution MIC (µg/mL)[a]		
Pathogen	**S**	**I**	**R**
Staphylococcus aureus (methicillin-susceptible and methicillin-resistant)	≤1	(b)	(b)
Streptococcus pyogenes, Streptococcus agalactiae, and *Streptococcus dysgalactiae* subsp. *equisimilis*	≤1	(b)	(b)
Enterococcus faecalis (vancomycin-susceptible only)	≤4	(b)	(b)

a. The MIC interpretive criteria for *S. aureus* and *E. faecalis* are applicable only to tests performed by broth dilution using Mueller-Hinton broth adjusted to a calcium content of 50 mg/L; the MIC interpretive criteria for *Streptococcus* spp. other than *S. pneumoniae* are applicable only to tests performed by broth dilution using Mueller-Hinton broth adjusted to a calcium content of 50 mg/L, supplemented with 2 to 5% lysed horse blood, inoculated with a direct colony suspension and incubated in ambient air at 35ºC for 20 to 24 hours.

b. The current absence of data on daptomycin-resistant isolates precludes defining any categories other than "Susceptible." Isolates yielding test results suggestive of a "Non-Susceptible" category should be retested, and if the result is confirmed, the isolate should be submitted to a reference laboratory for further testing.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable.

Quality Control

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the procedures. Standard daptomycin powder should provide the range of values noted in Table 4. Quality control microorganisms are specific strains of organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within bacteria; the specific strains used for microbiological quality control are not clinically significant.

Table 4. Acceptable Quality Control Ranges for Daptomycin to Be Used in Validation of Susceptibility Test Results

Quality Control Strain	Broth Dilution MIC Range (µg/mL)[a]
Enterococcus faecalis ATCC 29212	1-4
Staphylococcus aureus ATCC 29213	0.25-1
Streptococcus pneumoniae ATCC 49619[b]	0.06-0.5

a. The quality control ranges for *S. aureus* and *E. faecalis* are applicable only to tests performed by broth dilution using Mueller-Hinton broth adjusted to a calcium content of 50 mg/L; the quality control ranges for *S. pneumoniae* are applicable only to tests performed by broth dilution using Mueller-Hinton broth adjusted to a calcium content of 50 mg/L, supplemented with 2 to 5% lysed horse blood, inoculated with a direct colony suspension and incubated in ambient air at 35ºC for 20 to 24 hours.

b. This organism may be used for validation of susceptibility test results when testing *Streptococcus* spp. other than *S. pneumoniae*.

INDICATIONS AND USAGE

CUBICIN (daptomycin for injection) is indicated for the following infections (see also **DOSAGE AND ADMINISTRATION** and **CLINICAL STUDIES**):

Complicated skin and skin structure infections (cSSSI) caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subsp. *equisimilis*, and *Enterococcus faecalis* (vancomycin-susceptible isolates only). Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram-negative or anaerobic organisms.

***Staphylococcus aureus* bloodstream infections** (bacteremia), including those with right-sided infective endocarditis, caused by methicillin-susceptible and methicillin-resistant isolates. Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram-negative or anaerobic organisms.

The efficacy of CUBICIN in patients with left-sided infective endocarditis due to *S. aureus* has not been demonstrated. The clinical trial of CUBICIN in patients with *S. aureus* bloodstream infections included limited data from patients with left-sided infective endocarditis; outcomes in these patients were poor (see **CLINICAL STUDIES**). CUBICIN has not been studied in patients with prosthetic valve endocarditis or meningitis.

Patients with persisting or relapsing *S. aureus* infection or poor clinical response should have repeat blood cultures. If a culture is positive for *S. aureus*, MIC susceptibility testing of the isolate should be performed using a standardized procedure, as well as diagnostic evaluation to rule out sequestered foci of infection (see **PRECAUTIONS**).

CUBICIN is not indicated for the treatment of pneumonia.

Appropriate specimens for microbiological examination should be obtained in order to isolate and identify the causative pathogens and to determine their susceptibility to daptomycin.

Empiric therapy may be initiated while awaiting test results. Antimicrobial therapy should be adjusted as needed based upon test results.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of CUBICIN and other antibacterial drugs, CUBICIN should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

CUBICIN is contraindicated in patients with known hypersensitivity to daptomycin.

WARNINGS

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including CUBICIN, and may range in severity from mild to life-threatening. Therefore it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicated that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

If a diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *C. difficile*.

PRECAUTIONS

General

The use of antibiotics may promote the selection of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

Prescribing CUBICIN in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Persisting or Relapsing *S. aureus* Infection

Patients with persisting or relapsing *S. aureus* infection or poor clinical response should have repeat blood cultures. If a culture is positive for *S. aureus,* MIC susceptibility testing of the isolate should be performed using a standardized procedure, as well as diagnostic evaluation to rule out sequestered foci of infection. Appropriate surgical intervention (e.g., debridement, removal of prosthetic devices, valve replacement surgery) and/or consideration of a change in antibiotic regimen may be required.

Failure of treatment due to persisting or relapsing *S. aureus* infections was assessed by the Adjudication Committee in 19/120 (15.8%) CUBICIN-treated patients (12 with MRSA and 7 with MSSA) and 11/115 (9.6%) comparator-treated patients (9 with MRSA treated with vancomycin and 2 with MSSA treated with anti-staphylococcal semi-synthetic penicillin). Among all failures, 6 CUBICIN-treated patients and 1 vancomycin-treated patient developed increasing MICs (reduced susceptibility) by central laboratory testing on or following therapy. Most patients who failed due to persisting or relapsing *S. aureus* infection had deep-seated infection and did not receive necessary surgical intervention (see **CLINICAL STUDIES**).

Skeletal Muscle

In a Phase 1 study examining doses up to 12 mg/kg q24h of CUBICIN for 14 days, no skeletal muscle effects or CPK elevations were observed.

In Phase 3 cSSSI trials of CUBICIN at a dose of 4 mg/kg, elevations in CPK were reported as clinical adverse events in 15/534 (2.8%) CUBICIN-treated patients, compared with 10/558 (1.8%) comparator-treated patients.

In the *S. aureus* bacteremia/endocarditis trial, at a dose of 6 mg/kg, elevations in CPK were reported as clinical adverse events in 8/120 (6.7%) CUBICIN-treated patients compared with 1/116 (<1%) comparator-treated patients. There were a total of 11 patients who experienced CPK elevations to above 500 U/L. Of these 11 patients, 4 had prior or concomitant treatment with an HMG-Co A reductase inhibitor.

Skeletal muscle effects associated with CUBICIN were observed in animals (see **ANIMAL PHARMACOLOGY**).

Patients receiving CUBICIN should be monitored for the development of muscle pain or weakness, particularly of the distal extremities. In patients who receive CUBICIN, CPK levels should be monitored weekly, and more frequently in patients who received recent prior or concomitant therapy with an HMG-Co A reductase inhibitor. In patients with renal insufficiency, both renal function and CPK should be monitored more frequently. Patients who develop unexplained elevations in CPK while receiving CUBICIN should be monitored more frequently. In the cSSSI studies, among patients with abnormal CPK (>500 U/L) at baseline, 2/19 (10.5%) treated with CUBICIN, and 4/24 (16.7%) treated with comparator developed further increases in CPK while on therapy. In this same population, no patients developed myopathy. CUBICIN-treated patients with baseline CPK >500 U/L (N=19) did not experience an increased incidence of CPK elevations or myopathy relative to those treated with comparator (N=24). In the *S. aureus* bacteremia/endocarditis study, three (2.6%) CUBICIN-treated patients, including one with trauma associated with a heroin overdose and one with spinal cord compression, had an elevation in CPK >500 U/L with associated musculoskeletal symptoms. None of the patients in the comparator group had an elevation in CPK >500 U/L with associated musculoskeletal symptoms.

CUBICIN should be discontinued in patients with unexplained signs and symptoms of myopathy in conjunction with CPK elevation >1000 U/L (~5X ULN), or in patients without reported symptoms who have marked elevations in CPK >2,000 U/L (≥10X ULN). In addition, consideration should be given to temporarily suspending agents associated with rhabdomyolysis, such as HMG-CoA reductase inhibitors, in patients receiving CUBICIN.

In a Phase 1 study examining doses up to 12 mg/kg q24h of CUBICIN for 14 days, no evidence of nerve conduction deficits or symptoms of periperal neuropathy was observed. In a small number of patients in Phase 1 and Phase 2 studies at doses up to 6 mg/kg, administration of CUBICIN was associated with decreases in nerve conduction velocity and with adverse events (e.g., paresthesias, Bell's palsy) possibly reflective of peripheral or cranial neuropathy. Nerve conduction deficits were also detected in a similar number of comparator subjects in these studies. In Phase 3 cSSSI and community acquired pneumonia (CAP) studies, 7/989 (0.7%) CUBICIN-treated patients and 7/1018 (0.7%) comparator-treated patients experienced paresthesias. New or worsening peripheral neuropathy was not diagnosed in any of these patients. In the *S. aureus* bacteremia/endocarditis trial, a total of 11/120 (9.2%) CUBICIN-treated patients had treatment-emergent adverse events related to the peripheral nervous system. All of the events were classified as mild to moderate in severity, most were of short duration and resolved during continued treatment with CUBICIN or were likely due to an alternative etiology. In animals, effects of CUBICIN on peripheral nerve were observed (see **ANIMAL PHARMACOLOGY**). Therefore, physicians should be alert to the possibility of signs and symptoms of neuropathy in patients receiving CUBICIN.

Drug Interactions

Warfarin

Concomitant administration of CUBICIN (6 mg/kg q24h for 5 days) and warfarin (25 mg single oral dose) had no significant effect on the pharmacokinetics of either drug and the INR was not significantly altered. As experience with the concomitant administration of CUBICIN and warfarin is limited, anticoagulant activity in patients receiving CUBICIN and warfarin should be monitored for the first several days after initiating therapy with CUBICIN (see **CLINICAL PHARMACOLOGY, Drug-Drug Interactions**).

HMG CoA Reductase Inhibitors

Inhibitors of HMG-CoA reductase may cause myopathy, which is manifested as muscle pain or weakness associated with elevated levels of CPK. There were no reports of skeletal myopathy in a placebo-controlled Phase 1 trial in which 10 healthy subjects on stable simvastatin therapy were treated concurrently with CUBICIN (4 mg/kg q24h) for 14 days. In the Phase 3 *S. aureus* bacteremia/endocarditis trial, 5/22 CUBICIN-treated patients who received prior or concomitant therapy with an HMG-Co A reductase inhibitor developed CPK elevations >500 U/L. Experience with co-administration of HMG-CoA reductase inhibitors and CUBICIN in patients is limited, therefore, consideration should be given to temporarily suspending use of HMG-CoA reductase inhibitors in patients receiving CUBICIN (see **ADVERSE REACTIONS, Post-Marketing Experience**).

Drug-Laboratory Test Interactions

There are no reported drug-laboratory test interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in animals have not been conducted to evaluate the carcinogenic potential of daptomycin. However, neither mutagenic nor clastogenic potential was

found in a battery of genotoxicity tests, including the Ames assay, a mammalian cell gene mutation assay, a test for chromosomal aberrations in Chinese hamster ovary cells, an *in vivo* micronucleus assay, an *in vitro* DNA repair assay, and an *in vivo* sister chromatid exchange assay in Chinese hamsters.

Daptomycin did not affect the fertility or reproductive performance of male and female rats when administered intravenously at doses up to 150 mg/kg/day, which is approximately 9 times the estimated human exposure level based upon AUCs.

Pregnancy

Teratogenic Effects: Pregnancy Category B

Reproductive and teratology studies performed in rats and rabbits at doses of up to 75 mg/kg, 2 and 4 times the 6 mg/kg human dose respectively on a body surface area basis, have revealed no evidence of harm to the fetus due to daptomycin. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known if daptomycin is excreted in human milk. Caution should be exercised when CUBICIN is administered to nursing women.

Pediatric Use

Safety and efficacy of CUBICIN in patients under the age of 18 have not been established.

Geriatric Use

Of the 534 patients treated with CUBICIN in Phase 3 controlled clinical trials of cSSSI, 27.0% were 65 years of age or older and 12.4% were 75 years or older. Of the 120 patients treated with CUBICIN in the Phase 3 controlled clinical trial of *S. aureus* bacteremia/endocarditis, 25.0% were 65 years of age or older and 15.8% were 75 years of age or older. In Phase 3 clinical studies of cSSSI and *S. aureus* bacteremia/endocarditis, lower clinical success rates were seen in patients ≥65 years of age compared with those <65 years of age. In addition, treatment-emergent adverse events were more common in patients ≥65 years old than in patients <65 years of age.

ANIMAL PHARMACOLOGY

In animals, daptomycin administration has been associated with effects on skeletal muscle with no changes in cardiac or smooth muscle. Skeletal muscle effects were characterized by degenerative/regenerative changes and variable elevations in CPK. No fibrosis or rhabdomyolysis was evident in repeat dose studies up to the highest doses tested in rats (150 mg/kg/day) and dogs (100 mg/kg/day). The degree of skeletal myopathy showed no increase when treatment was extended from 1 month to up to 6 months. Severity was dose dependent. All muscle effects, including microscopic changes, were fully reversible within 30 days following cessation of dosing.

In adult animals, effects on peripheral nerve (characterized by axonal degeneration and frequently accompanied by significant losses of patellar reflex, gag reflex and pain perception) were observed at doses higher than those associated with skeletal myopathy. Deficits in the dogs' patellar reflexes were seen within 2 weeks of the start of treatment at 40 mg/kg (9 times the human C_{max} at the 6 mg/kg q24h dose), with some clinical improvement noted within 2 weeks of the cessation of dosing. However, at 75 mg/kg/day for 1 month, 7/8 dogs failed to regain full patellar reflex responses within the duration of a 3 month recovery period. In a separate study in dogs receiving doses of 75 and 100 mg/kg/day for 2 weeks, minimal residual histological changes were noted at 6 months after cessation of dosing. However, recovery of peripheral nerve function was evident.

Tissue distribution studies in rats have shown that daptomycin is retained in the kidney but appears to only minimally penetrate across the blood brain barrier following single and multiple doses.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Clinical studies sponsored by Cubist enrolled 1,667 patients treated with CUBICIN and 1,319 treated with comparator. Most adverse events reported in Cubist-sponsored Phase 1, 2 and 3 clinical studies were described as mild or moderate in intensity. In Phase 3 cSSSI trials, CUBICIN was discontinued in 15/534 (2.8%) patients due to an adverse event while comparator was discontinued in 17/558 (3.0%) patients. In the *S. aureus* bacteremia/endocarditis trial, CUBICIN was discontinued in 20/120 (16.7%) patients due to an adverse event while comparator was discontinued in 21/116 (18.1%) patients.

Gram-negative Infections

In the *S. aureus* bacteremia/endocarditis trial, serious Gram-negative infections and nonserious Gram-negative bloodstream infections were reported in 10/120 (8.3%) CUBICIN-treated and 0/115 comparator-treated patients. Comparator patients received dual therapy that included initial gentamicin for 4 days. Events were reported during treatment and during early and late follow-up. Gram-negative infections included cholangitis, alcoholic pancreatitis, sternal osteomyelitis/mediastinitis, bowel infarction, recurrent Crohn's disease, recurrent line sepsis, and recurrent urosepsis caused by a number of different Gram-negative organisms. One patient with sternal osteomyelitis following mitral valve repair developed *S. aureus* endocarditis with a 2 cm mitral vegetation and had a course complicated with bowel infarction, polymicrobial bacteremia, and death.

Other Adverse Reactions

The rates of most common adverse events, organized by body system, observed in cSSSI patients are displayed in Table 5.

Table 5. Incidence (%) of Adverse Events that Occurred in ≥2% of Patients in Either CUBICIN or Comparator Treatment Groups in Phase 3 cSSSI Studies

Adverse Event	CUBICIN 4 mg/kg (N=534)	Comparator* (N=558)
Gastrointestinal disorders		
Constipation	6.2%	6.8%
Nausea	5.8%	9.5%
Diarrhea	5.2%	4.3%
Vomiting	3.2%	3.8%
Dyspepsia	0.9%	2.5%
General disorders		
Injection site reactions	5.8%	7.7%
Fever	1.9%	2.5%
Nervous system disorders		
Headache	5.4%	5.4%
Insomnia	4.5%	5.4%
Dizziness	2.2%	2.0%
Skin/subcutaneous disorders		
Rash	4.3%	3.8%
Pruritus	2.8%	3.8%
Diagnostic investigations		
Abnormal liver function tests	3.0%	1.6%
Elevated CPK	2.8%	1.8%
Infections		
Fungal Infections	2.6%	3.2%
Urinary Tract Infections	2.4%	0.5%
Vascular disorders		
Hypotension	2.4%	1.4%
Hypertension	1.1%	2.0%
Renal/urinary disorders		
Renal failure	2.2%	2.7%
Blood/lymphatic disorders		
Anemia	2.1%	2.3%
Respiratory disorders		
Dyspnea	2.1%	1.6%
Musculoskeletal disorders		
Limb pain	1.5%	2.0%
Arthralgia	0.9%	2.2%

* Comparators included vancomycin (1 g IV q12h) and anti-staphylococcal semi-synthetic penicillins (i.e., nafcillin, oxacillin, cloxacillin, flucloxacillin; 4 to 12 g/day IV in divided doses).

Additional adverse events that occurred in 1 to 2% of patients in either CUBICIN (4 mg/kg) or comparator treatment groups in the cSSSI studies are as follows: edema, cellulitis, hypoglycemia, elevated alkaline phosphatase, cough, back pain, abdominal pain, hypokalemia, hyperglycemia, decreased appetite, anxiety, chest pain, sore throat, cardiac failure, confusion, and Candida infections. These events occurred at rates ranging from 0.2 to 1.7% in CUBICIN-treated patients and at rates of 0.4 to 1.8% in comparator-treated patients.

Additional drug-related adverse events (possibly or probably related) that occurred in <1% of patients receiving CUBICIN in the cSSSI trials are as follows:

Body as a Whole: fatigue, weakness, rigors, discomfort, jitteriness, flushing, hypersensitivity
Blood/Lymphatic System: leukocytosis, thrombocytopenia, thrombocytosis, eosinophilia, increased international normalized ratio (INR)
Cardiovascular System: supraventricular arrhythmia
Dermatologic System: eczema
Digestive System: abdominal distension, flatulence, stomatitis, jaundice, increased serum lactate dehydrogenase
Metabolic/Nutritional System: hypomagnesemia, increased serum bicarbonate, electrolyte disturbance
Musculoskeletal System: myalgia, muscle cramps, muscle weakness, osteomyelitis
Nervous System: vertigo, mental status change, paraesthesia
Special Senses: taste disturbance, eye irritation

The rates of most common adverse events, organized by System Organ Class (SOC), observed in *S. aureus* bacteremia/endocarditis (6 mg/kg CUBICIN) patients are displayed in Table 6.

Table 6. Incidence (%) of Adverse Events that Occurred in ≥5% of Patients in Either CUBICIN or Comparator Treatment Groups in the *S. aureus* Bacteremia/Endocarditis Study

Adverse Event	CUBICIN 6 mg/kg (N=120) n (%)	Comparator[a] (N=116) n (%)
Infections and infestations	**65 (54.2%)**	**56 (48.3%)**
Urinary tract infection NOS	8 (6.7%)	11 (9.5%)
Osteomyelitis NOS	7 (5.8%)	7 (6.0%)
Sepsis NOS	6 (5.0%)	3 (2.6%)
Bacteraemia	6 (5.0%)	0 (0%)
Pneumonia NOS	4 (3.3%)	9 (7.8%)
Gastrointestinal disorders	**60 (50.0%)**	**68 (58.6%)**
Diarrhoea NOS	14 (11.7%)	21 (18.1%)
Vomiting NOS	14 (11.7%)	15 (12.9%)
Constipation	13 (10.8%)	14 (12.1%)

Adverse Event	CUBICIN 6 mg/kg (N=120) n (%)	Comparator[a] (N=116) n (%)
Nausea	12 (10.0%)	23 (19.8%)
Abdominal pain NOS	7 (5.8%)	4 (3.4%)
Dyspepsia	5 (4.2%)	8 (6.9%)
Loose stools	5 (4.2%)	6 (5.2%)
Gastrointestinal haemorrhage NOS	2 (1.7%)	6 (5.2%)
General disorders and administration site conditions	**53 (44.2%)**	**69 (59.5%)**
Oedema peripheral	8 (6.7%)	16 (13.8%)
Pyrexia	8 (6.7%)	10 (8.6%)
Chest pain	8 (6.7%)	7 (6.0%)
Oedema NOS	8 (6.7%)	5 (4.3%)
Asthenia	6 (5.0%)	6 (5.2%)
Injection site erythema	3 (2.5%)	7 (6.0%)
Respiratory, thoracic and mediastinal disorders	**38 (31.7%)**	**43 (37.1%)**
Pharyngolaryngeal pain	10 (8.3%)	2 (1.7%)
Pleural effusion	7 (5.8%)	8 (6.9%)
Cough	4 (3.3%)	7 (6.0%)
Dyspnoea	4 (3.3%)	6 (5.2%)
Skin and subcutaneous tissue disorders	**36 (30.0%)**	**40 (34.5%)**
Rash NOS	8 (6.7%)	10 (8.6%)
Pruritus	7 (5.8%)	6 (5.2%)
Erythema	6 (5.0%)	6 (5.2%)
Sweating increased	6 (5.0%)	0 (0%)
Musculoskeletal and connective tissue disorders	**35 (29.2%)**	**42 (36.2%)**
Pain in extremity	11 (9.2%)	11 (9.5%)
Back pain	8 (6.7%)	10 (8.6%)
Arthralgia	4 (3.3%)	13 (11.2%)

Adverse Event	CUBICIN 6 mg/kg (N=120) n (%)	Comparator[a] (N=116) n (%)
Psychiatric disorders	**35 (29.2%)**	**28 (24.1%)**
Insomnia	11 (9.2%)	8 (6.9%)
Anxiety	6 (5.0%)	6 (5.2%)
Nervous system disorders	**32 (26.7%)**	**32 (27.6%)**
Headache	8 (6.7%)	12 (10.3%)
Dizziness	7 (5.8%)	7 (6.0%)
Investigations	**30 (25.0%)**	**33 (28.4%)**
Blood creatine phosphokinase increased	8 (6.7%)	1 (<1%)
Blood and lymphatic system disorders	**29 (24.2%)**	**24 (20.7%)**
Anaemia NOS	15 (12.5%)	18 (15.5%)
Metabolism and nutrition disorders	**26 (21.7%)**	**38 (32.8%)**
Hypokalaemia	11 (9.2%)	15 (12.9%)
Hyperkalaemia	6 (5.0%)	10 (8.6%)
Vascular disorders	**21 (17.5%)**	**20 (17.2%)**
Hypertension NOS	7 (5.8%)	3 (2.6%)
Hypotension NOS	6 (5.0%)	9 (7.8%)
Renal and urinary disorders	**18 (15.0%)**	**26 (22.4%)**
Renal failure NOS	4 (3.3%)	11 (9.5%)
Renal failure acute	4 (3.3%)	7 (6.0%)

a. Comparator: vancomycin (1 g IV q12h) or anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, flucloxacillin; 2 g IV q4h), each with initial low-dose gentamicin.

The following events, not included above, were reported as possibly or probably drug-related in the CUBICIN-treated group:

Blood and Lymphatic System Disorders: eosinophilia (1.7%), lymphadenopathy (<1%), thrombocythaemia (<1%), thrombocytopenia (<1%)
Cardiac Disorders: atrial fibrillation (<1%), atrial flutter (<1%), cardiac arrest (<1%)
Ear and Labyrinth Disorders: tinnitus (<1%)
Eye Disorders: vision blurred (<1%)
Gastrointestinal Disorders: dry mouth (<1%), epigastric discomfort (<1%), gingival pain (<1%), hypoaesthesia oral (<1%)

Infections and Infestations: candidal infection NOS (1.7%), vaginal candidiasis (1.7%), fungaemia (<1%), oral candidiasis (<1%), urinary tract infection fungal (<1%)
Investigations: blood phosphorous increased (2.5%), blood alkaline phosphatase increased (1.7%), INR ratio increased (1.7%), liver function test abnormal (1.7%), alanine aminotransferase increased (<1%), aspartate aminotransferase increased (<1%), prothrombin time prolonged (<1%)
Metabolism and Nutrition Disorders: appetite decreased NOS (<1%)
Musculoskeletal and Connective Tissue Disorders: myalgia (<1%)
Nervous System Disorders: dyskinesia (<1%), paraesthesia (<1%)
Psychiatric Disorders: hallucination NOS (<1%)
Renal and Urinary Disorders: proteinuria (<1%), renal impairment NOS (<1%)
Skin and Subcutaneous Tissue Disorders: heat rash (<1%), pruritus generalized (<1%), rash vesicular (<1%)

In Phase 3 studies of community-acquired pneumonia (CAP), the death rate and rates of serious cardiorespiratory adverse events were higher in CUBICIN-treated patients than in comparator-treated patients. These differences were due to lack of therapeutic effectiveness of CUBICIN in the treatment of CAP in patients experiencing these adverse events (see **INDICATIONS AND USAGE**).

Laboratory Changes

In Phase 3 comparator-controlled cSSSI and CAP studies, there was no clinically or statistically significant difference ($p<0.05$) in the incidence of CPK elevations between patients treated with CUBICIN and those treated with comparator. CPK elevations in both groups were generally related to medical conditions, for example, skin and skin structure infection, surgical procedures, or intramuscular injections; and were not associated with muscle symptoms.

In the Phase 3 cSSSI studies, 0.2% of patients treated with CUBICIN had symptoms of muscle pain or weakness associated with CPK elevations to greater than 4X ULN. The symptoms resolved within 3 days and CPK returned to normal within 7 to 10 days after discontinuing treatment (see **PRECAUTIONS, Skeletal Muscle**). Table 7 summarizes the CPK shifts from Baseline through End of Therapy in the cSSSI trials.

Table 7. Incidence (%) of Creatine Phosphokinase (CPK) Elevations from Baseline while on Therapy in Either CUBICIN or Comparator Treatment Groups in Phase 3 cSSSI Studies

	All Patients				Patients with Normal CPK at Baseline			
	CUBICIN (N=430)		Comparator (N=459)		CUBICIN (N=374)		Comparator (N=392)	
Change	%	N	%	N	%	N	%	N
No Increase	90.7%	390	91.1%	418	91.2%	341	91.1%	357
Maximum Value >1X ULN*	9.3%	40	8.9%	41	8.8%	33	8.9%	35
>2X ULN	4.9%	21	4.8%	22	3.7%	14	3.1%	12
>4X ULN	1.4%	6	1.5%	7	1.1%	4	1.0%	4
>5X ULN	1.4%	6	0.4%	2	1.1%	4	0.0%	0
>10X ULN	0.5%	2	0.2%	1	0.2%	1	0.0%	0

* ULN (Upper Limit of Normal) is defined as 200 U/L.

Note: Elevations in CPK observed in patients treated with CUBICIN or comparator were not clinically or statistically significantly different.

In the *S. aureus* bacteremia/endocarditis study, a total of 11 CUBICIN-treated patients (9.2%) had treatment-emergent elevations in CPK to >500 U/L, including 4 patients with elevations >10X ULN. Three of these 11 patients had CPK levels return to the normal range during continued CUBICIN treatment, 6 had values return to the normal range during follow-up, one had values returning toward baseline at the last assessment, and one did not have follow-up values reported. Three patients discontinued CUBICIN due to CPK elevation.

There was more renal dysfunction in comparator-treated patients than in CUBICIN-treated patients. The incidence of decreased renal function, defined as the proportion of patients with a creatinine clearance level <50 mL/min if baseline clearance was ≥50 mL/min or with a decrease of ≥10 mL/min if baseline clearance was <50 mL/min, is shown in Table 8.

Table 8. Incidence of Decreased Renal Function Based on Creatinine Clearance Levels

Study Interval	CUBICIN 6 mg/kg (N=120) n/N (%)	Comparator[a] (N=116) n/N (%)
Days 2 to 4	2/96 (2.1%)	6/90 (6.7%)
Days 2 to 7	6/115 (5.2%)	16/113 (14.2%)
Days 2 to End of Therapy	13/118 (11.0%)	30/114 (26.3%)

a. Comparator: vancomycin (1 g IV q12h) or anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, flucloxacillin; 2 g IV q4h), each with initial low-dose gentamicin.

Post-Marketing Experience

The following adverse reactions have been reported with CUBICIN in worldwide post-marketing experience. Because these events are reported voluntarily from a population of unknown size, estimates of frequency cannot be made and causal relationship cannot be precisely established.

Immune System Disorders: anaphylaxis; hypersensitivity reactions, including pruritus, hives, shortness of breath, difficulty swallowing, and truncal erythema.
Musculoskeletal System: rhabdomyolysis; some reports involved patients treated concurrently with CUBICIN and HMG CoA reductase inhibitors.

OVERDOSAGE

In the event of overdosage, supportive care is advised with maintenance of glomerular filtration. Daptomycin is slowly cleared from the body by hemodialysis (approximately 15% recovered over 4 hours) or peritoneal dialysis (approximately 11% recovered over 48 hours). The use of high-flux dialysis membranes during 4 hours of hemodialysis may increase the percentage of dose removed compared with low-flux membranes.

DOSAGE AND ADMINISTRATION

Complicated Skin and Skin Structure Infections

CUBICIN 4 mg/kg should be administered over a 30-minute period by IV infusion in 0.9% sodium chloride injection once every 24 hours for 7 to 14 days. In Phase 1 and 2 clinical studies, CPK elevations appeared to be more frequent when CUBICIN was dosed more frequently than once daily. Therefore, CUBICIN should not be dosed more frequently than once a day.

Staphylococcus aureus Bloodstream Infections (bacteremia), including those with right-sided endocarditis, caused by Methicillin-Susceptible and Methicillin-Resistant Strains

CUBICIN 6 mg/kg should be administered over a 30-minute period by IV infusion in 0.9% sodium chloride injection once every 24 hours for a minimum of 2 to 6 weeks. Duration of treatment should be based on the treating physician's working diagnosis. There are limited safety data for the use of CUBICIN for more than 28 days of therapy. In the Phase 3 study, there were a total of 14 patients who were treated with CUBICIN for more than 28 days, 8 of whom were treated for 6 weeks or longer.

In Phase 1 and 2 clinical studies, CPK elevations appeared to be more frequent when CUBICIN was dosed more frequently than once daily. Therefore, CUBICIN should not be dosed more frequently than once a day.

Patients with Renal Impairment

Because daptomycin is eliminated primarily by the kidney, a dosage modification is recommended for patients with creatinine clearance <30 mL/min, including patients receiving hemodialysis or CAPD, as listed in Table 9. The recommended dosing regimen is 4 mg/kg (cSSSI) or 6 mg/kg (*S. aureus* bloodstream infections) once every 24 hours for patients with CL_{CR} ≥30 mL/min and 4 mg/kg (cSSSI) or 6 mg/kg (*S. aureus* bloodstream infections) once

every 48 hours for CL_{CR} <30 mL/min, including those on hemodialysis or CAPD. In patients with renal insufficiency, both renal function and CPK should be monitored more frequently. When possible, CUBICIN should be administered following hemodialysis on hemodialysis days (see **CLINICAL PHARMACOLOGY**).

Table 9. Recommended Dosage of CUBICIN (daptomycin for injection) in Adult Patients

Creatinine Clearance (CL_{CR})	Dosage Regimen (cSSSI)	Dosage Regimen (*S. aureus* Bloodstream Infections)
≥30 mL/min	4 mg/kg once every 24 hours	6 mg/kg once every 24 hours
<30 mL/min, including hemodialysis or CAPD	4 mg/kg once every 48 hours	6 mg/kg once every 48 hours

Preparation of CUBICIN for Administration

CUBICIN is supplied in single-use vials containing 500 mg daptomycin as a sterile, lyophilized powder. The contents of a CUBICIN 500 mg vial should be reconstituted with 10 mL of 0.9% sodium chloride injection. Reconstituted CUBICIN should be further diluted with 0.9% sodium chloride injection to be administered by IV infusion over a period of 30 minutes.

Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparation of final IV solution. Stability studies have shown that the reconstituted solution is stable in the vial for 12 hours at room temperature or up to 48 hours if stored under refrigeration at 2 to 8°C (36 to 46°F). The diluted solution is stable in the infusion bag for 12 hours at room temperature or 48 hours if stored under refrigeration. The combined time (vial and infusion bag) at room temperature should not exceed 12 hours; the combined time (vial and infusion bag) under refrigeration, should not exceed 48 hours.

CUBICIN vials are for single-use only.

Parenteral drug products should be inspected visually for particulate matter prior to administration.

Because only limited data are available on the compatibility of CUBICIN with other IV substances, additives or other medications should not be added to CUBICIN single-use vials or infused simultaneously through the same IV line. If the same IV line is used for sequential infusion of several different drugs, the line should be flushed with a compatible infusion solution before and after infusion with CUBICIN.

Compatible Intravenous Solutions

CUBICIN is compatible with 0.9% sodium chloride injection and lactated Ringer's injection. CUBICIN is not compatible with dextrose-containing diluents.

HOW SUPPLIED

CUBICIN (daptomycin for injection) – Pale yellow to light brown lyophilized cake
Single-use 10 mL capacity vial, 500 mg/vial: Package of 1 (NDC 67919-011-01)

STORAGE

Store original packages at refrigerated temperatures 2 to 8°C (36 to 46°F); avoid excessive heat.

CLINICAL STUDIES

Complicated Skin and Skin Structure Infections

Adult patients with clinically documented cSSSI (Table 10) were enrolled in two randomized, multinational, multicenter, investigator-blinded studies comparing CUBICIN (4 mg/kg IV q24h) with either vancomycin (1 g IV q12h) or an anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, or flucloxacillin; 4 to 12 g IV per day). Patients known to have bacteremia at baseline were excluded. Patients with creatinine clearance (CL_{CR}) between 30 and 70 mL/min were to receive a lower dose of CUBICIN as specified in the protocol; however, the majority of patients in this subpopulation did not have the dose of CUBICIN adjusted. Patients could switch to oral therapy after a minimum of four days of IV treatment if clinical improvement was demonstrated.

One study was conducted primarily in the United States and South Africa (study 9801), and the second (study 9901) was conducted at non-US sites only. Both studies were similar in design, but differed in patient characteristics, including history of diabetes and peripheral vascular disease. There were a total of 534 patients treated with CUBICIN and 558 treated with comparator in the two studies. The majority (89.7%) of patients received IV medication exclusively.

The efficacy endpoints in both studies were the clinical success rates in the intent-to treat (ITT) population and in the clinically evaluable (CE) population. In study 9801, clinical success rates in the ITT population were 62.5% (165/264) in patients treated with CUBICIN and 60.9% (162/266) in patients treated with comparator drugs. Clinical success rates in the CE population were 76.0% (158/208) in patients treated with CUBICIN and 76.7% (158/206) in patients treated with comparator drugs. In study 9901, clinical success rates in the ITT population were 80.4% (217/270) in patients treated with CUBICIN and 80.5% (235/292) in patients treated with comparator drugs. Clinical success rates in the CE population were 89.9% (214/238) in patients treated with CUBICIN and 90.4% (226/250) in patients treated with comparator drugs.

The success rates by pathogen for microbiologically evaluable patients are presented in Table 11.

Table 10. Investigator's Primary Diagnosis in the cSSSI Studies (Population: ITT)

Primary Diagnosis	Study 9801 CUBICIN/Comparator[a] N=264/N=266	Study 9901 CUBICIN/Comparator[a] N=270/N=292	Pooled CUBICIN/Comparator[a] N=534/N=558
Wound Infection	99 (37.5%)/116 (43.6%)	102 (37.8%)/108 (37.0%)	201 (37.6%)/224 (40.1%)
Major Abscess	55 (20.8%)/43 (16.2%)	59 (21.9%)/65 (22.3%)	114 (21.3%)/108 (19.4%)
Ulcer Infection	71 (26.9%)/75 (28.2%)	53 (19.6%)/68 (23.3%)	124 (23.2%)/143 (25.6%)
Other Infection[b]	39 (14.8%)/32 (12.0%)	56 (20.7%)/51 (17.5%)	95 (17.8%)/83 (14.9%)

a. Vancomycin or anti-staphylococcal semi-synthetic penicillins.
b. The majority of cases were subsequently categorized as complicated cellulitis, major abscesses, or traumatic wound infections.

Table 11. Clinical Success Rates by Infecting Pathogen, Primary Comparative cSSSI Studies (Population: Microbiologically Evaluable)

Pathogen	Success Rate	
	CUBICIN n/N (%)	Comparator[a] n/N (%)
Methicillin-susceptible *Staphylococcus aureus* (MSSA)[b]	170/198 (85.9)	180/207 (87.0)
Methicillin-resistant *Staphylococcus aureus* (MRSA)[b]	21/28 (75.0)	25/36 (69.4)
Streptococcus pyogenes	79/84 (94.0)	80/88 (90.9)
Streptococcus agalactiae	23/27 (85.2)	22/29 (75.9)
Streptococcus dysgalactiae subsp. *equisimilis*	8/8 (100)	9/11 (81.8)
Enterococcus faecalis (vancomycin-susceptible only)	27/37 (73.0)	40/53 (75.5)

a. Vancomycin or anti-staphylococcal semi-synthetic penicillins.
b. As determined by the central laboratory.

S. aureus Bacteremia/Endocarditis

The efficacy of CUBICIN in the treatment of patients with *S. aureus* bacteremia was demonstrated in a randomized, controlled, multinational, multicenter open-label study. In this study, adult patients with at least one positive blood culture for *S. aureus* obtained within 2 calendar days prior to the first dose of study drug and irrespective of source were enrolled and randomized to either CUBICIN (6 mg/kg IV q24h) or standard of care [anti-staphylococcal semi-synthetic penicillin 2 g IV q4h (nafcillin, oxacillin, cloxacillin, or flucloxacillin) or vancomycin 1 g IV q12h, both with initial gentamicin 1 mg/kg IV every 8 hours for first 4 days]. Of the patients in the comparator group, 93% received initial gentamicin for a median of 4 days compared with one patient (<1%) in the CUBICIN group. Patients with prosthetic heart valves, intravascular foreign material that was not planned for removal within 4 days after the first dose of study medication, severe neutropenia, known osteomyelitis, polymicrobial bloodstream infections, creatinine clearance <30 mL/min, and pneumonia were excluded.

Upon entry, patients were classified for likelihood of endocarditis using the modified Duke criteria (Possible, Definite, or Not Endocarditis). Echocardiography, including a transesophageal echocardiogram (TEE), was performed within 5 days following study enrollment. The choice of comparator agent was based on the oxacillin susceptibility of the *S. aureus* isolate. The duration of study treatment was based on the investigator's clinical diagnosis. Final diagnoses and outcome assessments at Test of Cure (6 weeks after the last treatment dose) were made by a treatment-blinded Adjudication Committee, using protocol-specified clinical definitions and a composite primary efficacy endpoint (clincal and microbiological success) at the Test of Cure visit.

A total of 246 patients ≥18 years of age (124 CUBICIN, 122 comparator) with *S. aureus* bacteremia, were randomized from 48 centers in the US and Europe. In the ITT population, 120 patients received CUBICIN and 115 received comparator (62 anti-staphylococcal semi-synthetic penicillin and 53 vancomycin). Thirty-five patients treated with anti-staphylococcal semi-synthetic penicillins received vancomycin initially for 1 to 3 days, pending final susceptibility results for the *S. aureus* isolates. The median age among the 235 patients in the ITT population was 53 years (range: 21 to 91 years); 30/120 (25%) in the CUBICIN group and 37/115 (32%) in the comparator group were aged ≥65 years of age. Of the 235 ITT patients, there were 141 (60%) males and 156 (66%) Caucasians across the two treatment groups. In addition, 176 (75%) of the ITT population had systemic inflammatory response syndrome (SIRS) and 85 (36%) had surgical procedures within 30 days of onset of the *S. aureus* bacteremia. Eighty-eight patients (38%) had bacteremia caused by MRSA. Entry diagnosis was based on the modified Duke criteria and included 37 (16%) Definite, 144 (61%) Possible, and 54 (23%) Not Endocarditis. Of the 37 patients with an entry diagnosis of Definite Endocarditis, all (100%) had a final diagnosis of infective endocarditis, and of the 144 patients with an entry diagnosis of Possible Endocarditis, 15 (10%) had a final diagnosis of infective endocarditis as assessed by the Adjudication Committee. Of the 54 patients with an entry diagnosis of Not Endocarditis, 1 (2%) had a final diagnosis of infective endocarditis as assessed by the Adjudication Committee.

There were 182 patients with bacteremia and 53 patients with infective endocarditis as assessed by the Adjudication Committee in the ITT population, including 35 with right-sided and 18 with left-sided endocarditis. The 182 patients with bacteremia included 121 with complicated and 61 with uncomplicated *S. aureus* bacteremia.

Complicated bacteremia was defined as *S. aureus* isolated from blood cultures obtained on at least 2 different calendar days, and/or metastatic foci of infection (deep tissue involvement), and classification of the patient as not having endocarditis according to the modified Duke criteria. Uncomplicated bacteremia was defined as *S. aureus* isolated from blood culture(s) obtained on a single calendar day, no metastatic foci of infection, no infection of prosthetic material, and classification of the patient as not having endocarditis according to the modified Duke criteria. The definition of right-sided endocarditis (RIE) used in the clinical trial was definite or possible endocarditis according to the modified Duke criteria and no echocardiographic evidence of predisposing pathology or active involvement of either the mitral or aortic valve. Complicated RIE included patients who were not intravenous drug users, had a positive blood culture for MRSA, serum creatinine ≥2.5 mg/dL, or evidence of extrapulmonary sites of infection. Patients who were intravenous drug users, had a positive blood culture for MSSA, serum creatinine <2.5 mg/dL, and were without evidence of extrapulmonary sites of infection were considered to have uncomplicated RIE.

The co-primary efficacy endpoints in the study were the Adjudication Committee success rates at the Test of Cure visit (6 weeks after the last treatment dose) in the ITT and Per Protocol (PP) populations. The overall Adjudication Committee success rates in the ITT population were 44.2% (53/120) in patients treated with CUBICIN and 41.7% (48/115) in patients treated with comparator (difference = 2.4% [95% CI -10.2, 15.1]). The success rates in the PP population were 54.4% (43/79) in patients treated with CUBICIN and 53.3% (32/60) in patients treated with comparator (difference = 1.1% [95% CI -15.6, 17.8]).

Adjudication Committee success rates are shown in Table 12.

Eighteen (18/120) patients in the CUBICIN arm and 19/116 patients in the comparator arm died during the study. This includes 3/28 CUBICIN-treated and 8/26 comparator-treated patients with endocarditis, as well as 15/92 CUBICIN-treated and 11/90 comparator-treated patients with bacteremia. Among patients with persisting or relapsing *S. aureus* infections, 8/19 CUBICIN-treated and 7/11 comparator-treated patients died.

Overall, there was no difference in time to clearance of *S. aureus* bacteremia between CUBICIN and comparator. The median time to clearance in patients with MSSA was 4 days and in patients with MRSA was 8 days.

Failure of treatment due to persisting or relapsing *S. aureus* infections was assessed by the Adjudication Committee in 19/120 (15.8%) CUBICIN-treated patients (12 with MRSA and 7 with MSSA) and 11/115 (9.6%) comparator-treated patients (9 with MRSA treated with vancomycin and 2 with MSSA treated with anti-staphylococcal semi-synthetic penicillin). Among all failures, 6 CUBICIN-treated patients and 1 vancomycin-treated patient developed increasing MICs (reduced susceptibility) by central laboratory testing on or following therapy. Most patients who failed due to persisting or relapsing *S. aureus* infection had deep-seated infection and did not receive necessary surgical intervention (see **PRECAUTIONS**).

Table 12. Adjudication Committee Success Rates at Test of Cure (ITT)

Population	CUBICIN 6 mg/kg n/N (%)	Comparator[a] n/N (%)	Difference: CUBICIN − Comparator (Confidence Interval)
Overall	53/120 (44.2%)	48/115 (41.7%)	2.4% (−10.2, 15.1)[c]
Baseline Pathogen			
MSSA	33/74 (44.6%)	34/70 (48.6%)	−4.0% (−22.6, 14.6)[d]
MRSA	20/45 (44.4%)	14/44 (31.8%)	12.6% (−10.2, 35.5)[d]
Entry Diagnosis[b]			
Definite or Possible Infective Endocarditis	41/90 (45.6%)	37/91 (40.7%)	4.9% (−11.6, 21.4)[d]
Not Infective Endocarditis	12/30 (40.0%)	11/24 (45.8%)	−5.8% (−36.2, 24.5)[d]
Final Diagnosis			
Uncomplicated Bacteremia	18/32 (56.3%)	16/29 (55.2%)	1.1% (−31.7, 33.9)[e]
Complicated Bacteremia	26/60 (43.3%)	23/61 (37.7%)	5.6% (−17.3, 28.6)[e]
Right-Sided Infective Endocarditis	8/19 (42.1%)	7/16 (43.8%)	−1.6% (−44.9, 41.6)[e]
Uncomplicated Right-Sided Infective Endocarditis	3/6 (50.0%)	1/4 (25.0%)	25.0% (−51.6, 100.0)[e]
Complicated Right-Sided Infective Endocarditis	5/13 (38.5%)	6/12 (50.0%)	−11.5% (−62.4, 39.4)[e]
Left-Sided Infective Endocarditis	1/9 (11.1%)	2/9 (22.2%)	−11.1% (−55.9, 33.6)[e]

a. Comparator: vancomycin (1 g IV q12h) or anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, flucloxacillin; 2 g IV q4h), each with initial low-dose gentamicin

b. According to the modified Duke criteria[4]

c. 95% Confidence Interval

d. 97.5% Confidence Interval (adjusted for multiplicity)

e. 99% Confidence Interval (adjusted for multiplicity)

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Rx only

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Manufactured for:

Cubist Pharmaceuticals, Inc.
Lexington, MA 02421 USA

Distributed by:

Integrated Commercialization Solutions (ICS)
Brooks, KY 40109 USA

For all medical inquiries call: (866) 793-2786

REVISED
May 2006

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021572Orig1s008

SUMMARY REVIEW

May 25, 2006

NDA 21-572/S-008

Division Director Memorandum for Cubicin® (daptomycin for injection)

Indication Requested:

The treatment of *Staphylococcus aureus* bacteremia (SAB), including those with known or suspected endocarditis.

Indication Granted:

***Staphylococcus aureus* bloodstream infections** (bacteremia), including those with right-sided infective endocarditis, caused by methicillin-susceptible and methicillin-resistant isolates. Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram-negative or anaerobic organisms. The efficacy of CUBICIN in patients with left-sided infective endocarditis due to *S. aureus* has not been demonstrated. The clinical trial of CUBICIN in patients with *S. aureus* bloodstream infections included limited data from patients with left-sided infective endocarditis; outcomes in these patients were poor (see **CLINICAL STUDIES**). CUBICIN has not been studied in patients with prosthetic valve endocarditis or meningitis. Patients with persisting or relapsing *S. aureus* infection or poor clinical response should have repeat blood cultures. If a culture is positive for *S. aureus*, MIC susceptibility testing of the isolate should be performed using a standardized procedure, as well as diagnostic evaluation to rule out sequestered foci of infection (see **PRECAUTIONS**).

The pre-clinical and clinical reviewers have written very thorough reviews detailing the issues in their respective disciplines that describe the safety and efficacy of daptomycin in the treatment of patients with *Staphylococcus aureus* bacteremia, including patients with infective endocarditis (IE) due to methicillin-sensitive or methicillin- resistant *S. aureus* (MSSA or MRSA). The original efficacy supplement to the New Drug Application (NDA) was received September 22, 2005, and the Division filed the supplement as a priority review with a 6-month clock.

There is clearly a public health need to get information in the label recommending to physicians and other health care professionals that patients with *S. aureus* bacteremia, including those with known or suspected right-sided infective endocarditis (RIE), should be treated with the 6 mg/kg dose of daptomycin studied in bacteremia, as opposed to the 4 mg/kg dose approved for complicated skin and skin structure infections. We have information to suggest that many patients, currently treated off-label for *S. aureus* bacteremia/ endocarditis, receive an inadequate exposure to daptomycin (the lower dose of 4 mg/kg or too short a period of therapy, < 28 days) which is less likely to be effective in this serious illness.

There is a need for additional products to treat severe infections due to Gram-positive organisms, including not only methicillin-resistant *Staphylococcus aureus* (MRSA) but vancomycin-resistant enterococcal (VRE) infections, too. This submission addressed some but not all of the issues. No single trial ever does. I will very briefly mention preclinical findings, efficacy and safety, and then identify what I see as currently outstanding issues.

Preclinical (excerpted from the Office/Division Director Memo of September, 2003):

The major target organs of daptomycin toxicity in rat, dog, and monkey were muscle and peripheral nerves. Muscle damage consisted of muscle degeneration/ regeneration and usually resolved within 1 month of cessation of treatment. Muscle changes were sometimes accompanied by increases in creatine phosphokinase (CPK). Peripheral nerve damage occurred at higher doses and included loss of patellar/gag reflexes, loss of pain perception, decreases in nerve conduction velocity, and axonal degeneration. The dosing interval (q12h v. q24h) appeared to play a role in the development of muscle toxicity in animals, favoring q24h.

Clinical

The *S. aureus* bacteremia/endocarditis study, conducted by Cubist Pharmaceuticals Inc., represented the first multi-center randomized controlled clinical trial with long-term follow-up submitted to the Agency, to determine the safety and efficacy of daptomycin versus the standard of care (vancomycin/semi-synthetic penicillin plus gentamicin) for these conditions. Over 200 patients were enrolled, and the study met its primary endpoint. Issues arose within the review of the study by a multi-disciplinary FDA review team that necessitated a public discussion of the study design and its results.

The Anti-Infective Drugs Advisory Committee addressed the application on March 6, 2006. When asked the question "Do the data provide substantial evidence of safety and efficacy of daptomycin in the treatment of *S. aureus* bacteremia?", the panel voted 9 to 0 in favor of approval. Included in their deliberations was a discussion of the significance of patients with persistent or relapsing bacteremias, and those whose staphylococcal isolates had increasing minimum inhibitory concentrations (MICs) to daptomycin. Comments included the following:

- MICs should be monitored weekly or more frequently when treating patients with complicated or persistent bacteremia.
- Daptomycin should be used very judiciously, coupled with good culture and sensitivity techniques.
- Community-acquired MRSA is a different disease entity than hospital-acquired MRSA; therefore, clearance and complications of that organism can be expected to be different and more difficult to treat.

- The label should emphasize use of the appropriate dose, in order to discourage under dosing during therapy.
- Increasing MICs or failures may be an indication that the drug is being "pushed to the limit" and considerations for surgical intervention should be explored; many of these bacteremias require more than simply prescribing antibiotic therapy (e.g., surgery, debridement, hardware removal, etc.).

On the question of whether the data from this study provided substantial evidence of safety and efficacy of daptomycin in the treatment of patients with infective endocarditis, the panel voted 5 "yes" and 4 "no". Comments included the following:

- It is often difficult to make a diagnosis of endocarditis. The high risk nature of this patient population at the front end makes it critical to begin treating these patients with something, without knowing the precise diagnosis. Echocardiogram and clinical outcomes data may be the best we can do to make a diagnosis, although specificity is excellent, the sensitivity of echocardiography is not sufficiently high.
- Problems associated with concluding that there are sufficient data to determine efficacy in all types of endocarditis lie more with the study than the drug. There are not enough data in total numbers in the study, and even fewer in the subgroup populations, which is important in analyzing right-sided versus left-sided endocarditis. (See table at the end of this memorandum) Caution should be taken in extrapolating data from the intention-to-treat population because *S. aureus* endocarditis and *S. aureus* bacteremia are not equivalent diseases.
- Concerns were discussed regarding the – 20% non-inferiority margin and the difficulty in justifying a 20% non-inferiority margin when, in the left-sided group, there is a 22% control response rate. It is concerning that the control response rate varies dramatically by these diagnostic subgroups.
- The Committee discussed the significance of the echocardiographic results in the clinical setting, when treating these patients. They cited a study that showed initial therapy was rarely changed based on the results of the echocardiogram. The choice and duration of therapy was based primarily on clinician bias at the outset, even before the echocardiogram was performed.
- A labeling suggestion was added here that, if there is clear evidence of left-sided endocarditis by the presence of vegetation, the clinician needs to be cautioned that there are limited data available regarding efficacy for left-sided endocarditis, and that these data are not very compelling.
- Answering this question hinges on whether we define the population for infective endocarditis as entry diagnosis or final diagnosis. Using entry diagnosis, the study clearly showed daptomycin was non-inferior to control. Labeling should include statements clarifying that daptomycin has been studied and is non-inferior to the comparator for treatment of *S. aureus* endocarditis where the entry diagnosis used the Duke criteria for endocarditis. Additionally, labeling should address the need for adjunctive therapy for complicated bacteremia (i.e. drainage), in combination with medical therapy.

- Additional labeling suggestions by the committee included statements about the overall effectiveness being 44%, making it clear to clinicians that it was not compelling, while also clarifying that these data are based on small numbers.
- Given the sponsor's observation that 25% of off-label use of daptomycin is for bacteremia at 4 mg/kg, labeling should clarify that clinicians should be prescribing a 6 mg/kg dose for bacteremia/endocarditis.

The first cycle PDUFA goal date of March 24, 2006, came on the heels of the Advisory Committee deliberations for this supplemental NDA. At that time, Cubist received an "Approvable" letter. In response to the letter, the sponsor resubmitted a Class 1 information amendment on March 27, 2006, with a resultant Class 1 resubmission action date of May 26, 2006. This additional information has been evaluated in depth by the review team. There have been many discussions as to the scientific validity of the endocarditis study, the appropriate analyses of the data, the appropriateness of the indication, and the number of evaluable patients from the trial. There is agreement within the review team that the trial met its primary endpoint. The review team has not been able to reach consensus on the approvability of this application with regard to the experience in left- versus right-sided endocarditis. As Division Director, I have considered the input from each and every team member and listened to the sometimes discordant discussions. After dialogue with the review team, as well as the management of the Office of Antimicrobial Products and the Office of New Drugs, I have decided to grant the *S. aureus* bacteremia and right-sided endocarditis claims for daptomycin. The rationale behind this decision is given below.

At its core, this was a historical control study. We anticipate that close to 100% of patients with untreated IE will die, while perhaps 80% will survive with treatment (e.g., 19% in-hospital mortality for IE was reported in Early Predictors of In-Hospital Death in Infective Endocarditis, Chu, et al; Circulation. 2004;109:1745-1749.). Therefore, there was no scientifically justified need to have a control group in order to argue for the efficacy of the drug. This is one interpretation of what is recommended in the FDA 1992 Points-to-Consider document on developing anti-infective drugs for endocarditis. The presence of a randomized control serves to strengthen the argument for efficacy, in that similar cure rates and mortality rates argue for similar effectiveness between daptomycin and comparator. This also provides some comparative safety data. The argument that the cure rate was "too low" to prove efficacy is unwarranted, since the randomized control group had a similar cure rate. Because the patients studied do not represent a random sample from the general population of all IE patients, there is no reason to think that they will have the same cure rate as the population of all IE patients, or the cure rate reported in the medical literature.

It is inevitable that differences in cure rates will be seen among subgroups (males, females, young, old, etc.), and the observed differences can be alarmingly large when the sample sizes are small, even when there is no difference in the true cure rate. There is a body of literature to speak to the various kinds of endocarditis, particularly LIE versus RIE. That the infection of heart valves on the high-pressure side of the heart is more

problematic is biologically plausible. It is plausible that daptomycin and vancomycin are equally effective at treating RIE, but both are poor at treating LIE.

I have a hard time accepting the idea that the open nature of the study lead to underreporting of truly serious adverse events. Dizziness/syncope may be underreported, but the cases of acute renal failure and death are likely to be reported 100% of the time. In general, the open nature of the study (which FDA requested before the study began), while suboptimal for some scientific purposes, is unlikely to have any impact on study outcomes that are objectively measured. The 95% Confidence Intervals in the label are there to give a sense of the variability in the estimates, and how hard it is to tell if the response in the different subsets truly differ. The more one subsets, the smaller the "n", and the wider the interval.

Unresolved Issues:

There is a continued need for new products to treat serious Gram positive infections, and daptomycin, with its unique mechanism of action and its spectrum of activity, appears to be an important product in the therapeutic armamentarium. Tempering this enthusiasm are the results of studies conducted in serious conditions beyond the current indications. In a Community Acquired Pneumonia trial conducted by Cubist daptomycin performed also performed less well than would have been expected. It is believed that reduced penetration into the lung, due to binding to surfactant, is a factor in these results. The pneumonia data were sufficiently convincing that a statement appears in the "Indications and Usage" section of the product label that daptomycin is not indicated for community acquired pneumonia.

Finally, the optimal regimen for patients with all manner of endocarditis needs to be determined. The sponsor should pursue collecting additional clinical and microbiologic data, including the treatment of patients on combination antimicrobial therapies.

Table Adjudication Committee Success Rates at Test of Cure (ITT)

Population	CUBICIN 6 mg/kg n/N (%)	Comparator[a] n/N (%)	Difference: CUBICIN − Comparator (Confidence Interval)
Overall	53/120 (44.2%)	48/115 (41.7%)	2.4% (−10.2, 15.1)[c]
Baseline Pathogen			
MSSA	33/74 (44.6%)	34/70 (48.6%)	−4.0% (−22.6, 14.6)[d]
MRSA	20/45 (44.4%)	14/44 (31.8%)	12.6% (−10.2, 35.5)[d]
Entry Diagnosis[b]			
Definite or Possible Infective Endocarditis	41/90 (45.6%)	37/91 (40.7%)	4.9% (−11.6, 21.4)[d]
Not Infective Endocarditis	12/30 (40.0%)	11/24 (45.8%)	−5.8% (−36.2, 24.5)[d]
Final Diagnosis			
Uncomplicated Bacteremia	18/32 (56.3%)	16/29 (55.2%)	1.1% (−31.7, 33.9)[e]
Complicated Bacteremia	26/60 (43.3%)	23/61 (37.7%)	5.6% (−17.3, 28.6)[e]
Right-Sided Infective Endocarditis	8/19 (42.1%)	7/16 (43.8%)	−1.6% (−44.9, 41.6)[e]
Uncomplicated Right-Sided Infective Endocarditis	3/6 (50.0%)	1/4 (25.0%)	25.0% (−51.6, 100.0)[e]
Complicated Right-Sided Infective Endocarditis	5/13 (38.5%)	6/12 (50.0%)	−11.5% (−62.4, 39.4)[e]
Left-Sided Infective Endocarditis	1/9 (11.1%)	2/9 (22.2%)	−11.1% (−55.9, 33.6)[e]

a. Comparator: vancomycin (1 g IV q12h) or anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, flucloxacillin; 2 g IV q4h), each with initial low-dose gentamicin
b. According to the modified Duke criteria[4]
c. 95% Confidence Interval
d. 97.5% Confidence Interval (adjusted for multiplicity)
e. 99% Confidence Interval (adjusted for multiplicity)

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/s/

Janice Soreth
5/25/2006 06:17:07 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021572Orig1s008

CLINICAL REVIEW(S)

Medical Team Leader's Review

Reviewer	Sumathi Nambiar MD MPH
Application Type	NDA 21-572/SE-1-008
CDER Stamp Date	27 March 2006
PDUFA Goal Date	26 May 2006
Established Name	Daptomycin
Trade Name	Cubicin®
Applicant	Cubist Pharmaceuticals Inc.
Formulation	Injection
Dosing Regimen	6 mg/kg intravenously daily
Proposed Indication	*S. aureus* bloodstream infection (bacteremia) including those with right-sided infective endocarditis caused by methicillin-susceptible and methicillin-resistant strains
Intended Population	Adults

Background
An efficacy supplement, NDA 21-572/SE1-008 was submitted by Cubist Pharmaceuticals Inc. on September 26, 2005 for the proposed indication of daptomycin in the treatment of *Staphylococcus aureus* bacteremia including those with known or suspected endocarditis caused by methicillin-susceptible and methicillin-resistant strains. An approvable letter was issued on March 24, 2006 pending agreement on the product label in relation to the Indications and Usage, Clinical Studies, Dosage and Administration, and Clinical Pharmacology sections, and inclusion of data on persisting and relapsing *S. aureus* (PRSA) bacteremias, reduced susceptibility of *S. aureus* to study drug emerging during treatment, and implications of PRSA and reduced susceptibility for patient outcomes.

A complete response to the approvable letter was submitted by the Sponsor on March 27, 2006. The resubmission materials included proposed labeling, clarifying information and a meeting request. No new data were included in this submission.

This review will focus on the Sponsor's proposed label submitted March 27, 2006 and will be limited to the following sections: INDICATIONS AND USAGE, PRECAUTIONS, DOSAGE and ADMINISTRATION and CLINICAL STUDIES.

For the INDICATIONS AND USAGE and PRECAUTIONS sections, I have provided my proposed language followed by my reasoning under the Comments heading. For the DOSAGE and ADMINISTRATION and CLINICAL STUDIES sections, I am in agreement with most of the language proposed by the Sponsor. For sections where I disagree with the Sponsor's proposal, I have provided my rationale under the Comments heading.

INDICATIONS AND USAGE

Sponsor's proposal:

Staphylococcus aureus bloodstream infections (bacteremia), including those with right-sided infective endocarditis caused by methicillin-susceptible and methicillin-resistant strains.

The efficacy of CUBICIN in patients with left-sided infective endocarditis due to *S. aureus* has not been demonstrated. The clinical trial of CUBICIN in patients with S. aureus bloodstream infections included limited data from patients with left-sided infective endocarditis; outcomes in these patients were poor (see CLINICAL STUDIES). CUBICIN has not been studied in patients with prosthetic valve endocarditis or meningitis.

Patients with persisting or relapsing S. aureus infection or poor clinical response should have repeat blood culture and susceptibility testing by MIC using a standardized procedure, as well as diagnostic evaluation, to rule out sequestered foci of infection (see PRECAUTIONS).

My proposal:

Staphylococcus aureus bloodstream infections caused by methicillin-susceptible and methicillin-resistant strains. Efficacy of CUBICIN in patients with infective endocarditis has not been demonstrated. (See CLINICAL STUDIES) CUBICIN has not been studied in patients with prosthetic valve endocarditis, known osteomyelitis, or meningitis.

COMMENTS:

As discussed during the review of the original submission, data in study DAP-IE-01-02 did not provide substantial evidence of the efficacy and safety of daptomycin for the treatment of infective endocarditis (IE). The ability to draw conclusions regarding the efficacy of daptomycin in patients with IE was limited for the following reasons:

1. The number of patients with either left or right-sided infective endocarditis was very small.
2. Although majority of patients had definite or possible IE at study entry based on modified Duke criteria, only a small number of patients had a final diagnosis of definite IE. In a clinical practice setting, patients with possible IE may be treated as though they have definite IE. However, in a clinical trial wherein a test drug's performance is being assessed it is important that the disease condition being studied is well defined. Possible IE is not a well-defined clinical entity. All patients with *S. aureus* bacteremia who are febrile can potentially be classified as having possible IE.
3. IE is characterized by the presence of vegetations. Both antibacterial activity and ability of the drug to penetrate the vegetations are important in achieving cure. It is thus important that the efficacy of a test drug is demonstrated in patients with echocardiographic evidence of IE or in those with definite IE.
4. The specificity of diagnosis of IE is very important given that the pathophysiology of IE is distinct from that of bacteremia and that it is associated with high morbidity and mortality. In this study, specificity of diagnosis of IE was limited for the following reasons:
    - In patients with right-sided IE, the protocol did not require that echocardiographic criteria for IE should be present. It is certainly possible to have definite IE without echocardiographic evidence of IE. As outlined in the Duke criteria for definite IE, such patients have to meet other minor criteria such as presence of embolic phenomena, presence of immunologic phenomena, fever, or history of intravenous drug use.[1] Of the 35 patients with RIE, 17 did not have evidence of IE based on central echocardiograms, 13 in the daptomycin arm and 4 in the comparator arm; 7/17 (5 daptomycin-treated and 2 comparator-treated) patients had three or more minor criteria for the diagnosis of definite IE. Hence the number of patients with definite IE was limited to 11/19 patients in the daptomycin arm and 14/16 patients in the comparator arm.
    - The number of patients with RIE who had negative central echocardiograms was disproportionately higher in the daptomycin group compared to those treated with comparator;13/19 (68.4%) patients treated

with daptomycin and 4/16 (25%) treated with comparator did not have evidence of IE based on central echocardiograms.

- Inter-observer variability is expected in the reading of echocardiograms. Discrepancies between the local echocardiography and the Duke Core Echo laboratory assessments were noted in 18 patients (35%), 10 patients with positive central echocardiogram findings had negative local echocardiogram findings while 8 patients with negative central echocardiogram findings had positive local echocardiogram findings. The discrepancies in almost a third of echocardiogram results between local and central laboratory readings raise additional concerns about the specificity of the diagnosis of IE and limit the ability to accurately define a well-characterized group of patients with IE.

5. As the preponderance of evidence was in patients with no demonstrable vegetations, it limits the ability to extrapolate the efficacy of daptomycin from this group of patients to those patients with vegetations on the tricuspid or pulmonic valve.
6. The point estimates for the success rates in patients with right-sided IE were very low compared to that reported in the literature. Success rates in RIE in the intravenous drug using population have been reported to be > 85%.[2] In this study, as ~ 60% of patients with IE were intravenous drug users one would expect higher success rates.
7. The low success rates in both treatment arms and the wide confidence intervals around the treatment difference between the two groups raise concerns regarding the assay sensitivity of this trial.

PRECAUTIONS

Sponsor proposal:

(b) (4)

My proposal:

Persistent and relapsing *S. aureus* bacteremias were seen in 21/120 (17.5%) daptomycin-treated patients and in 11/115 (9.6%) comparator-treated patients (See CLINICAL STUDIES). Six daptomycin-treated patients with daptomycin-susceptible baseline *S. aureus* blood culture isolates developed rising MICs (≥2 µg/ml) to daptomycin during the study. All were failures. One comparator-treated patient, whose baseline *S. aureus* blood culture isolate developed MICs =2 µg/ml to vancomycin during the study was a failure. Daptomycin-treated patients with *S. aureus* bacteremia should be monitored for the development of persistent or relapsing *S. aureus* infections and reduced susceptibility to the drug. Blood cultures and daptomycin susceptibility testing by MIC using standardized procedures should be repeated on a regular basis.

COMMENTS:

1. The WARNINGS section of the label should include a statement regarding the observation made in the clinical trial of increasing MICs to daptomycin and its association with clinical failure, even though a causal relationship has not been demonstrated. The recommendation to include this information in the WARNINGS section is consistent with 21CFR §201.57 (e), which states that under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. In a severe illness such as *S. aureus* bacteremia, lack of efficacy is associated with increased morbidity and mortality and it is important that the practitioner be made aware of this observation.
2. Literature reports and post-marketing adverse event reports regarding clinical failures with daptomycin provide supportive information that development of non-susceptibility to daptomycin is a real phenomenon. [3-6]
3. The Sponsor's proposal to separate the comparator group into two groups, those treated with vancomycin and those treated with semi-synthetic penicillins is not appropriate for the following reasons: Most patients in the semi-synthetic penicillin (SSP) group received vancomycin for 1-3 days prior to being treated with SSP; secondly by splitting the comparator group post-hoc there is no certainty that the daptomycin-treated patients and vancomycin-treated patients are comparable as this division was performed post-randomization; lastly, all vancomycin-treated patients had MRSA as the baseline pathogen, while the daptomycin-treated patients had either MRSA or MSSA at baseline.
4. Though it is possible that most patients that failed due to persisting or relapsing *S. aureus* infection had deep seated infection and did not receive surgical intervention, it is not clear to what extent it caused persisting or relapsing infection. Also, we do not know that if patients had the surgical procedure the outcome would have been different. Hence, my proposal is to not include that statement in the label.

DOSAGE AND ADMINISTRATION

Sponsor's proposal:

***Staphylococcus aureus* Bloodstream Infections (bacteremia), including those with right-sided endocarditis, caused by Methicillin-susceptible and Methicillin-resistant Strains:**

(b) (4)

COMMENTS:

1. (b) (4) (b) (4) Thus the statement proposed by the Sponsor (b) (4) is incorrect.
2. The sentence (b) (4) (b) (4) is misleading (b) (4)
3. (b) (4) Thus, the safety information on > 28 days of therapy with daptomycin is limited. It is important that this be clearly stated in the label.

CLINICAL STUDIES

Sponsor's proposal:

S. aureus Bacteremia/Endocarditis

(b) (4)

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(b) (4)

COMMENTS:

1. In addition to the point estimates, the appropriate confidence intervals for the treatment difference should be included in the table to provide a clearer understanding of the variability of the results. This is consistent with the Guidance for Industry: Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format.
2. As the primary endpoint was based on the IEAC final diagnosis and not on the entry diagnosis, success rates by entry diagnosis should not be included in the table.
3. If efficacy data in patients with infective endocarditis is to be included in this section, it is important to inform the practitioner as to why the IE data was considered to be limited. This includes the fact that the numbers were small, efficay rates were low, and that definite IE was identified only in a limited number of patients.This information will provide the practitioner a better understanding of the limitations of the data.
4. As discussed in the WARNINGS section, it is not appropriate to divide the comparator group into those treated with vancomycin and those treated with semi-synthetic penicillin.
5. As uncomplicated and complicated RIE were considered different diagnostic subgroups in the IEAC determined final diagnoses, the data should be presented as such (b) (4)
6. Mortality data on left-sided IE patients need not be inlcuded in this section as left-sided IE is not being sought as an indication. As this was an all-comers study, it will suffice to limit the mortality data to all-comers rather than the sub-groups.

REFERENCES

1. Li JS, Sexton DJ, Mick N et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000.30(4):633-8.
2. Baddour LM, Wilson WR, Bayer AS et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. Circulation. 2005 Jun 14;111(23):e394-434.
3. Marty FM, Yeh WW, Wennersten CB, et al. Emergence of a clinical daptomycin-resistant Staphylococcus aureus isolate during treatment of methicillin-resistant Staphylococcus aureus bacteremia and osteomyelitis. J Clin Microbiol. 2006 Feb;44(2):595-7
4. Hirschwerk D, Ginocchio CC, Bythrow M, Condon S. Diminished susceptibility to daptomycin accompanied by clinical failure in a patient with methicillin-resistant Staphylococcus aureus bacteremia. Infect Control Hosp Epidemiol 2006 Mar;27(3):315-7.
5. Vikram HR, Havill NL, Koeth LM, Boyce JM. Clinical progression of methicillin-resistant Staphylococcus aureus vertebral osteomyelitis associated with reduced susceptibility to daptomycin. J Clin Microbiol. 2005 Oct;43(10):5384-7.
6. Patel JB, Jevitt LA, Hageman J, McDonald LC, Tenover FC. An association between reduced susceptibility to daptomycin and reduced susceptibility to vancomycin in Staphylococcus aureus. Clin Infect Dis. 2006 Jun 1;42(11):1652-3

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/s/

Sumathi Nambiar
5/10/2006 11:51:10 PM
MEDICAL OFFICER

Medical Officer Review

NDA Number:	21572
Document Numbers:	SE1-008
Submission:	Complete Response to Action Letter Dated March 24, 2006 Written Request for Meeting with FDA
Product:	Cubicin™ (daptomycin for injection)
Sponsor/Applicant:	Cubist Pharmaceuticals
Date of Submission:	March 27, 2006
Medical Officer:	Alfred F. Sorbello, DO

Submission Details: This document was received in print and electronic form as the complete response ("resubmission") from the applicant to the action letter dated March 24, 2006 for the priority review efficacy supplement that was originally submitted to the Division on September 26, 2005. The resubmission materials include a meeting request, proposed labeling, and clarifying information.

Background

The efficacy supplement SE1-008 for NDA 21572 was submitted by the applicant on September 26, 2005 for the proposed labeled indication of daptomycin in the treatment of *Staphylococcus aureus* bacteremia (SAB) including those with known or suspected endocarditis caused by methicillin-susceptible and methicillin-resistant strains. Following a priority review by the FDA, the supplement was assessed as approvable pending agreement on the product label in relation to the Indications and Usage, Clinical Studies, Dosage and Administration, and Clinical Pharmacology sections, and inclusion of data on persisting and relapsing *S. aureus* (PRSA) bacteremias, reduced susceptibility of *S. aureus* to study drug emerging during treatment, and implications of PRSA and reduced susceptibility for patient outcomes. The efficacy supplement was discussed at a meeting of the Anti-Infective Drug Advisory Committee on March 6, 2006 and at a CDER Regulatory Briefing on April 20, 2006.

Initial FDA Proposed Label based on Priority Review of the Efficacy Supplement:

In response to the Sponsor's original proposed labeled indication and based upon a thorough scientific and statistical assessment of the efficacy and safety data by the multidisciplinary FDA review team, the Division submitted a proposed label to the Sponsor on March 14, 2006 containing specific proposed text for the Indications and Usage, Warnings, and Clinical Studies Sections as follows:

INDICATIONS AND USAGE

Staphylococcus aureus bacteremia (SAB) without concomitant infective endocarditis caused by methicillin-susceptible and methicillin-resistant strains. The efficacy of CUBICIN in patients with infective endocarditis due to *S. aureus* has not been demonstrated. CUBICIN has not been studied in patients with osteomyelitis, prosthetic valve endocarditis, meningitis, and deep organ infections due to *S. aureus*.

WARNINGS

Persistent and relapsing *S. aureus* (PRSA) bacteremias were observed more frequently among daptomycin-treated patients compared to patients receiving standard of care. (See CLINICAL STUDIES). Six daptomycin-treated patients, including three patients with infective endocarditis, had *S. aureus* blood culture isolates that were susceptible to daptomycin at baseline and exhibited rising MICs (≥2 μg/ml) to daptomycin during or immediately following therapy. All six patients were failures at the primary efficacy endpoint, and two patients with infective endocarditis died subsequently. In order to monitor daptomycin-treated patients with *S. aureus* bacteremia for the development of PRSA infections and reduced susceptibility to the drug, blood cultures and daptomycin susceptibility testing by MIC using a standardized procedure should be repeated on a regular basis.

CLINICAL STUDIES

S. aureus *Bacteremia (SAB)*

(b) (4)

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Sponsor Responses, FDA-Sponsor Telecons, and Face-to-Face FDA-Sponsor Meetings

Following a review of the Division's proposed labeling, the Sponsor provided a written response on March 17, 2006 expressing dissatisfaction with the proposed labeling, and a follow-up telecom was held to discuss the labeling issues on March 20, 2006. An additional telecom was conducted with the Sponsor on March 21, 2006, and face-to-face meetings were conducted with the Sponsor on March 23, 2006 and March 24, 2006 (PDUFA action date). An approvable letter was issued to the Sponsor on March 24, 2006. A face-to-face meeting was conducted with the Sponsor, management from the Office of Antimicrobial Products and the Office of New Drugs, and the FDA Review Team on April 26, 2006.

Sponsor Proposed Label submitted as part of the Complete Response to Action Letter of March 24, 2006

The sponsor has proposed the following changes to the package insert text in the Indications and Usage, Precautions, Dosage and Administration, and Clinical Studies sections. Revisions to the Clinical Pharmacology section are not detailed in this report and should be referred to the report of the Clinical Pharmacology reviewer.

INDICATIONS AND USAGE

(b) (4)

(Medical Officer Comments: Based on the Clinical Review of efficacy supplement SE1-008, the data provided was insufficient to demonstrate the efficacy of daptomycin in the treatment of S. aureus infective endocarditis (including right- and left-sided disease) and does not satisfy the requirements of the regulations specified in 21 CFR 314.126 regarding adequate and well-controlled studies and substantial evidence of effectiveness. The specificity of the diagnosis of infective endocarditis was questionable in a substantial number of cases and was compounded by inter-observer variability in the interpretation of echocardiograms between the local and central echolabs. The efficacy of daptomycin in patients with osteomyelitis, prosthetic valve endocarditis, meningitis, and deep organ infections due to S. aureus was not a pre-specified objective or endpoint for the study, and the efficacy of the drug in patients with those complications was not assessed

prospectively in a systematic manner. As the study protocol did not require all study subjects to have a diagnostic imaging evaluation to rule out sequestered foci of infection, the potential relationship between persisting and relapsing bacteremais and sequestered foci cannot be elucidated completely from the study results.

The Sponsor's proposed text regarding patients with persisting and relapsing bacteremias is generic and is not clearly correlated with actual study results in this section. Among patients treated with daptomycin, the potentially serious implications of persisting and relapsing S. aureus bacteremias associated with reduced susceptibility to daptomycin emerging during treatment with the drug are not effectively communicated to the prescriber.)

PRECAUTIONS

(b) (4)

(Medical Officer Comments: In consideration of the high inherent morbidity and mortality associated with S. aureus bacteremia and endocarditis, the proposed labeling for the Precautions Section is not sufficient to communicate the potential risks of clinical failure, emergence of metastatic sites of infection, and death as observed among daptomycin-treated patients compared to comparator-treated patients in pivotal study DAP-IE-01-02. Based on the assessment of efficacy supplement SE1-008 as detailed in the Clinical Review report, labeling in the Warnings Section is warranted in view of the clinical concerns underscored by the frequency of clinical failures and deaths among daptomycin-treated patients with PRSA infections and S. aureus blood culture isolates that exhibit reduced susceptibility to daptomycin during or immediately following treatment with the drug. The regulations specified in 21 CFR 201.57(e) regarding warnings to describe serious adverse reactions, potential safety hazards, and special problems that may lead to death or serious injury for which a causal relationship need not have been proved are particularly pertinent to this recommendation.

In addition, the data in the second paragraph describing the experience in both treatment groups with respect to failure of treatment due to persisting or relapsing S. aureus infections (19/120 (15.8%) CUBICIN-treated, (b) (4) *vancomycin-treated, and*

(b) (4) *anti-staphylococcal semi-synthetic penicillin-treated patients) is incomplete and potentially misleading. Table 1 below summarizes the Sponsor and FDA data on persisting and relapsing bacteremias and persisting infections (without bacteremia) stratified by treatment group and baseline pathogen:*

Table 1: Persisting and Relapsing *S. aureus* (PRSA) Bacteremias and Persisting *S. aureus* Infections (without persisting bacteremia), ITT population

		Daptomycin N=120	Vancomycin N=53	SSP +/- Vancomycin* N=62
Sponsor	Total PRSA	n=19	n=9	n=2
	MSSA	7/74 (9.5%)	0/10 (0%)	2/60 (3.3%)
	MRSA	12/45 (26.7%)	9/43 (20.9%)	0/1 (0%)
	No baseline pathogen	1	0	1
FDA	Total PRSA	n=21	n=9	n=2
	MSSA	9/74 (12.2%)	0/10 (0%)	2/60 (3.3%)
	MRSA	12/45 (26.7%)	9/43 (20.9%)	0/1 (0%)
	No baseline pathogen	1	0	1

*SSP = semi-synthetic anti-staphylococcal penicillin; MSSA=methicillin-susceptible *S. aureus*; MRSA=methicillin-resistant *S. aureus*

The Sponsor identified a total of 30 persisting and relapsing S. aureus (PRSA) bacteremias and persistent infections, including 19 in the daptomycin group and 11 in the comparator group (vancomycin plus SSP+/-vancomycin). Two additional PRSA cases among daptomycin-treated patients were identified during the FDA review of the efficacy supplement bringing the total to 21 in the daptomycin group. The two cases involved patients with PRSA bacteremia due to methicillin-susceptible S. aureus (MSSA).

In terms of the overall frequency of PRSA bacteremias and persistent infections, the study was designed to compare daptomycin to combined comparator (vancomycin plus SSP+/-vancomycin experience) for which the data revealed 19/120 (15.8%) daptomycin-treated and 11/115 (9.6%) comparator-treated patients based on the Sponsor's compilation of PRSA cases. The overall frequency of PRSA bacteremias and persistent infections based on the FDA analysis was almost two-fold higher in the daptomycin group [21/120 (17.5%)] compared to comparator-treated patients [11/115 (9.6%)]. However, the data was not depicted in this format by the Sponsor.

The data depicted in the Precautions Section of the Sponsor's proposed labeling separates the combined comparator arm into two treatment subgroups for which the study was not designed nor powered, and the Sponsor does not distinguish the demographics of the daptomycin and comparator subgroups by baseline pathogen. In that regard, there were 74 daptomycin-treated patients with MSSA and 45 with methicillin-resistant S. aureus (MRSA) bacteremia, 10 vancomycin-treated patients with MSSA and 43 with MRSA bacteremia, and 60 SSP+/- vancomycin-treated patients with MSSA and one with MRSA bacteremia. As depicted in Table 1, the frequency of PRSA bacteremias and persisting infections in the daptomycin group was much higher compared to the experience among vancomycin- and SSP+/-vancomycin treated patients

irrespective of the methicillin susceptibility of the baseline S. aureus isolate. This data should be described in the label to accurately reflect the study's results.
The Sponsor attributed failures due to PRSA bacteremias to deep-seated infections for which the patients did not receive surgical intervention. However, this is a presumptive clinical statement for which the Sponsor has not provided adequate objective supportive data from clinical trials or the medical literature to substantiate the efficacy of the daptomycin in comparable subjects with PRSA bacteremia and deep-seated infections for whom appropriate surgical interventions had been performed.)

DOSAGE AND ADMINISTRATION

***Staphylococcus aureus* Bloodstream Infections (bacteremia), including those with right-sided endocarditis, caused by Methicillin-susceptible and Methicillin-resistant Strains:**

(b) (4)

(Medical Officer Comments: (b) (4) *According to the FDA analysis, the following table depicts the median duration of treatment for patients who completed therapy in the daptomycin group in pivotal study DAP-IE-01-02:*

Table 2: Duration of Daptomycin Therapy among Patients who Completed Treatment (ITT)

IEAC Final Diagnosis	n	Median (days)	Minimum (days)	Maximum (days)
Left IE	4	14	12	42
Complicated Right IE	8	28	14	42
Uncomplicated Right IE	4	14	14	28
Complicated bacteremia	37	23	11	74
Uncomplicated bacteremia	27	14	11	28

IE=infective endocarditis; IEAC=Independent External Adjudication Committee
n=number of patients

(b) (4)

(b) (4)

Finally, as previously described in the Clinical Review report, the data provided in the efficacy supplement do not provide substantial evidence of the efficacy of daptomycin in the treatment of S. aureus infective endocarditis [including right- and left-sided disease]. The performance of daptomycin in patients with infective endocarditis (as identified by the Adjudication Committee) could not be determined for the following reasons: All cases were not echocardiographically-confirmed, local and central echocardiogram interpretations were disparate in 18/53 (34%) patients indicative of substantial inter-observer variability, and the low success rates, small sample size, and lack of assay sensitivity in both treatment groups limited the ability to determine a true treatment effect. Consequently, all references to right-sided endocarditis in the subtitle and all recommendations related to the dosage and administration of daptomycin in the treatment of right-sided endocarditis should be removed from this section.)

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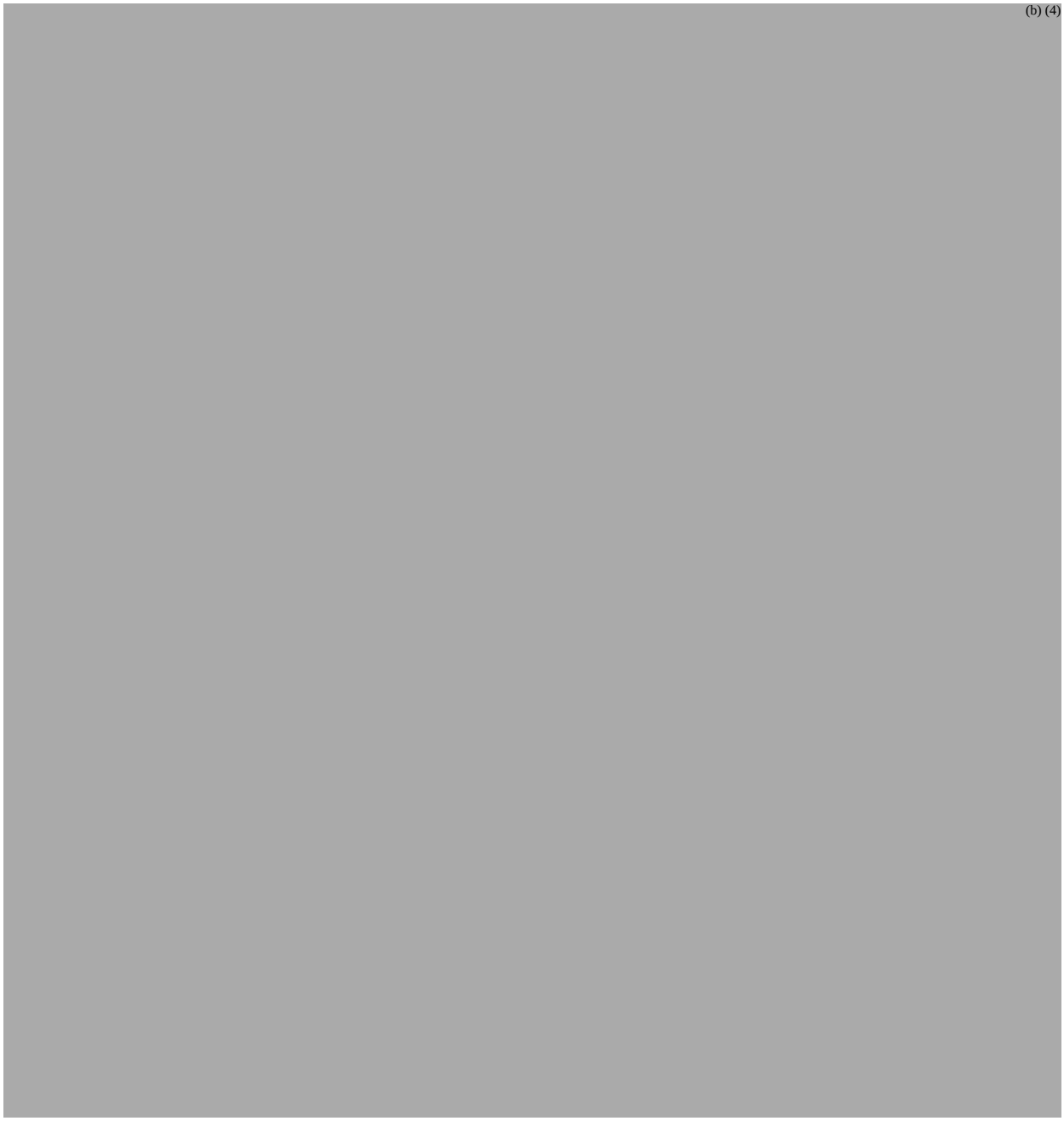
CLINICAL STUDIES

S. aureus Bacteremia/Endocarditis



(Medical Officer Comments: To more accurately reflect the experience in the pivotal study, the paragraph above should also state that 76% of study subjects had an infection within 30 days of onset of the S. aureus bacteremia. In addition, as classification of study subjects at entry based on modified Duke criteria lacks specificity, there should be information added to the end of the paragraph to reflect the final diagnoses of the patients in each of the Entry diagnosis categories: definitie, possible, and not

endocarditis. Table 2 below depicts the poor correlation between Possible endocarditis as an entry diagnosis and infective endocarditis (IE) as the patient's final diagnosis.

Table 2:Correlation of IEAC Entry and Final Diagnoses

		IEAC Final Diagnosis			
		Daptomycin (n=120)		Comparator (n=115)	
		Bacteremias*	IE**	Bacteremias	IE
IEAC Entry Diagnosis	Definite IE	0	17	0	20
	Possible IE	63	10	66	5
	Not IE	29	1	24	0
	Totals	*92*	*28*	*90*	*25*

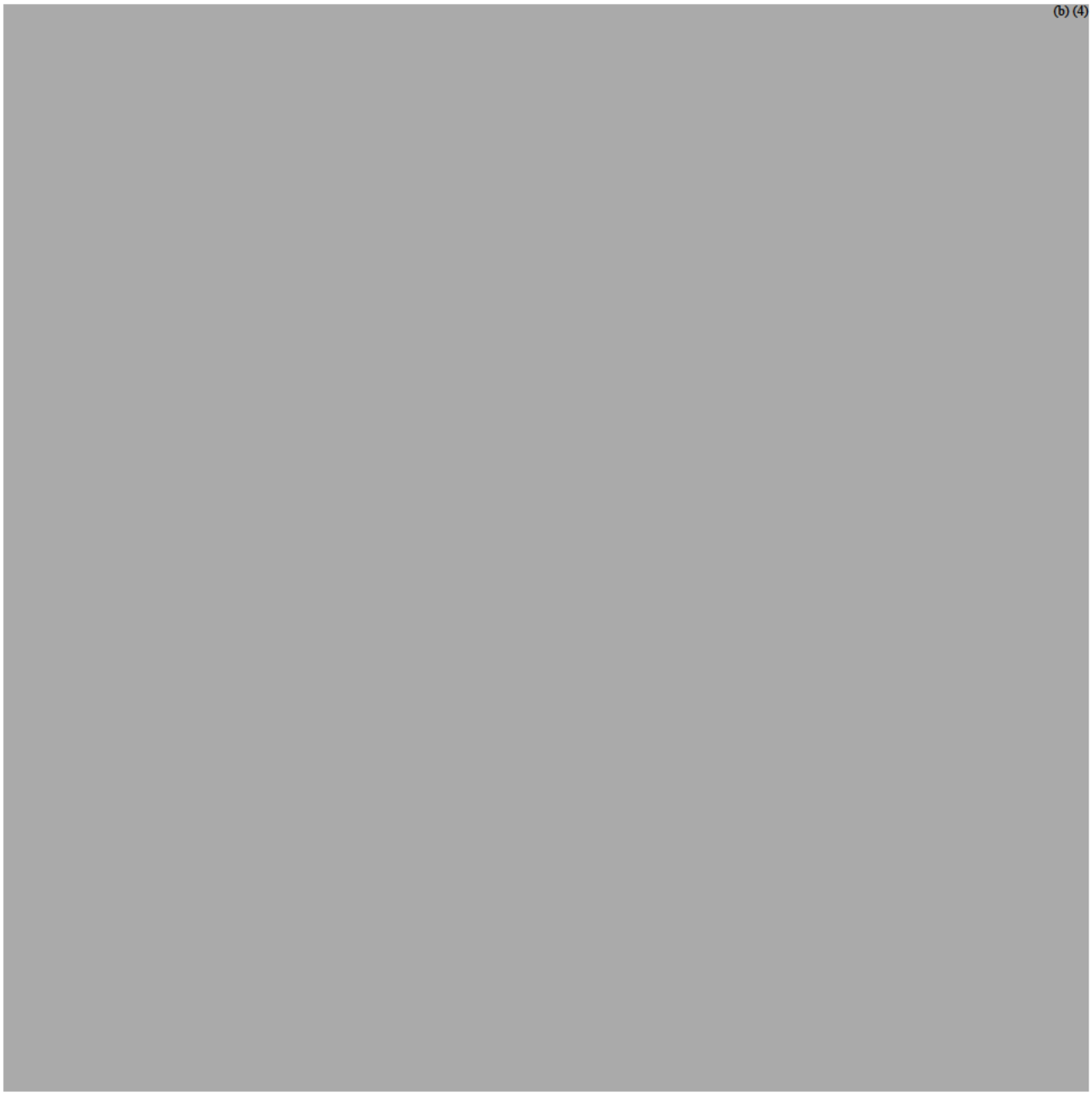
*includes complicated and uncomplicated bacteremia
**includes complicated and uncomplicated right IE and left IE

As depicted above, only 13.7% of daptomycin-treated subjects classified as having possible IE at entry actually had IE as the final diagnosis. Similarly, only 7% of comparator-treated sujects classified as having possible IE at entry actually had a IE as the final diagnosis.)

(b) (4)

(Medical Officer Comments: There are no provisions regarding (b) (4) (b) (4) *in the protocol-specified criteria for complicated and uncomplicated bacteremia. According to the protocol-specified definitions, the patient must not have IE according to modified Duke criteria. Thus, the proposed wording about* (b) (4) (b) (4) *is vague and confusing for prescribers and does not reflect the actual criteria used in the study. Due to lack of specificity, modified Duke criteria should not be misconstrued* (b) (4)

(b) (4)



(Medical Officer Comments: Table 12 should be labeled to indicate that the data is derived from the Intent-to-Treat (ITT) population. In addition to the point estimates, the appropriate confidence intervals should be included in the table to provide evidence of the variability of the results.

The lisings of success rates by Entry Diagnosis should be deleted from the table and only the success rates by Final Diagnosis should be included. (b) (4) (b) (4) (b) (4) *. In uncomplicated RIE, the Adjudication Committee success rates were 3/6 (50%) for daptomycin and 1/4 (25%) for comparator. In complicated RIE, the Adjudication Committee success rates were 5/13 (38.5%) for daptomycin and 6/12 (50%) for comparator).*

(b) (4)

(Medical Officer Comments: A sentence should be added to this section to describe the deaths among subjects with bacteremia. In that regard, there were 15/92 in the CUBICIN arm and 11/90 in the comparator arm with bacteremia who died during the study.)

(b) (4)

(Medical Officer Comments: In relation to the paragraph regarding failure of treatment due to persisting and relapsing S. aureus infections, please refer to the comments following the Sponsor's proposed text for the Precautions Section of the label.)

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Medical Officer Review of US Food and Drug Administration AERS Reports

Based on a retrospective review of post-marketing adverse event reports submitted to the US FDA Adverse Event Reporting System (AERS) during 2004-2006, nine cases of clinical and microbiological failure and PRSA infections associated with reduced susceptibility of *S. aureus* to daptomycin emerging during treatment with the drug were identified. The cases are summarized in Table 3 below:

Table 3: Post-marketing AERS reports involving clinical and microbiological failure, PRSA infections, and reduced susceptibility of *S. aureus* to daptomycin emerging during treatment with the drug

Year of report	Age/Gender	Infection site	Pathogen	Dosage of Daptomycin	Initial MIC	Highest MIC	Death
2004	49/M	prosthetic valve endocarditis	MRSA	6 mg/kg q48h	1	2-4	yes
2004	87/F	septic arthritis, bacteremia, epidural abscess	MRSA	6 mg/kg q24h-q48h	0.25	4	no
2004	61/F	bacteremia and vertebral osteomyelitis	MRSA/VISA	6 mg/kg q24h	0.5	4	no
2005	45/M	bacteremia and osteomyelitis	MRSA	5.3 - 6 mg/kg q24h	0.25	1	no
2005	73/M	left knee prosthetic joint	MRSA	4 - 6 mg/kg q24h	0.25	1.5	no
2005	64/M	wound infection, thigh abscess, infected right prosthetic hip, bacteremia	MRSA	6 mg/kg q24h	0.5	8	yes
2006	64/F	Bacteremia, septic arthritis left ankle*, cSSSI right leg	MRSA	6 – 8 mg/kg q24h	NR	4	no
2006	61/M	bacteremia and osteomyelitis	MRSA	6 mg/kg q24h	0.5	2-4	no
2006	92/F	bacteremia, infected pacemaker site with vegetation on pacer wire	MRSA	6 mg/kg q24h	<0.75	2	yes

M=male; F=female; MRSA = methicillin-resistant *Staphylococcus aureus*; VISA = vancomycin-intermediate *S. aureus*; cSSSI=complicated skin and skin structure infection; NR=not reported; MIC=minimum inhibitory concentration (µg/ml); *eventually required left below-the-knee amputation

As depicted in the table above, all of the cases involved MRSA as the principal pathogen. The patients had varied primary infections sites, including endocarditis, prosthetic device-related infections, or complicated bacteremias with sequestered foci of infection. The dosage of daptomycin administered was 6 mg/kg every 24 hours (similar to the dosage used in the pivotal study provided in the efficacy supplement) in all cases, except for one patient with chronic renal failure on hemodialysis who was dosed on an every 48 hours basis. There were three deaths among the nine patients. Of the cases listed in the table above, three have been published in peer-reviewed medical journals [1-3]. The true

incidence of clinical and microbiological failure, PRSA infections, and reduced susceptibility of *S. aureus* to daptomycin emerging during treatment with the drug could not be determined on the basis of the case reports cited in AERS. As AERS includes mandatory reports submitted by pharmaceutical drug manufacturers and voluntary reports submitted by consumers and health professionals, voluntary reporting tends to underestimate the actual occurrence rate of adverse drug reactions. The total at-risk population of individuals treated with daptomycin for bacteremia, infective endocarditis, and complicated deep organ staphylococcal infections is unknown.

Case Reports from the Medical Literature

A PubMed search of the English-language medical literature revealed two case reports of clinical failure associated with reduced susceptibility to daptomycin during the course of daptomycin therapy [4, 5]. The reports described patients with bacteremia and osteomyelitis due to methicillin-resistant *S. aureus* (MRSA).

Medical Officer Comments and Conclusions

From the clinical perspective, the Sponsor's resubmission (including revised labeling) does not provide any new scientific evidence to substantiate labeling daptomycin for use in right-sided endocarditis. In addition, the proposed label does not provide adequate risk communication to prescribers related to persisting and relapsing *S. aureus* bacteremia, reduced susceptibility to daptomycin emerging during treatment with the drug, and subsequent clinical failure, metastatic foci of infection, and death. As described in this report, nine cases of clinical failure (including three deaths) have been reported in the AERS system since 2004 involving the emergence of daptomycin-nonsusceptible *S. aureus* strains during daptomycin therapy, and five cases have been published in the medical literature [1-5]. This is critical information that must be clearly and prominently communicated to prescribers in view of the potentially serious implications for patient outcome.

As described in the Clinical Review of efficacy supplement SE1-008 for NDA 21572, daptomycin was non-inferior to standard of care (semi-synthetic antistaphylococcal penicillin or vancomycin) in the treatment of *S. aureus* bacteremia in adults due to methicillin-susceptible and methicillin-resistant strains based on an all-comers analysis. However, the data was insufficient to demonstrate the efficacy of daptomycin in the treatment of *S. aureus* infective endocarditis (right-and left-sided disease). The efficacy of daptomycin in patients with osteomyelitis, prosthetic valve endocarditis, meningitis, and deep organ infections due to *S. aureus* was not assessed. There was no uniform requirement for all study subjects to have systematic diagnostic imaging studies for evidence of sequestered foci of infection prospectively. Thus, the magnitude and extent of metastatic complications of *S. aureus* bacteremia and endocarditis in the study population and the efficacy of daptomycin in eradicating such foci of infection could not be assessed. Pivotal study DAP-IE-01-02 involved a pathogen-driven, all-comers target population having at least one positive blood culture for *S. aureus* irrespective of the underlying clinical setting. However, the relevance of the findings in the all-comers target population to the reference population of all subjects with *S. aureus* bacteremia and infective endocarditis was limited. As a consequence of limitations related to study

design, conduct, and generalizability, the lack of substantial evidence for efficacy in infective endocarditis from study DAP-IE-01-02, and the lack of corroborative data from earlier phase 2 and 3 studies, the following labeling recommendations are reproduced from the Clinical Review report:

(1) INDICATIONS AND USAGE Section: *Staphylococcus aureus* bacteremia (SAB) without concomitant infective endocarditis caused by methicillin-susceptible and methicillin-resistant strains. The efficacy of CUBICIN in patients with infective endocarditis due to *S. aureus* has not been demonstrated. CUBICIN has not been studied in patients with osteomyelitis, prosthetic valve endocarditis, meningitis, and deep organ infections due to *S. aureus*.

(2) WARNINGS: Persistent and relapsing *S. aureus* (PRSA) bacteremias were observed more frequently among daptomycin-treated patients compared to patients receiving standard of care. (See CLINICAL STUDIES). Six daptomycin-treated patients, including three patients with infective endocarditis, had *S. aureus* blood culture isolates that were susceptible to daptomycin at baseline and exhibited rising MICs $\geq$2 μg/ml to daptomycin during or immediately following therapy. All six patients were failures at the primary efficacy endpoint, and two patients with infective endocarditis died subsequently. In order to monitor daptomycin-treated patients with *S. aureus* bacteremia for the development of PRSA infections and reduced susceptibility to the drug, blood cultures and daptomycin susceptibility testing by MIC using a standardized procedure should be repeated on a regular basis. Antibiotic treatment should be adjusted based on test results.

The labeling recommendations above are underpinned by the following evidence: (1) the lack of substantial evidence from study DAP-IE-01-02 to demonstrate the efficacy of daptomycin in the treatment of right-and left-sided infective endocarditis due to *S. aureus,* and (2) the clinical concerns underscored by the frequency of clinical failures and deaths among daptomycin-treated patients with PRSA bacteremias and *S. aureus* blood culture isolates that exhibit reduced susceptibility to daptomycin during or immediately following treatment with the drug. The analysis of post-marketing experience from the AERS system and the case reports from the medical literature further buttresses concerns about the association of reduced susceptibility of *S. aureus* to daptomycin emerging during treatment with the drug, clinical and microbiological failures, and PRSA infections. The recommendations for the Indications and Usage Section and the Warnings Section are in accordance with the labeling requirements for prescription drugs as described in 21 CFR 201.57. In addition, the regulations specified in 21 CFR 314.126(b) regarding substantial evidence of effectiveness and 21 CFR 201.57(e) regarding warnings to describe serious adverse reactions, potential safety hazards, and special problems that may lead to death or serious injury for which a causal relationship need not have been proved are particularly pertinent to the above recommendations. It is recommended that the text described above for the Warning Section should be in bold type.

References

1. Hirschwerk D, Ginocchio CC, Bythrow M, Condon S. Diminished susceptibility to Daptomycin accompanied by Clinical Failure in a Patient with Methicillin-Resistant *Staphylococcus aureus* Bacteremia. *Infect Control Hosp Epidemiol* 2006;27:315-317.

2. Marty FM, Yeh WW, Wennersten CB, Venkataraman L, Albano E, Alyea EP, Gold HS, Baden LR, Pillai SK. Emergence of a Clinical Daptomycin-Resistant *Staphylococcus aureus* isolate during Treatment of Methicillin-Resistant *Staphylococcus aureus* Bacteremia and Osteomyelitis. *J Clin Microbiol* 2006;44(2):595-597.

3. Skiest DJ. Treatment Failure resulting from Resistance of *Staphylococcus aureus* to Daptomycin. *J Clin Microbiol* 2006;44(2):655-656.

4. Hayden MK, Rezai K, Hayes RA, Lolans K, Quinn JP, Weinstein RA. Development of Daptomycin Resistance in vivo in Methicillin-Resistant *Staphylococcus aureus*. *J Clin Microbiol* 2005;43(10):5285-5287.

5. Vikram HR, Havill NL, Koeth LM, Boyce JM. Clinical Progression of Methicillin-Resistant *Staphylococcus aureus* Vertebral Osteomyelitis associated with Reduced Susceptibility to Daptomycin. *J Clin Microbiol* 2005;43(10):5384-5387.

Submitted on May 5, 2006
Submitted by Alfred Sorbello, DO

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Alfred Sorbello
5/5/2006 10:48:31 AM
MEDICAL OFFICER

Sumathi Nambiar
5/5/2006 01:48:17 PM
MEDICAL OFFICER

CLINICAL SAFETY REVIEW

Application Type	NDA 21,572
Submission Number	
Submission Code	
Letter Date	3/24/06
Stamp Date	
PDUFA Goal Date	3/24/06
Reviewer Name	Chuck Cooper, M.D.
Review Completion Date	3/26/06
Established Name	daptomycin
(Proposed) Trade Name	Cubicin
Therapeutic Class	Antibiotic
Applicant	Cubist
Priority Designation	{ P }
Formulation	I.V.
Dosing Regimen	6 mg/kg q 24 hours
Indication	*Staphylococcus aureus* bacteremia
Intended Population	Adult

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY - SAFETY

1.1 Recommendation on Regulatory Action

It is recommended that daptomycin be approved for the treatment of *Staphylococcus aureus* bacteremia, but specifically excluding endocarditis and bacteremia with metastatic sites of infection. In addition, the unique finding of increasing daptomcyin MICs that was observed to have occurred while *on therapy* and was associated with clinical failure should be prominently communicated in the label. Finally, the increased risk of persisting or relapsing *Staphylococcus aureus* infection associated with the use of daptomycin should also be prominently displayed in the label.

1.2 Summary of Clinical Findings - Safety

There were similar numbers of death in each treatment arm, 19 deaths in the comparator arm vs. 18 deaths in the daptomycin arm. However, there was an shorter time to death in the daptomycin arm when compared to comparator, particularly for those patients who died within 42 days of the last dose of therapy. This difference in early death rates may be at least, in part, explained by increased rates of persisting or relapsing Staphylococcus aureus infections in the daptomycin arm (17.5% in the daptomycin arm vs. 9.5% in the comparator arm). Beyond 42 days, the rates of death become similar between the two treatment arms and the causes of death are less clearly linked to a lack of treatment effect.

There were higher rates of infection-related serious adverse events (SAE's) in the daptomycin arm when compared to the comparator arm. In particular, there were higher rates of SAE's that appear to be related to measures of clinical efficacy including the following serious adverse events: Staphylococcus aureus bacteremia, sepsis NOS, and osteomyelitis. These three were the most common serious adverse events in both treatment arms but occurred at a greater rate in the daptomycin arm, 14.2% (17 events) vs. 7.7% (9 events) in the comparator arm. Since these events are likely to be related to the disease under study, such a difference is consistent with decreased efficacy in the daptomycin arm, which may be explained by the finding that daptomycin was associated with increased rates of the on-therapy development of increasing MIC's and subsequent microbiologic failure with increased rates of persisting or relapsing Staphylococcus aureus infection.

Interestingly, there were also higher rates of serious gram-negative infections and gram-negative bacteremias in the daptomycin arm vs. the comparator arm, 10 (8.3%) vs. 0 (0.0%). 6 of these events occurred either on therapy or within 8 days of study drug exposure, and the rest occurred later. One of the daptomycin-treated patients died as a result of their gram-negative infection. This finding may be a reflection of the effect of gentamicin (in the comparator arm) on the gram-negative flora which could extend beyond the average gentamicin exposure of 4 to 5 days.. Because gram-negative bloodstream infections are associated with significant morbidity and mortality, this is an important safety signal and should be communicated prominently in the product label.

Rates of discontinuation due to microbiologic failure were higher in the daptomycin arm than comparator arm, 9 (7.5%) vs. 3 (2.6%), which supports the conclusion that daptomycin may have decreased efficacy compared to comparator. Further supporting this conclusion is the observation that there were increased rates of discontinuation of study drug in the daptomycin arm (5.8% vs. 1.7%) for reasons that might be related to lack of efficacy, specifically, bacteremia, epidural abscess, septic shock, staphylococcal bacteremia, staphyloccoal pneumonia, and osteomyelitis. Numbers of discontinuation due to adverse events overall were similar between the 2 treatment arms, 21 (18.1%) in the comparator arm vs. 20 (16.7%) in the daptomycin arm. There was an increased rate of discontinuation due to renal events in the comparator arm vs. the daptomycin arm, 4.3% vs. 0.8%.

Overall, there were more non-serious common adverse events in the comparator arm than the daptomycin arm. There were increased rates of non-serious nausea (19.8% vs. 10.0%) and diarrhea (18.1% vs. 11.7%) in comparator-treated patients compared to daptomycin-treated patients. There were also increased rates of non-serious peripheral edema (13.8% vs. 6.7%) and arthralgia (11.2% vs. 3.3%) in comparator-treated patients compared to daptomycin-treated patients. Other notable differences include an increased rate of non-serious pneumonia in the comparator-treated patients and an increased rate of pharyngolaryngeal pain in the daptomycin-treated patients.

An analysis of renal toxicity using reported adverse events was difficult to comprehend. This is possibly explained by the open label nature of the trial and the expectation of renal toxicity in the comparator arm. There was no standardized reporting method for renal adverse events, and examination of the data revealed widespread inconsistencies in renal adverse event reporting. For this reason, renal adverse event rates were not helpful in terms of understanding the differences in renal toxicity between the two treatment arms. Therefore, a separate analysis was performed in which renal toxicity was defined as an increase in creatinine percentage by at least 25% and a peak creatinine that increased to above the ULN. Using this definition, there were 25 (21.6%) renal toxic events in the comparator arm vs. 17 (14.2%) in the daptomycin arm. However, the two treatment arms were not balanced with regard to the sub-population with the highest risk of renal toxicity. Specifically, there were more patients in the comparator arm who were 60 years of age or older who received more than the median duration of therapy (26 of these patients in the comparator arm vs. only 11 in daptomycin arm). When this imbalance is corrected and rates of renal toxicity are recalculated, they are found to be 17.2% (20 events) in the comparator arm vs. 14.2% (17 events) in the daptomycin arm.

There was an increased rate of CPK elevations to above 500 U/L for daptomycin-treated patients in this study compared to prior studies, 7.5% in the daptomycin arm vs. 0.9% in the comparator arm. The rate observed in the daptomycin arm of 7.5% was higher than the rate observed in daptomycin-treated patients in the complicated skin and skin structure infection trials where the rate was under 3%. This is likely due to the fact that the drug was being administered at a higher dose (6 mg/kg vs. 4 mg/kg). These events were not serious and did resolve with discontinuation of daptomycin, or in some cases even with continuation of therapy. Prior or concomitant administration of HMG Co-A reductase inhibitors was associated with a higher rate of CPK

elevation to above 500 U/L than in the population without prior or concomitant exposure to HMG Co-A reductase inhibitors (16.7% vs. 5.2%). Three patients discontinued study medication due to increases in CPK.

There were no new findings to suggest hepatotoxicity or neurological toxicity.

The pivotal study provided very limited data on the safety of patients exposed to greater than 28 days of therapy with this disease at this dose, since there were only 14 such patients. This is a potentially important issue because the proposed treatment duration extends to as long as 42 days of therapy. The patient population most likely to require treatment duration longer than 28 days includes those patients with endocarditis or those patients with bacteremia with metastatic sites of infection. Based on the submitted data from the pivotal trial, the safety of this drug at this dose for durations longer than 28 days cannot be determined.

2 INTEGRATED REVIEW OF SAFETY

This review consists of a safety review of the single, pivotal phase 3 study (DAP-0102) submitted by the sponsor. A variety of materials were reviewed including datasets, CRF's, patient profiles, and sponsor reports. Several review tools were utilized including JMP, CrossGraphs, and IReview.

2.1 Adverse Events

2.1.1 Deaths

There were a total of 19 deaths in the comparator arm (16.4%) vs. 18 deaths in the daptomycin arm (15%). Table 1 shows the causes for these deaths.

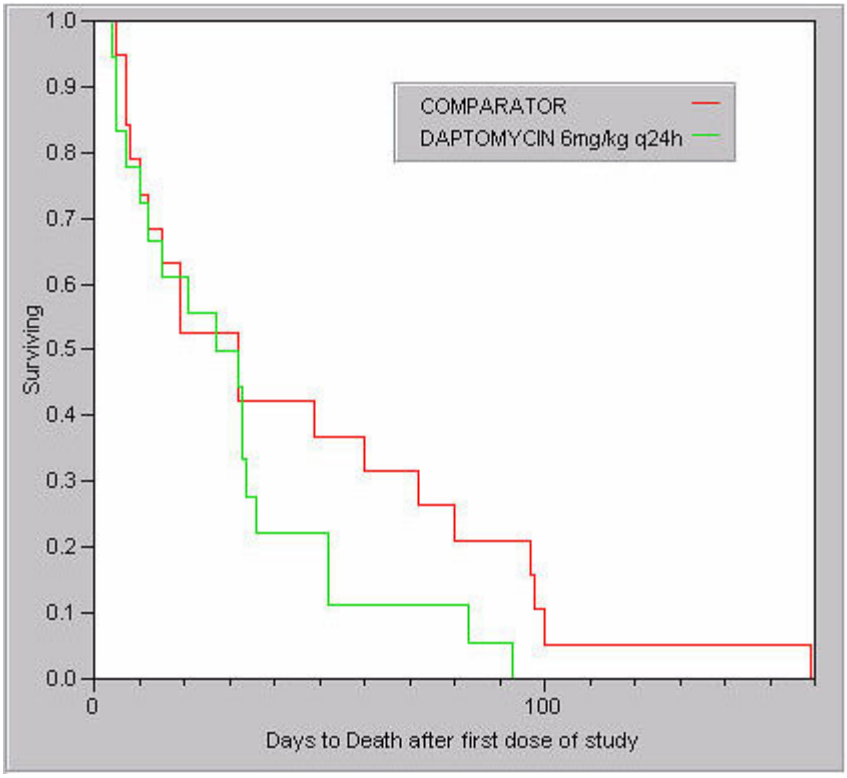
Table 1. Causes of Death by Treatment Arm.

	Daptomycin (n=120)	Comparator (n=116)
	n (%)	n (%)
Total	18 (15%)	19 (16.4)
Sepsis, or Septic Shock	2 (1.7)	4 (3.5)
MI, Cardiac Failure, Cardiac arrest	4 (3.3)	2 (1.7)
Malignancy-related	1 (0.8)	3 (2.6)
Respiratory failure or insufficiency	1	3 (2.6)
Cardiorespiratory arrest	2 (1.7)	0
Multi-organ failure	2 (1.7)	0
Bacteremia	1 (0.8)	0
Hypoxia	1 (0.8)	0
Depression	1 (0.8)	0
Systemic candida, Candida sepsis	1 (0.8)	1 (0.9)
Thrombocytopenia	1 (0.8)	0
Pulmonary embolism	1 (0.8)	0
Infective endocarditis	0	1 (0.9)
Circulatory collapse	0	1 (0.9)
CVA	0	1 (0.9)
Pulmonary embolism	0	0
Diabetes mellitus	0	1 (0.9)
Renal Failure	0	1 (0.9)
Myocardic abscess	0	1 (0.9)

The distribution of causes of death are similar between the two treatment arms. After detailed review of the cases of death, it was difficult to determine causality for reasons related to the complexity of the natural history of the underlying disease under study, the associated morbidity and mortality of the underlying disease, as well as the low success rates in both arms.

One interesting observation was that although the overall number of deaths were similar between the two treatment arms, there was a clear difference in the timing of the deaths. Deaths up until about 28 days after the first dose of study medication were similar in terms of days to death. However, between 28 and 50 days after the first dose of study drug, a greater proportion of daptomycin-treated patients died than did control-treated patients. This finding was confirmed by Dr. Sorbello's calculation of relative risk of death which was higher for daptomycin (2.2) at study day 42 (please see Dr. Sorbello's review). Graph 1 shows the time to death for all deaths according to treatment arm.

Graph 1. Days to Death for All Deaths in Study. (daptomycin=green, comparator = red)



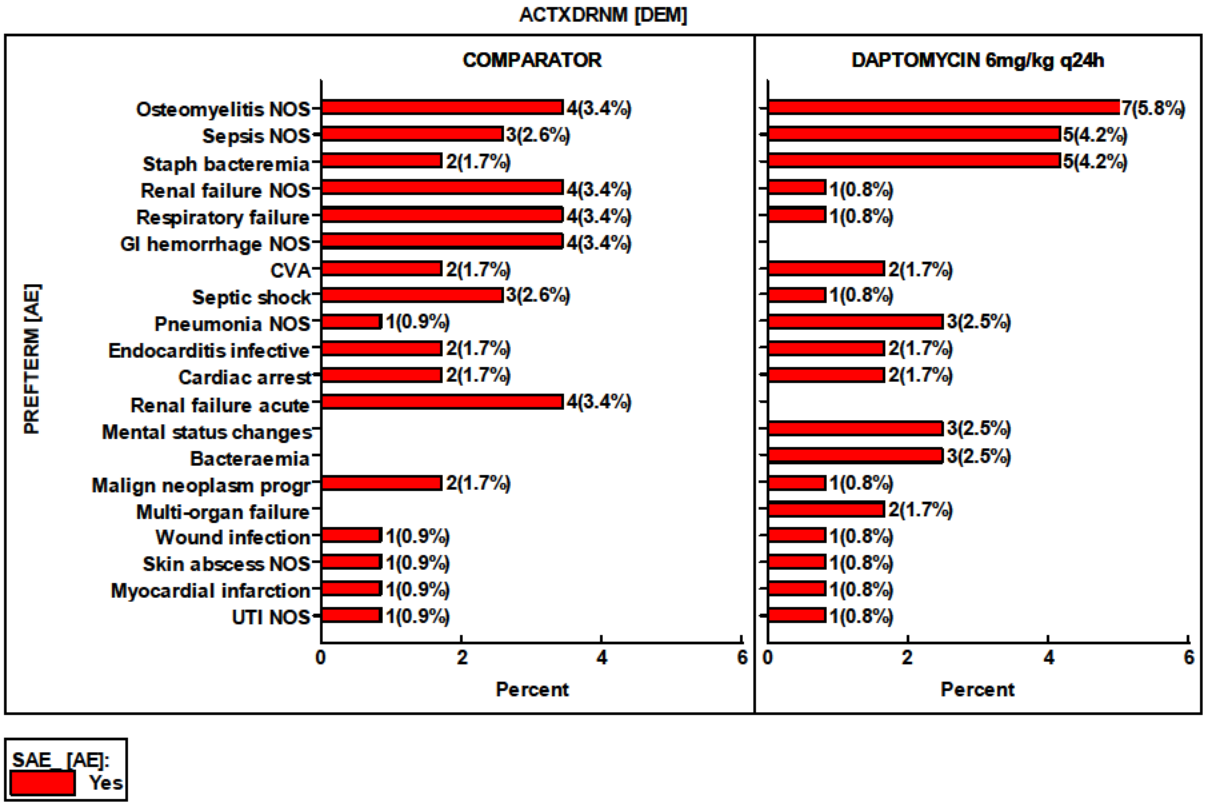
Because the overall number of deaths is relatively small compared to the total number of patients in the study, this difference in time to death is not seen as clearly in a Kaplan-Meir curve which includes non-deaths as well. The association of daptomycin with a more rapid time to death raises questions about possible decreased efficacy mainly because of the increased rate of persistent and relapsing *Staphylococcus aureus* (PRSA) infections seen prior to study day 42 since PRSA was associated with death. By contrast, the deaths that occurred later in the comparator arm were not associated with persistent and relapsing *Staphylococcus aureus* infection. So, although overall there were similar numbers of deaths between the treatment arms, there were more deaths early on in the daptomycin-treated patients, which are partially explained by increased numbers of daptomycin-associated PRSA infections. This is in contrast to the later occurring deaths in the comparator arm which are not as clearly linked to an obvious lack of treatment effect. Also, although not always the case, it is generally understood that the farther out from study drug exposure a death occurs, the less likely it is to be related to the study drug exposure. Indeed, if patients are followed long enough, they all will die, making both treatment arms exactly the same with regard to rates of death. This could potentially partially explain the delayed evening out of the death rates seen in the later window, given the high inherent mortality in this patient population who have multiple co-morbidities.

Other than a possible decrease in efficacy for daptomycin-treated patients resulting in earlier death, there were no clear patterns of causes of death that could be clearly associated with either treatment arm.

2.1.2 Other Serious Adverse Events

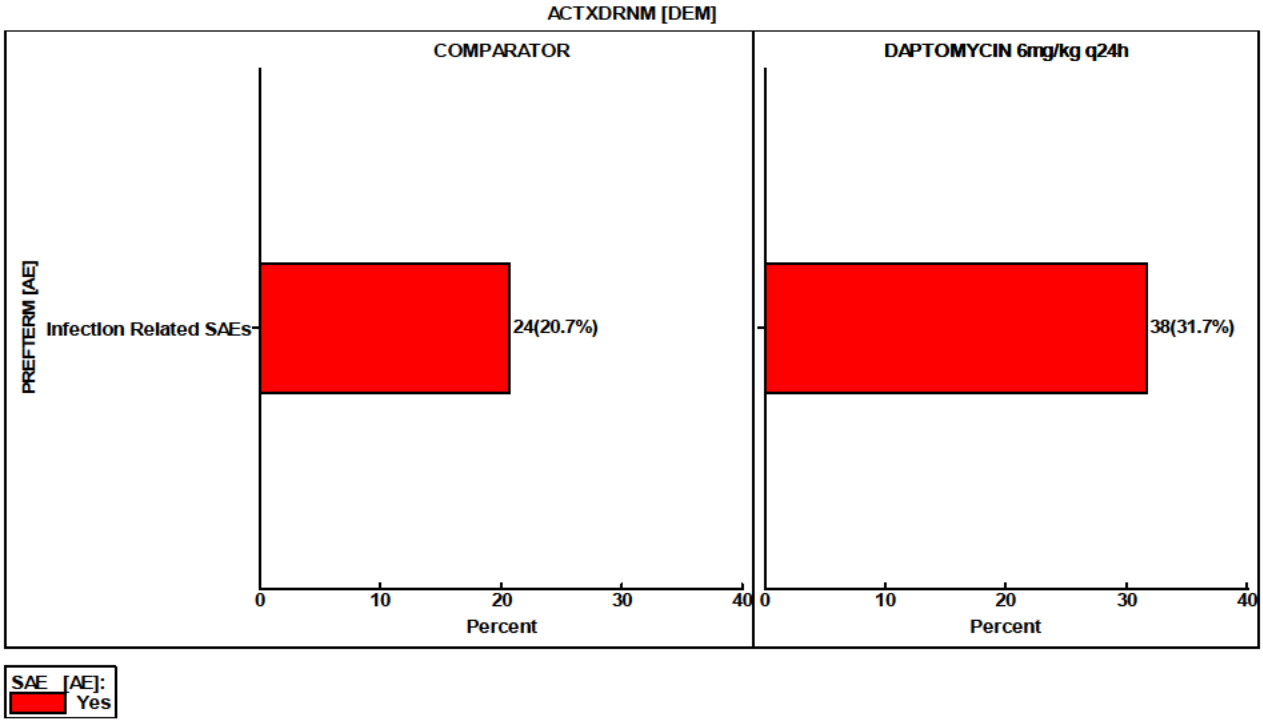
Graph 2 shows the most common serious adverse events by treatment arm. Patients with more than one of the same adverse event are counted only once.

Graph 2. Most Common Serious Adverse Events by Treatment Arm.



Renal SAE's are discussed in detail in sections 2.1.4 and 2.1.5. There were more infection-related SAE's in the daptomycin arm than in the comparator arm and more renal SAE's in the comparator arm than the daptomycin arm. Because of the increased number of infection-related adverse events in the daptomycin arm, analyses were performed looking only at the infection-related SAE's. Graph 3 shows the total number of infection-related SAE's by treatment arm by unique patient number. Patients who experienced more than one SAE are counted once. There were a total of 34 (28.3%) patients who experienced infection-related SAE's in the daptomycin arm vs. 21 (18.1%) in the comparator arm. Graph 3 shows the total number of infection-related SAE's by treatment arm. In this graph, the total number of infection-related SAE's is represented.

Graph 3. Number of Patients Who Experienced an Infection-related SAE by Treatment Arm.



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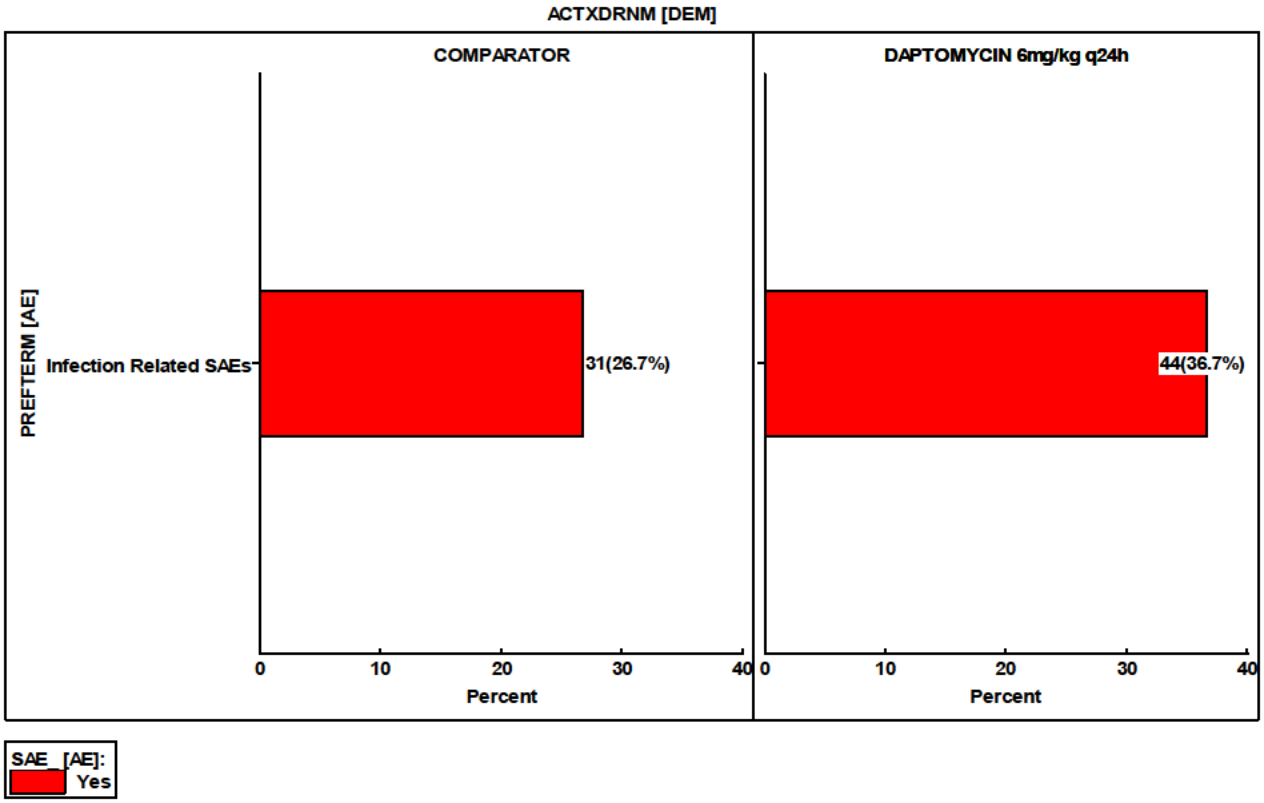
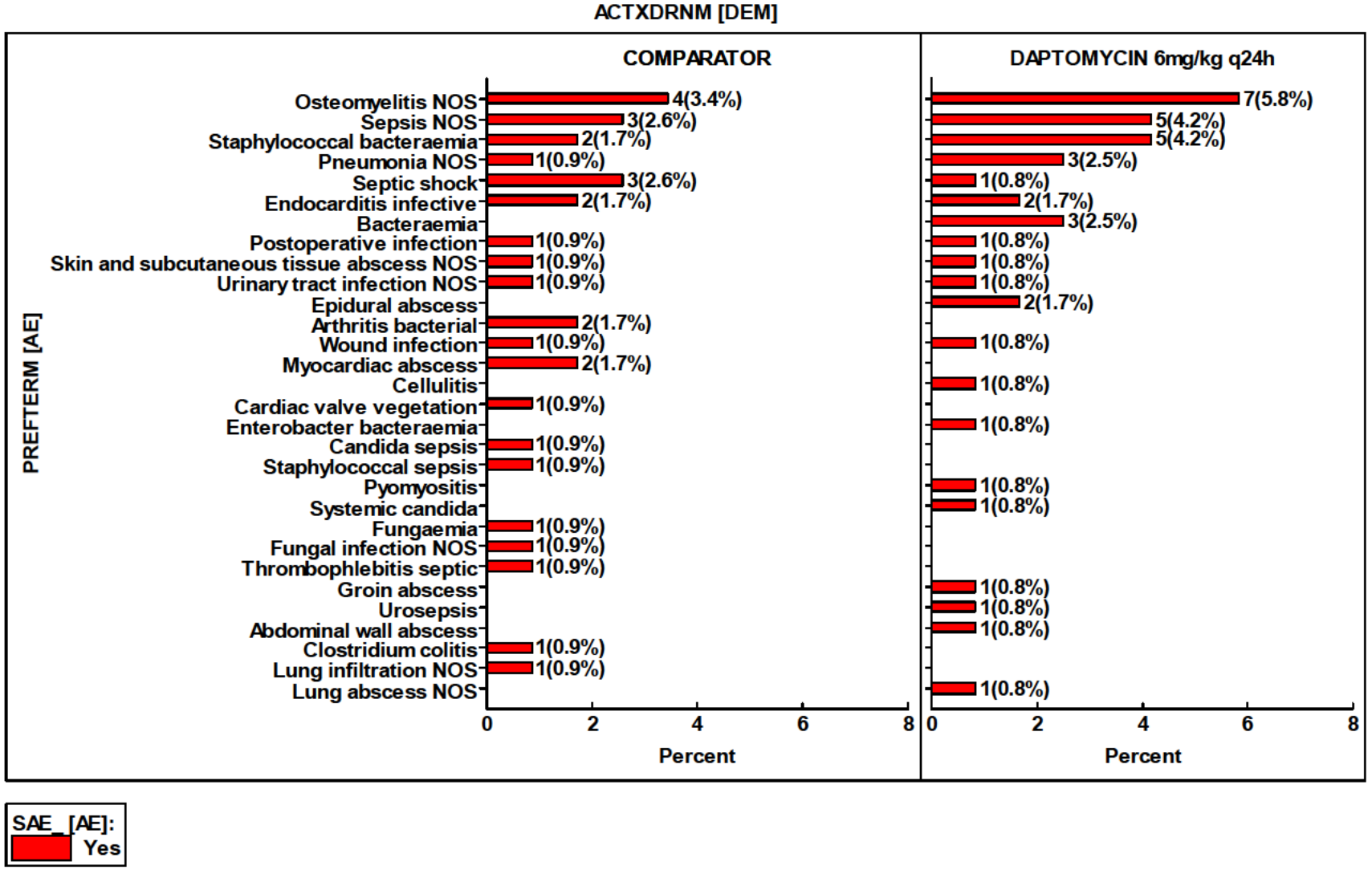
Graph 4. Total Number of Infection-related SAE's by Treatment Arm.



Additional analyses were conducted to understand what was causing this difference in the rates of infection-related SAE's. Graph 5 shows infection-related SAE's by treatment arm and preferred term.

Graph 5. Rates of Infection-related SAEs by Treatment Arm.



Review of infection-related SAE's reveals that there are more instances of infection-related SAE's that are possibly related to the underlying disease under study in the daptomycin arm vs. the comparator arm. These include SAE's such as osteomyelitits NOS, sepsis NOS, and staphylococcal bacteremia which occurred at a rate of 14.2% in the daptomycin arm and 7.7% in the comparator arm. This finding supports other analyses that suggest that the study drug may have decreased efficacy in comparison to the comparator and, therefore, results in more disease-related SAE's. The sponsor has attempted to explain this difference as well as the increased rates in the daptomycin arm of persisting or relapsing *Staphylococcus aureus* infections by claiming that the patients in the daptomycin arm had an increased number of metastatic infections at baseline which were not clearly identified at the time of enrollment. However, because there was no systematic assessment of the presence or absence of metastatic infection at the time of enrollment, this explanation can only be seen as speculation. An equally possible explanation is that patients in the daptomycin arm developed increased rates of metastatic infection as a result of failure to clear the organism from the blood (as evidenced by the increased rate of PRSA and microbiologic failure requiring discontinuation of the drug). Another possible explanation is that daptomycin is not as effective in treating metastatic complications of the underlying disease, which is an explanation with a plausible mechanism given that this drug's activity is highly calcium dependant and given the expected lower calcium concentrations that may exist at the sites of metastatic infection. Given the high inherent morbidity and mortality associated with endocarditis, metastatic *Staphylococcus aureus* infection, and treatment failure of *Staphylococcus aureus* bacteremia, clear data substantiating efficacy in these sub-populations is critical. .

Additional review of the infection-related SAE's revealed an imbalance between the two treatment arms with regard to gram-negative related SAE's. All gram-negative bacteremias were reviewed. There were a total of 36 positive blood cultures from daptomycin-treated patients and 2 positive-blood cultures from comparator-treated patients. The 2 positive blood cultures from 2 patients in the comparator arm were considered as contaminants and included *Pseudomonas oryzihabitans* and *Moraxella atlantae* neither of which required treatment with antibiotics. The 36 positive gram-negative blood cultures in the daptomycin arm came from 13 different patients. 2 of these patients had their gram-negative bacteremia at baseline and one was considered to be a contaminant. The remaining 10 daptomycin-treated patients had gram-negative infections that required antibiotic therapy. These patients are presented in Table 2.

Table 2. Rates of Gram-negative SAEs and Gram-negative Bacteremias Requiring Antibiotic Therapy by Treatment Arm.

	Daptomycin (n=120)	Comparator (n=116)
Gram-negative Infection		
Total	10/120 (8.3%)	0/116 (0.0)
Bacteremia due to *Enterobacter aerogenes*	1 (0.83)	0 (0.0)
Urosepsis with *Pseudomonas aeruginosa* from blood and urine	1 (0.83)	0 (0.0)
Bacteremia due to *Acinetobacter calcoaceticus*	1 (0.83)	0 (0.0)
Bacteremia due to *Klebsiella pneumoniae*	1 (0.83)	0 (0.0)
Sepsis due to gram-negative rod in blood *	1 (0.83)	0 (0.0)
Sepsis due to *Burkholderia spp.* in blood *	1 (0.83)	0 (0.0)
Sepsis due to *Klebsiella pneumoniae* in blood	1 (0.83)	0 (0.0)
Bacteremia due to *Serratia marcescens***		
Bacteremia due to *Klebsiella pneumoniae* **		
Bacteremia due to *Prevotella bivia*	1 (0.83)	0 (0.0)
Bacteremia due to *Serratia marcescens*	1 (0.83)	0 (0.0)
Bacteremia due to *Pseudomonas aeruginosa* and *E. coli****	1 (0.83)	0 (0.0)

*These SAE's occurred at separate times during the study to the same patient. They are included in the total as only 1.
** These two gram-negative bacteremias occurred in the same patient at different times during the study. They are included in the total as only 1.
*** This patient developed hypotension and died. Blood cultures done at time of decompensation revealed these gram-negative organisms.

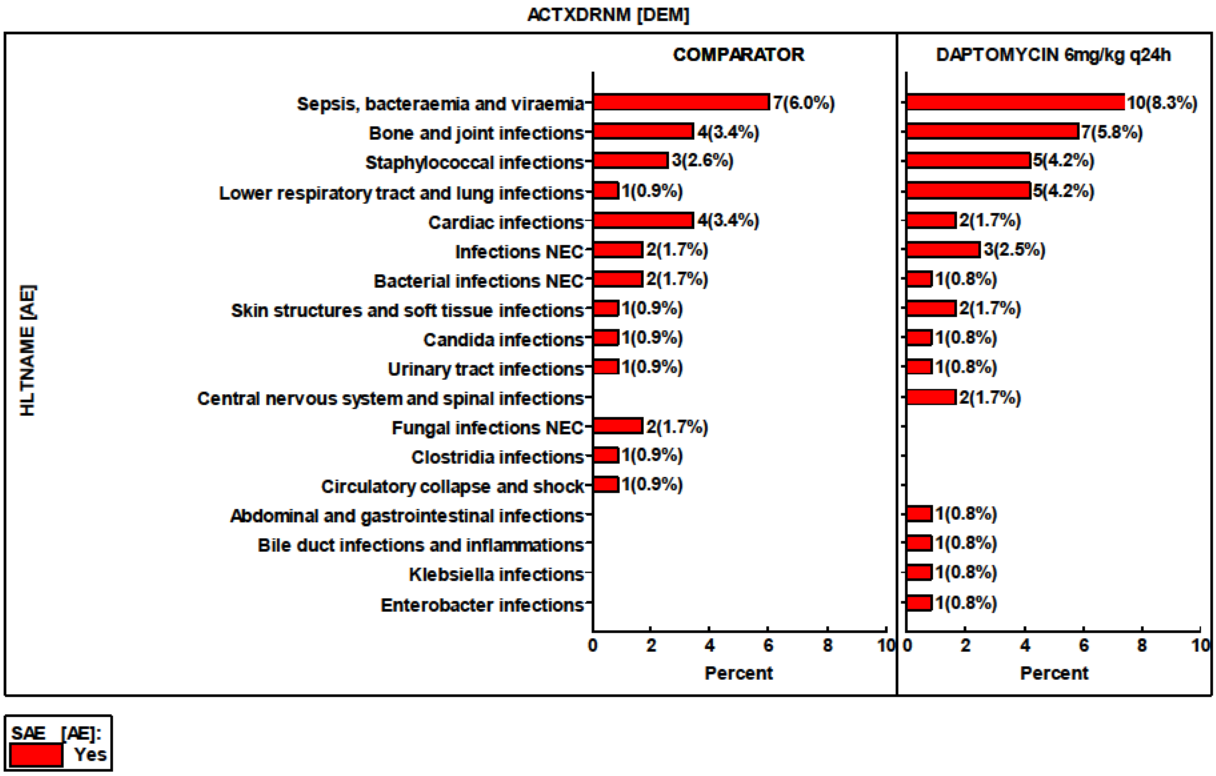
Of these patients, there was one death that likely resulted from the gram-negative infection. Patient (b) (6) who experienced a sudden deterioration and rapidly died. Blood cultures done at the time of deterioration were positive for *E. coli* and *Pseudomonas aeruginosa.*

The gram-negative infections in the daptomycin arm occurred at time points throughout the study. 6 of these 10 patients had their gram-negative infection occur either on therapy or within 8 days of the last dose of therapy. The other 4 patients had their gram-negative infection occur beyond 8 days after the last dose of therapy. This clear trend towards increased numbers of gram-negative infections in the daptomycin arm is possibly related to the use of gentamicin in the comparator arm. Although the gentamicin was only used for 4 or 5 days for the majority of patients who received it, it is possible that this exposure to gentamicin was enough to alter the gram-negative flora to a degree that subsequent gram-negative infections were not seen. Another possibility is that there is some as yet unexplained mechanism for why daptomycin use at this dose in this patient population may result in increased gram-negative infection, such as increased bacterial translocation across the intestinal mucosa.

An analysis was performed looking at infection-related SAEs by MedDRA High Level Group Term and is shown in Graph 6. The purpose of this analysis was to assess the overall number of other non-bacterial infection-related adverse events, in particular, fungal infections. It had been

stated in the advisory committee meeting that although there were more gram-negative SAE's in the daptomycin arm, this was somewhat offset be an increase in fungal SAEs in the comparator arm. This analysis shows that there were a total of 3 fungal SAEs in the comparator arm vs. 2 in the daptomycin arm. This difference is small enough that it cannot be viewed as offsetting the increase in serious gram-negative infections seen in daptomycin-treated patients.

Graph 6. Infection-related SAEs by MedDRA High Level Group Term and Treatment Arm.



2.1.3 Discontinuations and Other Significant Adverse Events

There were a total of 20 patients (16.7%) in the daptomycin arm and 21 patients (18.1%) in the comparator arm who discontinued study medication due to an adverse event. Table 3 shows the adverse events which caused the premature termination of study drug.

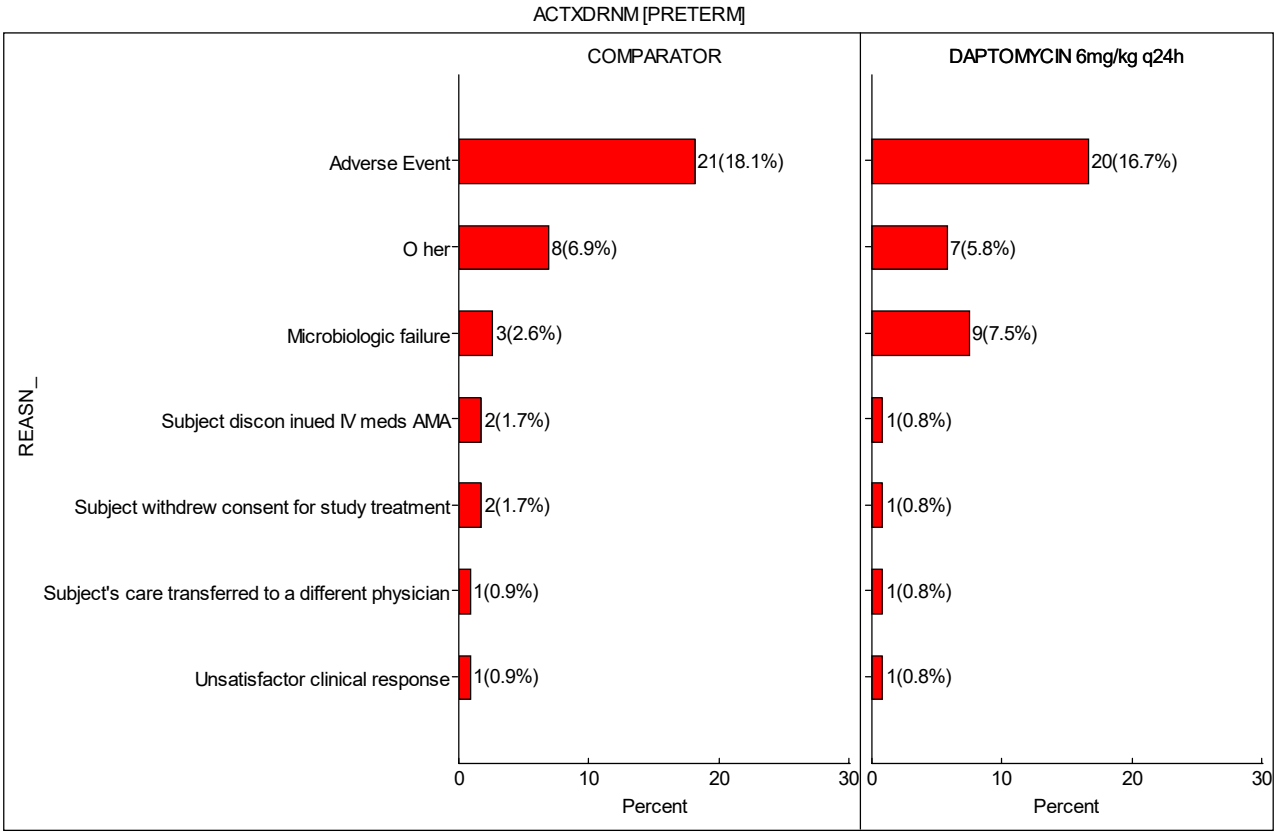
Table 3. Premature Termination of Study Drug by Adverse Event and Treatment Arm.

	Daptomycin (N=120)	Comparator (N=116)
Adverse Event Resulting in D/C of Study Med	n (%)	n (%)
Total	20 (16.7)	21 (18.1)
CPK increased	3 (2.5)	0
Bacteremia	2 (1.7)	0
Rash	3 (2.5)	3 (2.6)
Pyrexia	0	2 (1.7)
Renal failure	1 (0.83)	3 (2.6)
Cardiac arrest	1 (0.83)	1 (0.86)
Diabetic gastroparesis	1 (0.83)	0
Epidural abscess	1 (0.83)	0
Hypoxia	1 (0.83)	0
Osteomyelitis	1 (0.83)	0
Pneumonia staphyloccal	1 (0.83)	0
Septic shock	1 (0.83)	1 (0.86)
Staphycoccal bacteremia	1 (0.83)	0
Thrombocytopenia	1 (0.83)	0
Bacterial urinary tract infection	1 (0.83)	0
Vomiting NOS	1 (0.83)	0
Sepsis	0	1 (0.86)
CVA	0	1 (0.86)
Circulatory collapse	0	1 (0.86)
Red man syndrome	0	1 (0.86)
Toxic nephropathy/ interstitial nephritis	0	2 (1.7)
Hypersensitivity	0	1 (0.86)
Anaphylactic reaction	0	1 (0.86)
Respiratory failure	0	1 (0.86)
Dermatitis bullous/ dermatitis medicamentosa	0	2 (1.7)

There were more instances of discontinuations in the daptomycin arm for reasons that may be related lack of treatment effect than were seen in the comparator arm; specifically, there were 7 (5.8%) discontinuations in the daptomycin arm for reasons that might be related to efficacy (osteomyelitis, bacteremia, epidural abscess, septic shock, staphylococcal bacteremia, staphylococcal pneumonia, sepsis) vs. only 2 (1.7%) in the comparator arm. The comparator arm had more instances of discontinuation due to renal events (5 vs. 1) and allergy-related events (6 vs. 3).

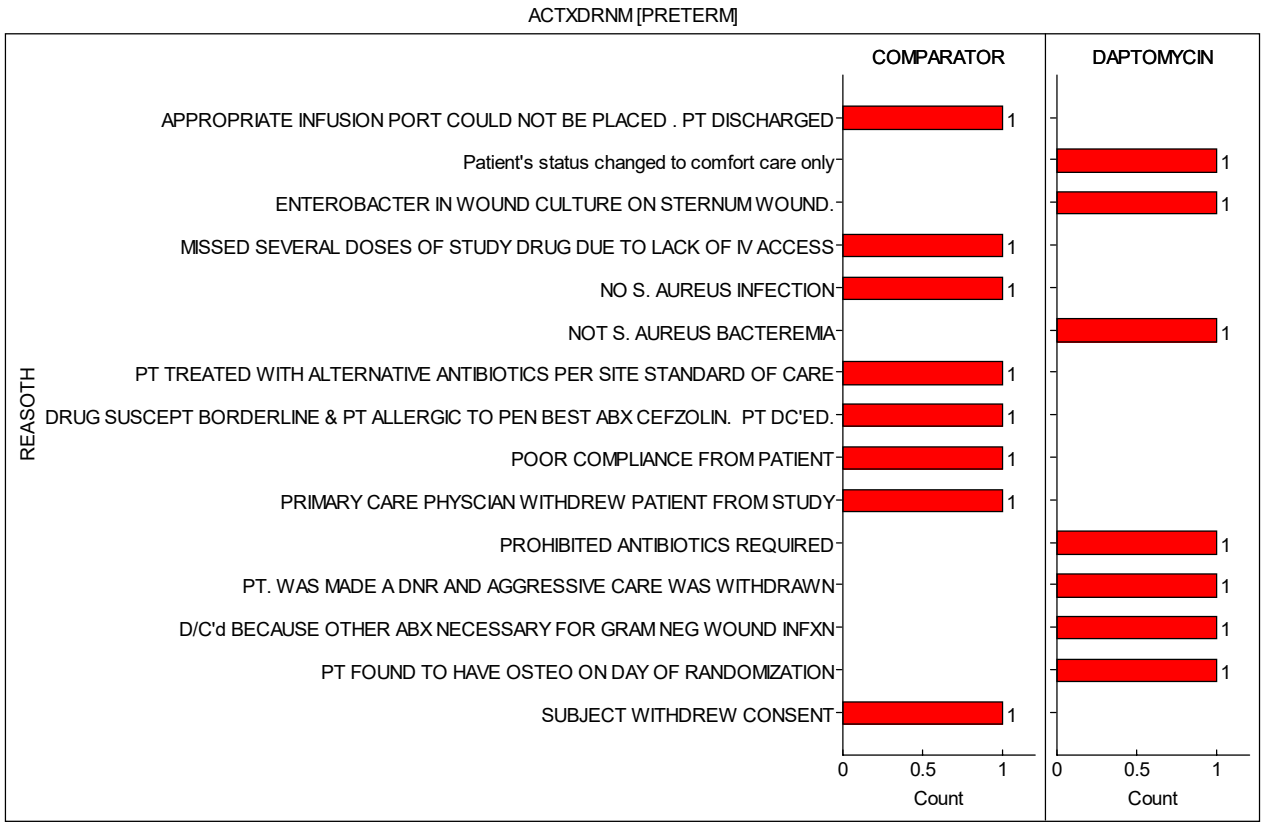
Graph 7 shows all reasons for discontinuation of study medication including those not related to adverse events. Overall, the reasons for discontinuation are similar between the two treatment arm with the exception that there were more cases of discontinuation due to microbiologic failure in the daptomycin arm than in the comparator arm, 9 (7.5%) vs. 3 (2.5%). This difference may be indicative of decreased efficacy for daptomycin compared to comparator.

Graph 7. All Reasons for Premature Discontinuation of Study Drug by Treatment Arm.



Graph 8displays the specific causes for study discontinuation that are referred to as “other” in graph 7. It is interesting to note that two patients in the daptomycin arm in this “other” category actually discontinued due to a gram-negative infection. These patients should have been categorized as having discontinued therapy due to the adverse event of a gram-negative infection. Inclusion of these patients in the “other” category is not appropriate.

Graph 8. Causes for Study Drug Discontinuation in "other" Category by Treatment Arm.



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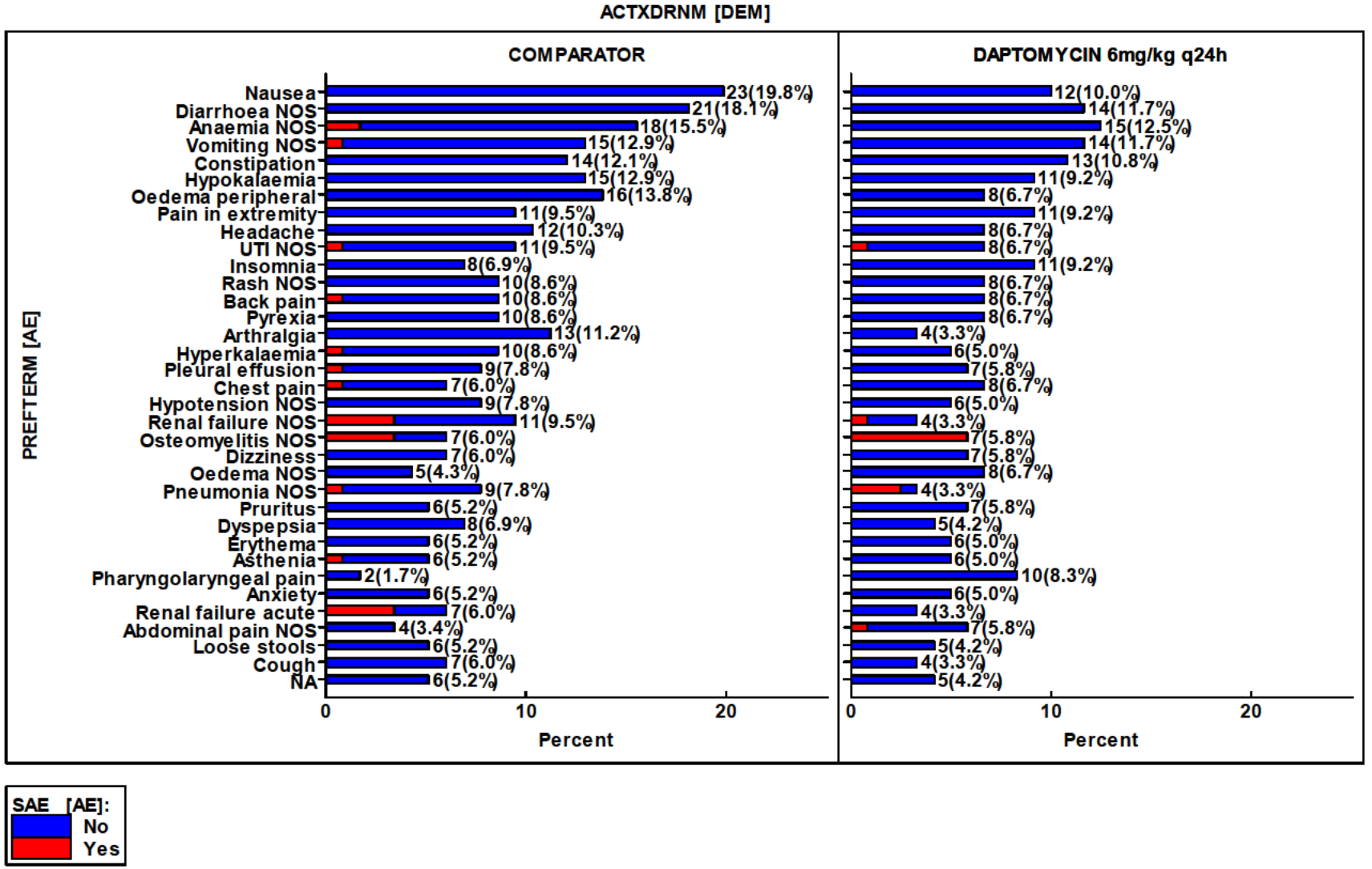
2.1.4 Common Adverse Events

Graph 9 shows the numbers and rates of the most common adverse events by preferred term by treatment group and with non-serious AEs in blue and serious AEs in red. Patients with more than one of the same adverse event are counted only once per preferred term.

Graph 9. Most Common Adverse Events by Treatment Arm. Serious AEs are in Red.

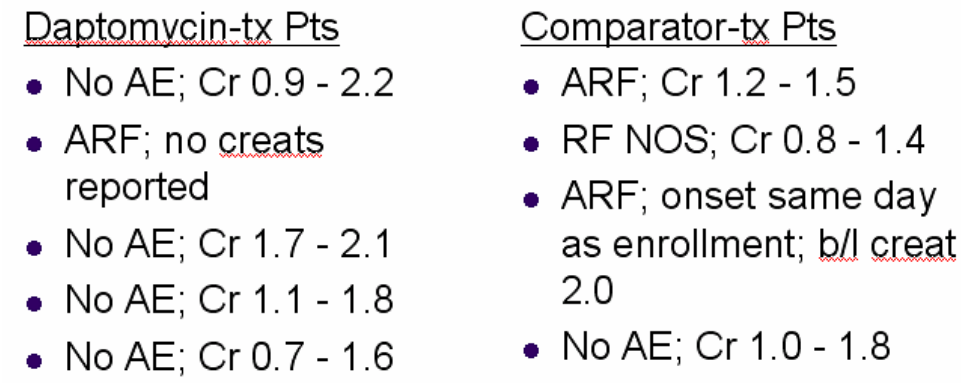


Overall, there were more non-serious adverse events in the comparator arm. There were increased rates of non-serious nausea (19.8% vs. 10.0%) and non-serious diarrhea (18.1% vs. 11.7%) in the comparator-treated patients compared to daptomycin-treated patients. There were also increased rates of non-serious peripheral edema (13.8% vs. 6.7%) and non-serious arthralgia (11.2% vs. 3.3%) in comparator-treated patients compared to daptomycin-treated patients. Other notable differences include an increased rate of non-serious pneumonia in the comparator-treated patients and an increased rate of non-serious pharyngolaryngeal pain in the daptomycin-treated patients.

Appropriateness of adverse event categorization and preferred terms

Because this study was an open label trial in which it can be presumed that an expectation of renal adverse events existed in the comparator arm (which included gentamicin) but not in the study drug arm, there was a concern regarding potential bias in the reporting of renal adverse events. In addition, also because of the open label design of the study, there is the potential that comparator-treated patients may have received treatment for longer duration of time because the comparator arm is considered the standard of care. For these reasons, renal AEs were examined for reporting inconsistencies. Graph 10 shows specific patients according to whether an adverse event was reported as well as the corresponding change in creatinine. This assessment shows some of the inconsistencies which were found during this review. There were patients with creatinine measurements which increased did not exceed the ULN and yet were reported as having renal failure, while other patients with similar or greater increases in creatinine were not reported as having any renal adverse event at all.

Graph 10. Inconsistencies in Renal Adverse Event Reporting by Treatment Arm.



AE = adverse event; ARF = acute renal failure; RF NOS = renal failure not otherwise specified; ULN for creatinine was 1.5

This review shows that there were significant inconsistencies in the study regarding when a particular patient's renal dysfunction was or was not reported as a renal adverse event. No standard definition for renal adverse events was used throughout the study. For this reason, the reporting of renal adverse events was left up to the individual discretion of each investigator which is why there is so much variability in terms of what was reported as a renal adverse event. It is also critical to note that the disease under study has an inherent expected rate of renal events that is high enough that the standardization of renal adverse event reporting is absolutely

necessary in order to understand what differences may occur between the two treatment arms. This is especially important because of the open label design of the study.

Because of time constraints, a detailed assessment of whether or not the inconsistencies in renal adverse event reporting were differential in nature was not done.

Given the clear lack of standardization of renal adverse event reporting, a different method was used to attempt to better understand the renal toxicity profile of the therapies under study. This analysis is presented in section 2.1.5.

2.1.5 Additional analyses and explorations

Because of the limitations of the study's renal adverse event reporting methodology, a different method was sought to attempt to understand the relative renal toxicity of the two treatment arms. After discussion with Dr. Juan Pelayo, a neprhologist at the FDA, a decision was made to compare the rates of percentage increases in creatinine between the two treatment arms for those patients whose peak creatinine increased to above 25% over baseline and above the ULN (1.5 mg/dl) during therapy or within 30 days after the last dose of therapy. It is not necessary to perform this analysis using calculated creatinine clearances for GFR. This is because the only variable that changes in the MDRD or Cockcroft-Gault equations, over the relatively short time period of study conduct, is the serum creatinine. Patient age, race, gender, and weight are not expected to change, so these calculations are really not necessary in terms of trying to understand decreases in renal function; percentage changes from baseline creatinine are sufficiently adequate for trying to understand renal toxicity for the purposes of this analysis.

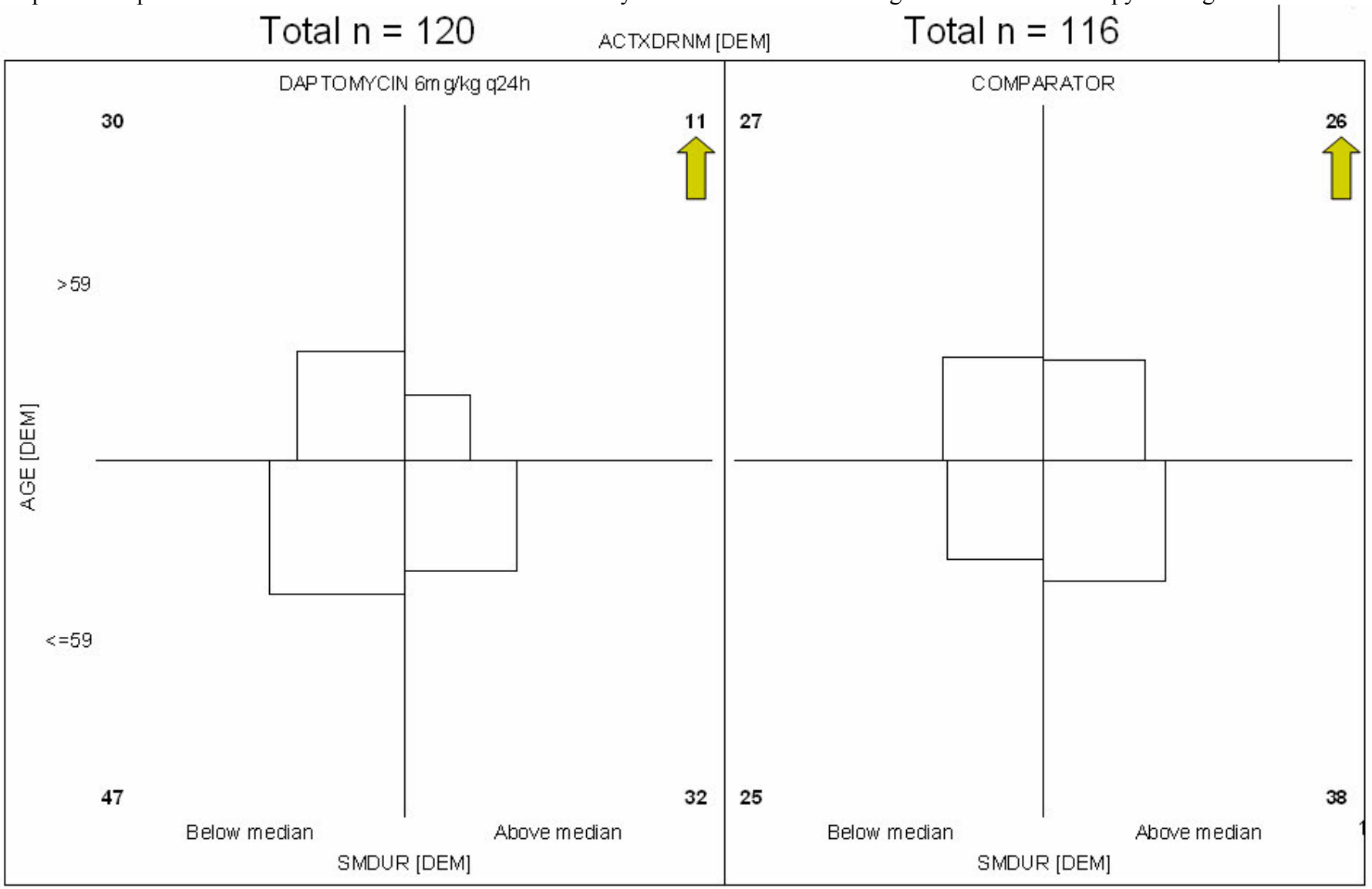
Using this definition, there were a total of 25 (21.6%) comparator treated patients with renal toxicity vs. 17 (14.2%) daptomycin-treated patients with renal toxicity. Although this analysis appears to represent a marked increase in the rate of renal toxicity in the comparator arm, there were problems with the interpretation of the results because of inherent differences in the patient populations with regard to key characteristics which predisposed the comparator arm to greater rates of renal toxicity. Specifically, there were greater numbers of patients in the comparator arm than the daptomycin arm who were 60 years old or older who received prolonged therapy (26 vs. 11) as shown in Graph 11. This is the sub-population with the highest rate of renal toxicity.

The association of drug-related renal toxicity and increased age has been noted in numerous publications [1) Thomson NM. Drugs and the kidney in the elderly. Med J Aust 1995; 162: 543—547. 2) MuhlbergW, Platt D. Age-dependent changes of the kidneys: pharmacological implications. Gerontology 1999; 45:243—253. 3) Streetman DS, Nafziger AN, Destache CJ, Bertino AS Jr. Individualized pharmacokinetic monitoring results in less aminoglycoside-associated nephrotoxicity and fewer associated costs. Pharmacotherapy 2001; 21:443—451. 4) Vance-Bryan K, Rotschafer JC, Gilliland SS, et al. A comparative assessment of vancomycin-associated nephrotoxicity in the young versus the elderly hospitalized patient. J Antimicrob Chemother 1994; 33:811—821. 5) AilabouniW, Eknoyan G. Nonsteroidal anti-inflammatory drugs and acute renal failure in the elderly. A risk-benefit assessment.Drugs Aging 1996;

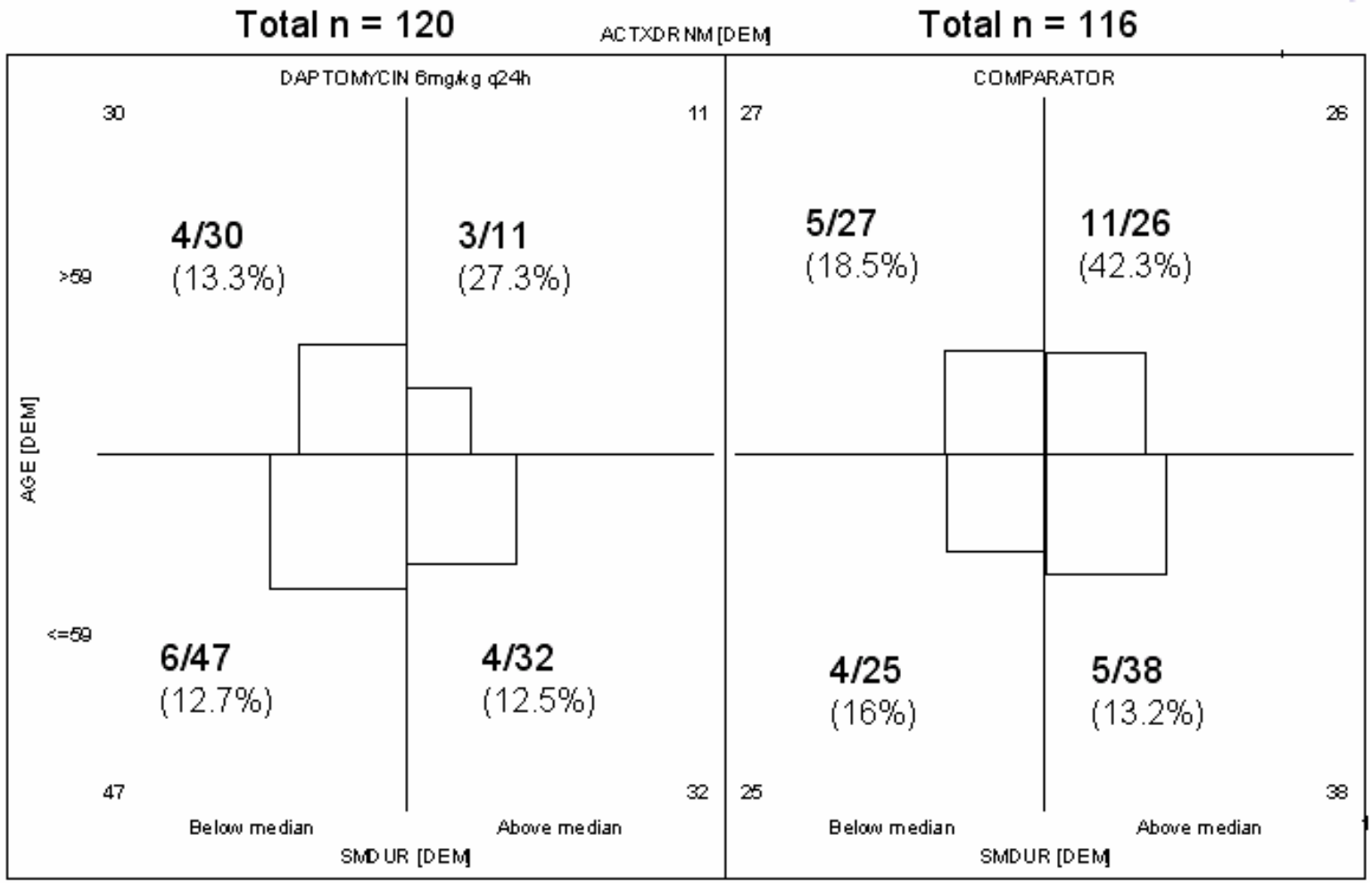
9:341—351. 6) Knight EL, Glynn RJ, McIntyre KM, et al. Predictors of decreased renal function in patients with heart failure during angiotensin-converting enzyme inhibitor therapy: results from the studies of left ventricular dysfunction (SOLVD). Am Heart J 1999; 138:849—855.].

Prolonged duration of therapy only increases the exposure of the patient to the drug as well as increasing the window during which time renal events might occur. In addition, because the patient population who is at least 60 years of age and who received greater than the median duration of therapy had the highest rate of renal toxicity, it is reasonable to conclude that there are inherent characteristics to the patients in this subgroup that put them at greater risk for renal toxicity. So even if the renal events in this group occurred early in treatment, there is still an imbalance between treatment arms in terms of the numbers of patients who are most at risk for renal toxicity.

Graph 11. Graphical 2 x 2 Table with Distribution of Patients by Treatment Arm According to Duration of Therapy and Age.



Graph 12. Distribution of Renal Toxicity Events Broken Down by Quadrant.



Graph 12 shows that patients 60 years of age and older who received greater than the median duration of therapy (which was 14 days) had the highest rate of renal toxicity events. The rate of renal events in this sub-population appears to be higher in the comparator arm, although, because of small numbers, this difference cannot be definitively concluded. It is clear, however, that a significant portion of the overall number of renal toxicity events in the comparator arm is derived from this sub-population and that this is at least partly responsible for the overall difference in rates of renal toxicity between the two treatment arms.

The analysis of overall rates of renal toxicity can be corrected for this imbalance. First, the comparator's 116 patients are redistributed in a way that is proportionally equivalent to the distribution that exists in the daptomycin arm. Then the observed comparator rates of renal events within each quadrant can be applied to the redistribution. When the analysis is corrected in this way for the imbalance in the patient sub-populations that exists between the two treatment arms, the rates of renal toxicity events changes from a total of 25 (21.6%) comparator-treated patients with renal toxicity vs. 17 (14.2%) daptomycin-treated patients with renal toxicity to a corrected total of 20 (17.2%) comparator-treated patients with renal toxicity vs. 17 (14.2%) in the daptomycin-treated patients. This analysis shows that the rates of renal toxicity are still slightly higher in the comparator arm, but overall, relatively similar between the two treatment arms.

One limitation of this analysis is that it only focuses on drug-related toxicity resulting in decreases in glomerular filtration. Semi-synthetic penicillins are known to cause other types of renal toxicity such as interstitial nephritis. In the study, there was a single case of comparator-associated interstitial nephritis.

Another limitation is that it doesn't correct for other differences that may exist between the two treatment arms. For example, examination of the renal toxicity cases revealed that a large number of them had temporally related hypoperfusion events that likely caused or at least contributed to the decline in renal function.

An attempt was made to understand possible differences between the two treatment arms. A hypoperfusion event was defined as including one or more of the following: SBP<90, treatment with pressors, one or more of the following AEs: hypotension NOS, septic shock, GI hemorrhage, CHF, cardiac arrest. Using this definition, it was determined that there were a total of 39 patients in the comparator arm who experienced a hypoperfusion event vs. 32 in the daptomycin arm. Of the patients in the comparator arm, a greater number of hypoperfusion events, 12 (30.8%), occurred in the sub-population of patients who were 60 years old or older and who received greater than the median duration of therapy. In the daptomycin arm, there were only 4 such patients (12.5%). Of the twelve patients in the comparator arm who experienced a significant hypoperfusion event and who were 60 years old or older and who were treated for longer than the median duration of therapy, 6 met the specified definition for renal toxicity while there were 0 in the daptomycin arm. This is another example of how some portion of the difference between the two treatment arms in terms of renal toxicity could be potentially explained by differences in the two treatment populations instead of solely due to differences in drug-related renal toxicity.

At the Advisory Committee Meeting, the sponsor presented mean changes in renal function for patients receiving gentamicin vs. those not receiving gentamicin. Their analysis showed an increase in the mean change in renal function for those receiving gentamicin vs. those not receving gentamicin. However, this analysis is not informative because there were fundamental differences in the patient populations between those patients receiving gentamicin vs. those who did not receive gentamicin. The primary difference is that the patients who did not receive gentamicin were not as severely ill as those who did receive gentamicin. Among the patients who did not receive gentamicin, there was a total of 1 out of 8 (12.5%) who had a hypoperfusion event. This is in contrast to the gentmicin group in which 38 out of 108 (35.2%) did experience a hypoperfusion event. Furthermore, in the gentamicin group, there were 22/108 (20.4%) who were determined by the IEAC to have had a diagnosis of endocarditis, while in the non-gentamicin group, there were 0/8 who had endocarditis.

In summary, the overall rates of renal toxicity are relatively similar between the two treatment arms, with slightly higher rate of renal toxicity cases in the comparator arm than in the daptomycin arm.

2.1.6 Other Less Common Adverse Events

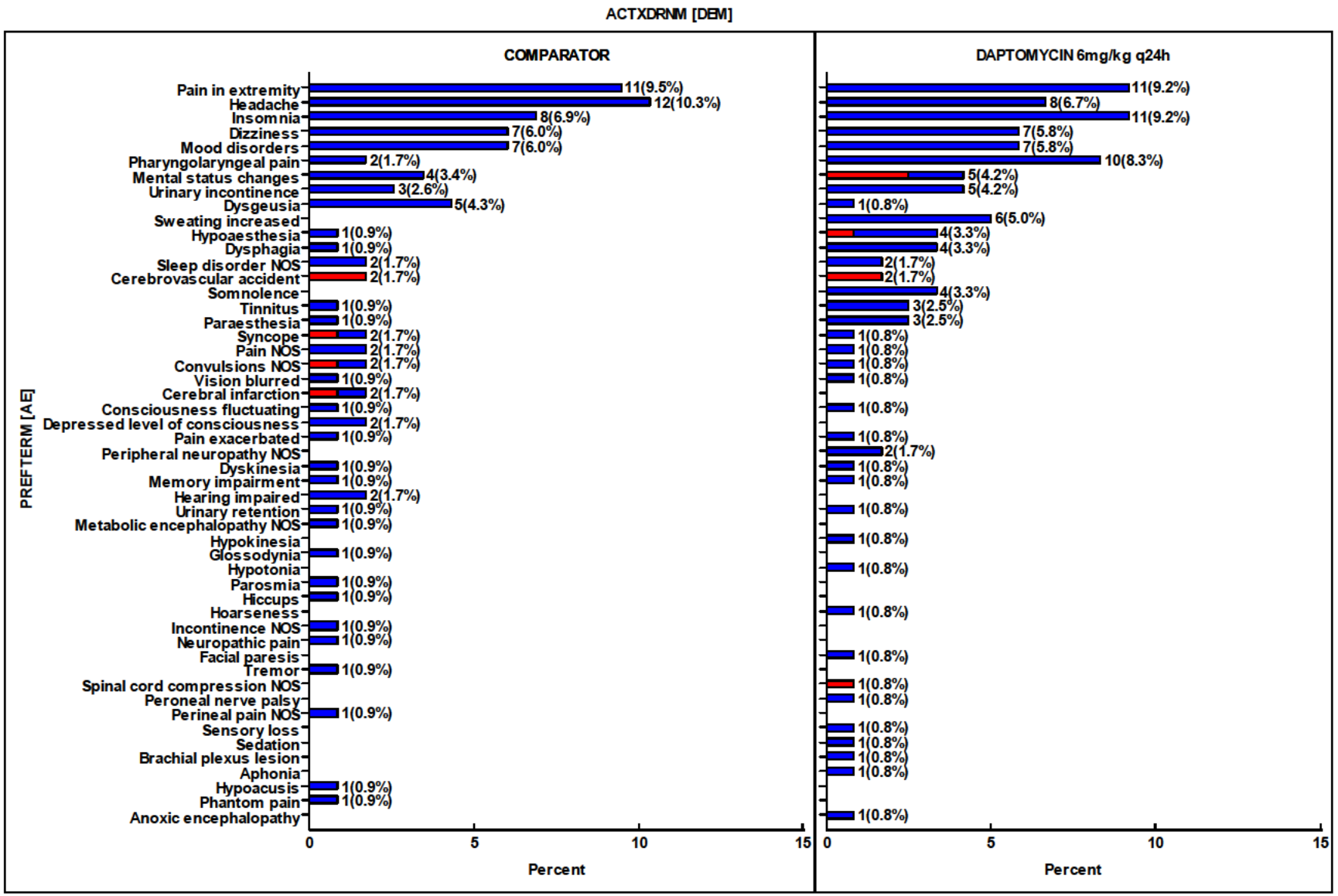
2.1.6.1 Hepatotoxicity

A search was made for patients whose hepatic laboratories were possibly suggestive of a hepatocellular pattern of liver injury. There were a total of 15 patients with ALT measurements over 3x ULN. 11 of these were in the comparator arm and 4 in the daptomycin arm. Only 2 of these 15 patients (both in the daptomycin arm) also had concomitant increases in total bilirubin measurement above the ULN. Patient (b) (6) had a peak ALT of 167 at the time of enrollment. This patient's alkaline phosphatase was elevated at 234 suggesting some component of cholestasis. The patient's ALT trended downwards during the study and normalized by study day 57. Because the elevated ALT was a baseline finding and not treatment emergent, daptomycin-related heaptotoxicity is not considered to be a possibility in this patient. Patient (b) (6) was a 79 year old woman with a history of coronary artery disease who had an ALT which was essentially normal until day 28 of the study (2 days after last dose of daptomycin) at which time it increased to 332. The alkaline phosphatase also increased to 136 from 62, but remained normal (ULN for alkaline phosphatase was 147). No further measurements were collected for this patient. This patient's course was complicated by renal failure, cardiac failure, intestinal infarction requiring total abdominal colectomy, and respiratory failure necessitating intubation. The patient eventually died 7 days after the last dose of therapy with gram-negative organisms cultured out of her blood. It is difficult to clearly link this patient's liver enzyme abnormalities to drug exposure because of the multiple confounding events that the patient experienced.

2.1.6.2 Neurotoxicity

Because pre-clinical data suggests a possible dose-related neurotoxicity for daptomycin, an analysis was done to look for potential safety signals consistent with neurotoxocity. It should be noted that there was no systematic assessment of neurotoxicity as part of the trial which may have limited the ability of the trial to detect possible differences in the rates of neurotoxicity, if such difference actually exists. Graph 13 shows all possible neurological adverse events by treatment arm. Serious events are in red and non-serious in blue.

Graph 13. Rates of Neurological Adverse Events by Treatment Arm. Serious Events Are in Red.



Most of the neurological adverse events in Graph 13 occur in similar rates between the two treatment arms. It is difficult to form conclusions about differences between the two treatment arms because of the low overall rates. There were a few differences which appear potentially significant. There were 14 daptomycin-treated patients (11.7%) who experienced pharyngolaryngeal pain or dysphagia vs. only 3 (2.6%) such comparator-treated patients. None of these events were serious, but 7 daptomycin-treated patients did require therapy with a concomitant medication. Other noticeable differences included an increased rate of non-serious "sweating increased" in the daptomycin arm compared to the comparator arm (6 or 5% vs. 0). There was also an increased rate of somnolence in daptomycin-treated patients (4 or 3.3% vs. 0). There was an increased rate of dysguesia in the comparator arm (5 or 4.3% vs. 1 or 0.8%).

2.2 Laboratory Findings

2.2.1 Overview of laboratory testing in the development program

Review of laboratory data including hematology, chemistry, and coagulation did not reveal marked differences between the two treatment arms. The only analysis which did show what could be considered to be potentially clinically meaningful differences with regard to laboratory findings was the CPK analysis.

2.2.2 Special assessments

2.2.2.1 CPK Analysis

Because of a previously recognized toxicity involving exposure to daptomycin and increased serum CPK measurements, a detailed analysis of CPK elevations was performed for this study.

CPK measurement were checked very frequently during the course of the study. However, there were difficulties in assessment of this data. Specifically, almost 2/3 of the CPK data was not assessed by a central laboratory and was only measured using local laboratories. Problems resulting from this became apparent when central and local results for the same samples were compared and viewed in relation to the differing reference ranges. The upper limit of normal (ULN) for the various local laboratories ranged from 135 U/L to 397 U/L, however, this difference in reference ranges did not appear to represent a simple difference in proportions. There were instances where CPK results from the same sample but measured both in local and central labs were similar in value despite markedly different ULN's and there were other instances where lab results from local and central labs were relatively different despite ULN's which were similar. Based on this assessment, it was determined that the local laboratory data could not mixed with the central lab data for the purposes of assessing CPK elevation and therefore, only central lab data was used in the analyses in this section. Even given this limitation, there were still over 1,200 total central lab measurements done for CPK in 236 patients, thus providing a reasonable amount of data to analyze.

Graph 14 is a delta graph which shows every patient in the study who received treatment with a study drug. Those patients who did not experience any increase in CPK levels from baseline throughout the study are represented as a blue dot. Those patients who did experience an increase in CPK at sometime during the study are shown as red lines. The starting point of the red lines (on the left) represents the baseline value and the ending point (on the right) represents that maximum peak measurement. Only central lab data were used in this analysis. The green line represents 500 U/L. This analysis shows that there are a total of 11 daptomycin-treated patients who had CPK's that increased during the study and whose peak CPK was above 500 U/L. Two of these patients had CPK levels that were above the level of 500 U/L at baseline and then increased further during the study. The other 9 patients had baseline level that were below 500 U/L. The rate of 7.5% (9/120) represents a meaningful increase over what was seen in the cSSSI studies where the rate of increase to over 500 U/L was under 3%. 3 of these patients had CPK's

which normalized on therapy, while 4 of these patients returned to baseline after discontinuation of daptomycin. The other 2 patients experienced an increase in CPK which occurred after the final dose of daptomycin. Associated reported AE's which could have been related to the CPK elevations included one patient with arthralgia and one patients with asthenia that were temporally related to the CPK increase. In addition, there was one patient who was reported to have had rhabdomyolysis, however, the peak CPK level in the patient was under 1,000 U/L.

One interesting observation was that patients with prior or concomitant exposure to an HMG-Co A reductase inhibitor appeared to have a higher rate of CPK increase to over 500 U/L as is shown in Table 4.

Table 4. Rates of CPK Elevations to Above 500 U/L by Treatment Group

	Comparator	**Daptomycin**
	n/N (%)	**n/N (%)**
Overall Study patients with CPK>500 U/L	1/116 (0.90)	9/120 (7.5)*
With prior concomitant treatment with a statin	0/20 (0.0)	4/24 (16.7)
No Prior or concomitant treatment with a statin drug	0/96 (0.0)	5/96 (5.2)

*Does not include the 2 patients whose baseline CPK measurements were over 500 U/L

This analysis suggests that prior or concomitant treatment with an HMG-Co A reductase inhibitor may interact with daptomycin in such a way to increase the risk of rhabdomyolysis. This may not have been seen in prior studies because other studies used lower doses of daptomycin.

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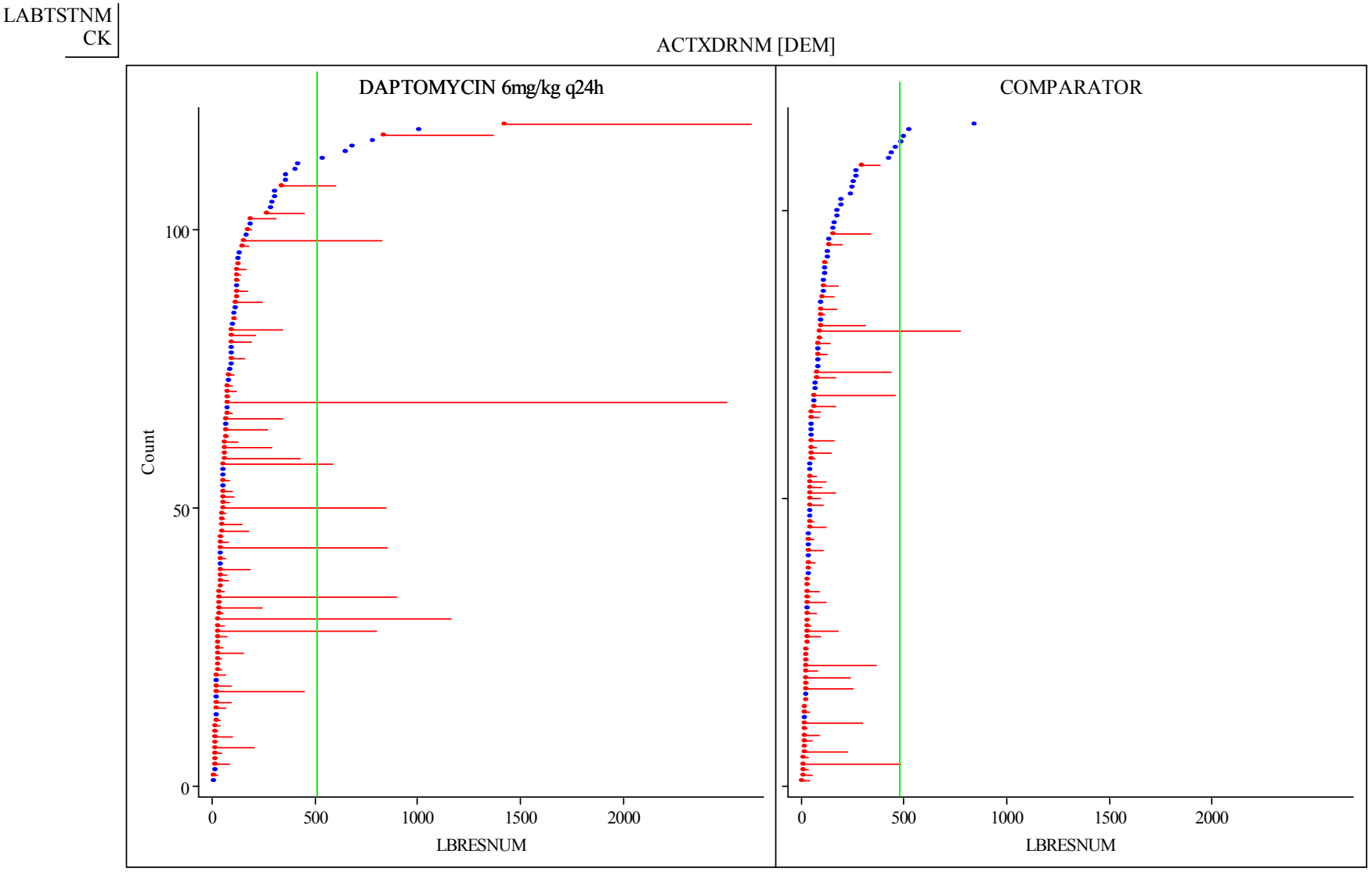
Graph 14. Delta Graph of CPK Elevations.



2.3 Vital Signs

Vital signs were assessed looking at measures of central tendency, outliers, and dropouts for vital sign abnormalities. No clear signals were detected from these analyses.

2.4 Electrocardiograms (ECGs)

A detailed review of ECG assessment for this drug is contained in the Chuck Bonapace's review for the initial approval of this drug at which time it was an NME. The review includes a dedicated QT study as well as additional analyses which indicated that there was a low likelihood that daptomycin had any significant effect on cardiac electrophysiology.

For the purposes of this study, the sponsor submitted ECG data from the patients in the study which included shifts from normal to abnormal ECG by clinical significance as well as a table displaying all ECG abnormalities reported as adverse events. These analyses were reviewed and no new safety signal was noted.

2.5 Adequacy of Patient Exposure and Safety Assessments

2.5.1 Study type and design/patient enumeration

The study was a controlled, open-label design. This design has disadvantages from the perspective of safety for a few reasons. One relates to the expectation of renal adverse events that exists for patients in the gentamicin-containing comparator arm and potentially biased the investigator's likelihood of reporting renal changes as adverse events. The other relates to the fact that the comparator is the standard of care, and so, in an open label design, there is the risk that more patients in the comparator arm will be treated for longer durations of time. Such a discrepancy is what was observed and prolonged drug exposure in one arm vs. the other has the potential to effect rates of adverse events, since there can be expected to be a greater number of treatment-emergent adverse events in the arm with prolonged exposure. This potentially may explain some of the differences between the two treatment arms with regard to differing adverse event rates, however, such an analysis was done because of time constraints.

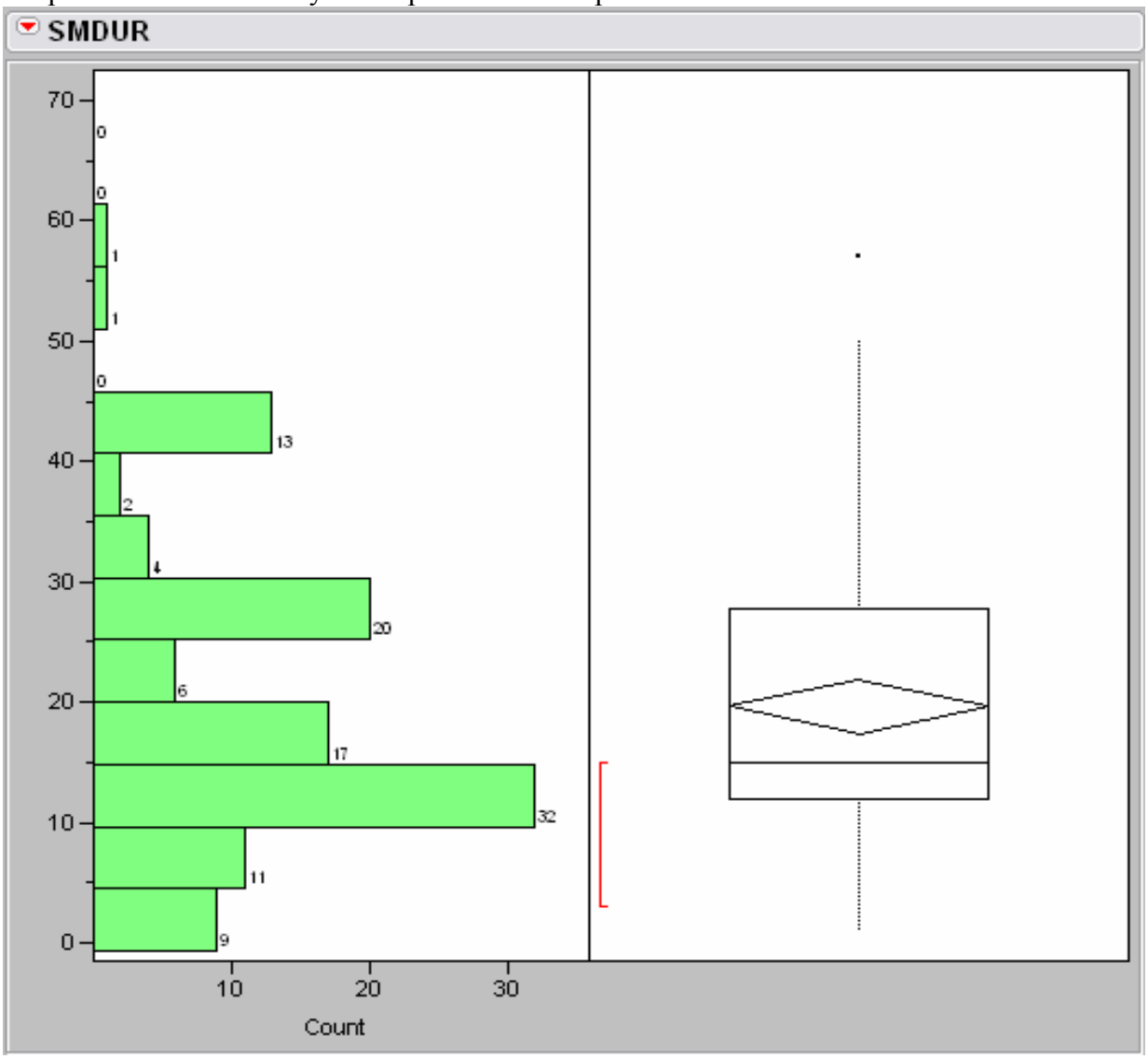
2.5.2 Demographics

Demographic data were reviewed. In general, the two treatment arms had roughly similar distribution of patients according to the various common demographic characteristics. Patients in the comparator arm were slightly older on average than daptomycin patients (56.4 y.o.vs. 52.6 y.o.). Other baseline characteristics such as gender, race, BMI, and creatinine clearance were similar between the two treatment arms.

2.5.3 Extent of exposure (dose/duration)

Graph 15 shows the extent of exposure in days for comparator-treated patients and Graph 16 shows the extent of exposure in days for daptomycin-treated patients.

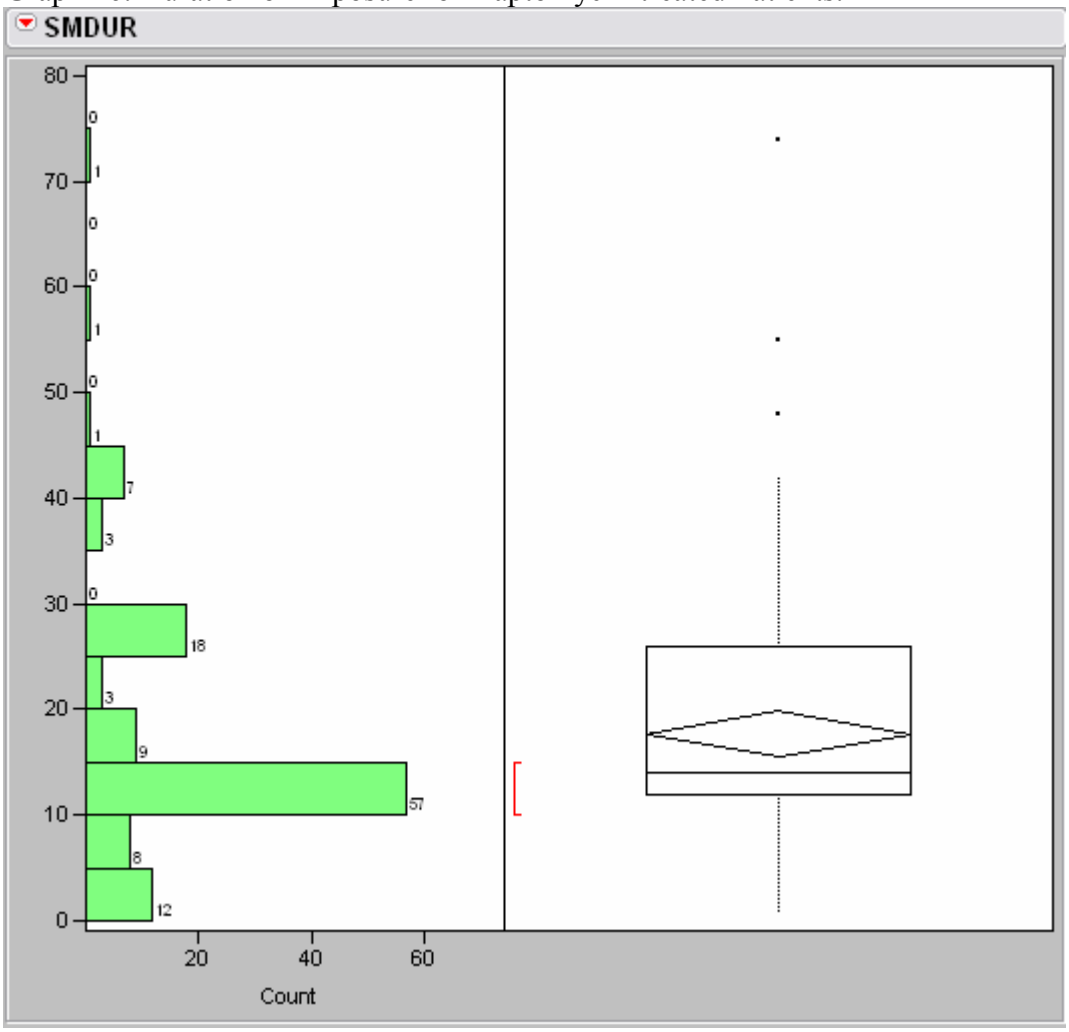
Graph 15. Duration in Days of Exposure for Comparator-treated Patients.



These two graphs (Graphs 15 and 16) show that there were more patients who were treated for longer duration in the comparator arm than in the daptomycin arm. Of particular note, there were only 14 patients in the daptomycin arm who received more than 28 days of therapy and 22 patients in the comparator arm who receveid more than 28 days of therapy. Since the expected duration of therapy in the treatment of certain subsets of patients with staphylococcal bacteremia, particularly those with endocarditis or metastatic sites of infection, is often more than 28 days, it

is important to note that the safety profile of this drug at this dose for over 28 days duration cannot be determined.

Graph 16. Duration of Exposure for Daptomycin-treated Patients.



2.6 Postmarketing Experience

This drug has been marketed for use in the treatment of complicated skin and skin structure infections. It has been prescribed an estimated (b) (4) times. The sponsor has reported that the post-marketing adverse event database for this drug is consistent with what is known about the drug's adverse event profile. A specific analysis of the post-marketing data has not been done for the purposes of this review.

2.7 Explorations for dose dependency for adverse findings

Multiple exploratory analyses were done examining the effects of BMI, weight, and renal function on the rate of adverse events. Because this drug does not have a large volume of distribution and because it is dosed according to weight, there is the potential for relative overdosing in patients with higher BMI's. The analyses performed were unable to detect differences in adverse event rates according to these various parameters. The major limitation of these analyses includes the fact that numbers for individual adverse events within subgroups were low. Therefore, these analyses do not exclude a possible dose effect in the rate of adverse events related to relative overdosing because of increased BMI.

3 ADDITIONAL CLINICAL ISSUES

3.1 Dosing Regimen and Administration

This drug is dosed at 6mg/kg IV q day. Because of the limited safety data available at this dose (6mg/kg) for treatment durations of greater than 28 days of therapy (only 14 patients), it is not possible to assess whether there are differences in the safety profile for patients who received more than 28 days of therapy. This is potentially significant because the treatment duration that the sponsor is proposing extends out to 42 days of therapy, presumably for those patients with endocarditis and/or metastatic sites of infection.

3.2 Drug-Drug Interactions

In vitro studies with human hepatocytes indicate that daptomycin does not inhibit or induce the activities of the following human cytochrome (CYP) P450 isoforms: 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4. It is unlikely that daptomycin will inhibit or induce the metabolism of drugs metabolized by the CYP P450 system. It is unknown whether daptomycin is a substrate of the CYP P450 system. In addition, concomitant administration of daptomycin (6 mg/kg once every 24 hours for 5 days) and warfarin (25 mg single oral dose) had no significant effect on the pharmacokinetics of either drug and the INR was not significantly altered.

3.3 Special Populations

The primary safety issue in special populations is that associated with patients who have decreased renal function or increased age. In these groups, there is a decrease in efficacy rates which was not observed in the comparator arm (see Dr. Sorbello's review). This finding was also seen in the complicated skin and skin structure infection studies. Rates of adverse events did not appear to be significantly different in these populations, however, because of small numbers of patients and events, it is difficult to conclude that such differences do not exist.

3.4 Pediatrics

No pediatric patients were studied in this study. The company has requested a deferral for the study of pediatric patients and are currently planning on conducting a PK study in pediatric patients.

3.5 Advisory Committee Meeting

An Advisory Committee Meeting was held on 3/6/06. Overall, informative and useful discussion took place, however, there were some key limitations to the meeting. First, several AC members were either absent or conflicted. Second, the FDA was not able to secure an SGE with special expertise in endocarditis and staphylococcal infection for the purposes of consultation and participation at the meeting. Thirdly, the discussions that took place during the meeting clearly indicated several critical concepts were not fully grasped by the committee. This may have been the result of the difficulty in presenting such complex information in such a limited period of time.

For example, perhaps the most critical issue was that of increasing daptomycin MICs which occurred on therapy. A clear understanding by Advisory Committee members of concerns over this issue did not fully materialize. According to a rigorous and scientifically based definition, daptomycin-treated patients had a higher rate of development of decreased staphylococcus susceptibility *while still on therapy* which was then associated with treatment failure. This rigorous definition included those patients who had all of the following: a two-tube fold increase in MIC, a persisting or relapsing *Staphylococcus aureus* infection, and an increase in MIC's to the level of clinical significance (≥2.0 mcg/ml). This occurred at a rate of 6/120 (5%) in the daptomycin arm vs. 1/116 (0.9%) in the comparator arm. The one comparator treated patient was questionable because of multiple conflicting MIC measurements, some of which did not show an increase of MIC's by 2-tube dilutions. The sponsor has presented differing numbers by using less stringent and less scientifically supportable criteria, which, for example, include patients whose isolates displayed only a 1-tube fold dilution increase (which is within the normal variability of the assay) or by including a mix of local and central lab data. This less rigorous approach only serves to obscure the finding of increasing daptomycin MICs while on therapy. The rate of increase in MICs to daptomycin to a level of clinical significance, which was not seen in the vancomycin arm, and which occurred *on therapy,* is highly unusual and different from other antibiotics. The sponsor has pointed to a publication by Sakoulas in the Journal of Antimicrobial Chemotherapy as evidence that such a phenomenon of increasing MIC's has been observed with vancomycin as well. However, that study is not informative and does not support the sponsor's conclusion because the isolates in that study were exposed to prolonged, low levels of vancomycin which is not reflective of what occurs in properly treated patients. In addition, after over 30 years of use, there is scant other evidence to support this conclusion.

In addition, there was confusion regarding additional analyses which support the possibility of decreased efficacy associated with daptomycin. For example, daptomycin had a decreased efficacy rate for patients with increasing age as well as those with decreasing renal function that *was not seen* with comparator-treated patients. Members of the Advisory Committee did not

understand that these differences were not seen in the comparator arm. In the end, the most concerning issues were not resolved as a result of the AC Meeting.

3.6 Literature Review

There are concerning publications that seem to support the finding that daptomcyin behaves differently than other antibiotics. First, the drug's activity appears to be highly calcium dependant. The activity of daptomycin is significantly reduced when there is an absence of calcium. A previous study showed that the effect of daptomycin on the *Staphylococcus aureus* membrane is dependant on the presence of calcium. (Alborn WE, et al. Daptomycin disrupts membrane potential in growing *Staphylococcus aureus.* Antimicrob Agents Chemother. 1991 Nov; 35(11):2282-7. This is important because the MICs as measured by laboratory methods requires the maintenance of calcium at physiologic levels that mimic the calcium content of blood. However, in other locations of the body, particularly at metastatic foci of infection the calcium concentrations are likely to be lower and thus may predispose patients to treatment failure. Such a scenario is well supported by the results of this study where there were increased rates of AE's and SAE's related to metastatic sites of infection. Of course, the higher rates of PRSA and increased propensity for MIC elevations *while on therapy* may also be contributing factors which suggest a potential problem with efficacy. Another publication (Skiest D. Treatment failure from resistance of Staphylococcus aureus to daptomycin. J Clin Micro. Feb 2006; p655-6, Vol 44, no. 2) describes a patient who required leg amputation as a result of properly dosed daptomycin treatment failure secondary to rising organism MICs *while on therapy*. The observed increased rates of clinical failure in the pivotal study on daptomycin therapy due to rising MIC's was not observed in the comparator group nor has it been noted in the published medical literature for other antibiotics that are used for this indication. Given the potentially fatal nature of the infection under study, such a finding is concerning.

4 OVERALL ASSESSMENT OF SAFETY

4.1 Conclusions

The primary safety issue identified in this study is a question of the lack of efficacy. The findings of this safety review support the efficacy review conducted by Dr. Fred Sorbello and call into question the effectiveness of daptomycin in the treatment of endocarditis and staphylococcus bacteremia with metastatic sites of infection. Given these uncertainties, in the absence of clear data that show otherwise, daptomcyin should not be indicated for these purposes. In addition, there is insufficient safety data to assess this drug's safety profile when used for >28 days. The sub-group most likely to require treatment for >28 days includes those patients with endocarditis or staphyloccoal bacteremia with metastatic sites of infection, sub-groups which carry the highest inherent mortality and also have the least amount of efficacy data.

4.2 Recommendation on Regulatory Action

There are multiple analyses which seem to indicate a possible problem with decreased efficacy for daptomycin. These include the following: increased rates of persisting or relapsing *Staphylococcus aureus* infection (PRSA) in daptomycin-treated patients, decreased efficacy rates in patients with reduced renal function not seen in the comparator, decreased efficacy rates in older patients not seen in the comparator, increased rates of study drug discontinuation due to microbiologic failure compared to comparator, increased rates of disease-related SAE's compared to comparator, increased rates of discontinuation due to disease-related SAE's compared to comparator, and increasing MIC's with resulting clinical failure while on therapy. There have also been published reports of clinical failure due to rising MIC's with resulting dire consequences, a failed pneumonia study, a phase 2 endocarditis study which showed an inferior point estimate compared to control, a failed Eli Lilly endocarditis study. Because this is a disease with a very high inherent mortality, it is critical to grant only an indication which includes the treatment of patients for which the sponsor has clearly demonstrated efficacy. More specifically, because the sponsor has not clearly demonstrated efficacy in the sub-group of endocarditis or patients with metastatic sites of infection, these sub-populations should be clearly excluded from the indication.

In addition, any label must contain prominently displayed information that communicates daptomycin's unique risk of increasing MIC's while on therapy and subsequent clinical failure due to persisting or relapsing *Staphyloccos aureus* (PRSA) infection. Such communication should only use the numbers which represent organisms which (using central lab data only) underwent a 2-tube fold increase in MIC, reached an MIC consistent with clinically significant decreased susceptibility (≥2 mcg/dl), and had PRSA. Because treatment failure due to PRSA or rising on-therapy MICs is associated with high rates of morbidity and mortality this information should be communicated in the WARNINGS section of the label so that clinicians has the opportunity to make the best possible risk-benefit assessment when treating patients . In addition, information in the label should convey the increased risk of CPK elevations to above the level of 500 U/L as well as the apparent increased risk of CPK elevation for daptomycin-treated patients with prior or concomitant exposure to HMG-Co A reductase inhibitors. With regard to renal toxicity, the information about the differences between the two treatment arms should be portrayed in a clinically meaningful way without the use of "shift" tables which are confusing. Finally, the label should accurately reflect that fact that daptomycin-treated patients had an increased risk of serious gram-negative infections and gram-negative bacteremias (9/120 or 7.5% vs. 0/116 or 0.0%) when compared to comparator-treated patients.

4.3 Labeling Review

No label was agreed upon during labeling negotiations. In particular, among other things, the sponsor was not amenable to wording in the WARNINGS section which included information regarding the associated increased risk of treatment failure due to persisting or relapsing *Staphylococcus aureus* infections and treatment failure due to rising MICs while *on therapy*. Because this disease has a high inherent mortality, the review team felt that this information should be communicated in the WARNINGS section so that clinicians have the best possible

opportunity to make an accurate risk-benefit assessment when deciding whether to use this drug for this disease. In addition, because of the potentially fatal consequences of PRSA or micobiologic failure due to the on-therapy development of decreasing daptomycin susceptibility, the inclusion of this information in the WARNINGS section is appropriate from a regulatory perspective. The sponsor proposed more generic wording regarding the issue of decreasing on-therapy susceptibility that did not alert clinicians to this unique, and potentially harmful observed on-therapy phenomenon.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Charles Cooper
3/27/2006 11:10:34 AM
MEDICAL OFFICER

Corrections made, thanks, please sign

Sumathi Nambiar
3/27/2006 11:52:27 AM
MEDICAL OFFICER

CLINICAL REVIEW

Review Type:	**Efficacy Supplement/Resubmission**
Reviewer:	**Alfred Sorbello, DO Medical Officer**

Application Type:	NDA
Submission Number:	21572
Submission Code:	SE1-008
PDUFA Goal Date:	March 24, 2006
Reviewer Name:	Alfred Sorbello, DO
Review Completion Date:	March 22, 2006
Established Name:	Daptomycin
Trade Name:	Cubicin™
Therapeutic Class:	cyclic lipopeptide antibacterial agent
Applicant:	Cubist Pharmaceuticals
Priority Designation:	Priority Review
Formulation:	Intravenous
Dosing Regimen:	6 mg/kg every 24 hours
Indication:	*Staphylococcus aureus* bacteremia (SAB) including those with known or suspected endocarditis (SAIE) caused by methicillin-susceptible and methicillin-resistant strains
Intended Population:	Adults

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1. EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The efficacy supplement SE1-008 for NDA 21572 regarding the use of daptomycin in the treatment of *Staphylococcus aureus* bacteremia (SAB) including those with known or suspected endocarditis is approvable pending agreement on the product label from a clinical perspective only for the indication of *S. aureus* bacteremia without concurrent infectious endocarditis caused by methicillin-susceptible and methicillin-resistant strains. In accordance with 21 CFR 314.126 of the Code of Federal Regulations (1), the data provided in this supplement do not provide substantial evidence to support a claim of efficacy for daptomycin in the treatment of patients with infective endocarditis due to *S. aureus*. Based on the data provided in this NDA supplement, there is insufficient scientific evidence to support the use of daptomycin in the treatment of patients with *S. aureus* bacteremia who are assessed as having definite endocarditis based on modified Duke criteria. In addition, there is insufficient scientific evidence to support the use of daptomycin in the treatment of patients with evidence of endocardial involvement by echocardiography that is indicative of infective endocarditis. The empiric use of daptomycin in patients with *S. aureus* bacteremia who are at risk of infective endocarditis should be considered with extreme caution and limited to patients for whom the potential benefits outweigh the potential risks. Patients with *S. aureus* bacteremia associated with deep soft tissue involvement may require surgical drainage and debridement as adjunctive treatment measures. The efficacy of daptomycin in osteomyelitis, meningitis, prosthetic valve endocarditis, and deep organ infections was not studied. The efficacy of daptomycin in pediatric patients with *S. aureus* bacteremia and endocarditis has not been established.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

A prospective registry should be established for patients who are treated with daptomycin for the indications cited above who experience persistent or relapsing bacteremias and have *S. aureus* blood isolates that exhibit rising MICs to daptomycin during or immediately following the course of daptomycin therapy. In addition, post-marketing reports should be scrutinized for off-label use of the drug for suspected or proven infective endocarditis, with particular attention to cases in which the *S. aureus* isolate exhibited increasing MICs during or immediately following therapy compared to baseline and for cases in which doses higher than the labeled 6 mg/kg q24h dosage for this indication were used by the prescriber.

1.2.2 Required Phase 4 Commitments

Please refer to Section 1.2.3 below.

1.2.3 Other Phase 4 Requests

If the Sponsor desires to pursue a labeled indication for infective endocarditis due to *S. aureus*, the following phase 4 studies should be pursued:

(1) Extensive studies of the rabbit model of *S. aureus* endocarditis, in which concentrations of daptomycin are measured in cardiac vegetation tissues and a subset of treated animals are observed for several weeks to months following completion of therapy (but prior to sacrifice) for evidence of relapse or metastatic complications. Studies of the effects of daptomycin in tissue biofilms should also be pursued.

(2) A comparative randomized clinical study of subjects with definite endocarditis by modified Duke criteria having sufficient size and power to permit meaningful statistical inferences about drug performance. All enrolled study subjects should have cardiac echocardiography and a protocol-specified diagnostic imaging assessment for metatstatic complications as part of the pre-randomization evaluation. A substantial proportion of the study subjects should have echocardiographically-demonstrable evidence of endocardial involvement that is suggestive of infective endocarditis.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Daptomycin (Cubicin™) is a cyclic lipopeptide antibacterial agent that is administered intravenously. The drug was assessed for the proposed indication of *Staphylococcus aureus* bacteremia (SAB) including those with known or suspected endocarditis (SAIE) caused by methicillin-susceptible and methicillin-resistant strains in this efficacy supplement. The submission included pivotal study DAP-IE-01-02 and an integrated summary report, compiling limited additional clinical data based on two previous Phase 2 trials conducted by Eli Lilly & Company, two Phase 2 studies conducted by Cubist Pharmaceuticals, and two phase 3 studies of complicated skin and skin structure infections also conducted by Cubist Pharmaceuticals.

The pivotal study submitted in support of this efficacy supplement was study DAP-IE-01-02, a randomized, open-label, non-inferiority trial comparing i.v. daptomycin with conventional i.v. therapy [SSP (nafcillin, oxacillin, cloxacillin, or flucloxacillin) or

vancomycin] in patients with infective endocarditis (IE) or bacteremia due to *S. aureus*. There were 246 randomized subjects with an intent-to-treat (ITT) population of 235 patients who were treated for 10 to 42 days with study drug on an inpatient or outpatient basis.

1.3.2 Efficacy

Based on the FDA review of the results of study DAP-IE-01-02, daptomycin was non-inferior compared to standard of care (SSP or vancomycin) in treating patients with *Staphylococcus aureus* bacteremia (SAB). The data do not provide substantial evidence to support a claim of efficacy for daptomycin in the treatment of patients with infective endocarditis due to *S. aureus*, and the product labeling should indicate this limitation. If the applicant plans to pursue the indication of infective endocarditis due to *S. aureus*, additional phase 4 studies are warranted.

The analysis of the treatment effect of the study drug was complicated by multiple study design issues, including the following: (1) open-label trial design, (2) lack of assay sensitivity with respect to the endocarditis subgroups, (3) lack of adequate size and statistical power to assess efficacy in the patients with infective endocarditis as well as inconsistencies in efficacy across the IE subgroups of complicated and uncomplicated right IE and left IE, (4) lack of appropriate characterization of the study population in terms of prognostic factors that could affect outcome assessment at the primary and secondary endpoints in the all-comers and final diagnosis subgroups, (5) study design and conduct issues that tended to reduce observable differences between the two treatment groups, thereby supporting the conclusion of non-inferiority, (6) inconsistencies in endpoint assessment by the Independent External Adjudication Committee (IEAC), and (7) use of post-randomization data by the IEAC to assess outcomes and to classify subjects in final diagnosis subgroups.

1.3.3 Safety

Please refer to the report of Dr. Charles Cooper for full details and discussion of the integrated safety review for this submission.

1.3.4 Dosing Regimen and Administration

Daptomycin was dosed at 6 mg/kg q24h in study DAP-IE-01-02, which is a higher dosage compared to the current package labeling of 4 mg/kg q24h IV for the indication of complicated skin and skin structure infections.

1.3.5 Drug-Drug Interactions

Please refer to the report of Dr. Charles Cooper for full details on drug-drug interactions and discussion of the integrated safety review for this submission.

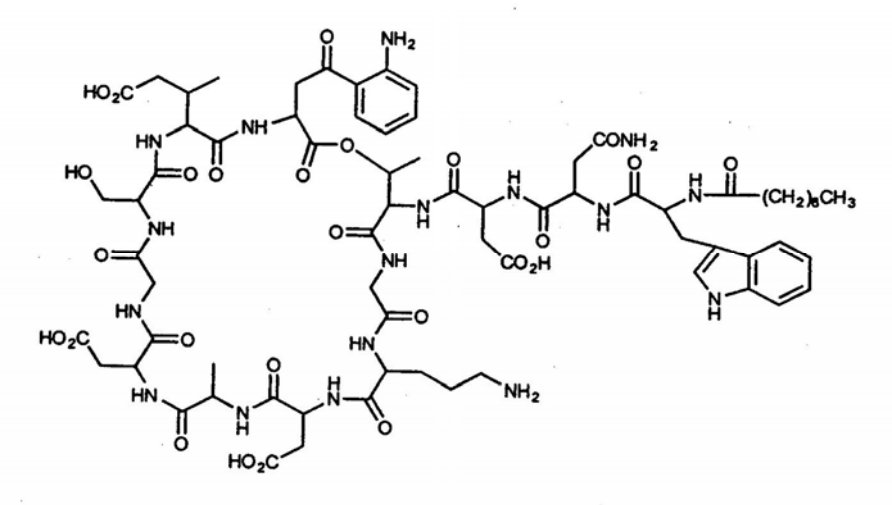
1.3.6 Special Populations

Pivotal study DAP-IE-01-02 involved subjects aged ≥18 years, including patients with diabetes mellitus, prior endocarditis, intravenous drug use, and HIV infection. Pediatric patients were not included in the study population.

2. INTRODUCTION AND BACKGROUND

2.1 Product Information

1. Drug Name: Daptomycin (Cubicin™)
2. Drug Class: cyclic lipopeptide antibacterial agent
3. Sponsor: Cubist Pharmaceuticals
4. Proposed Indications and Labeling Change:
   "*Staphylococcus aureus* bacteremia (SAB) including those with known or suspected endocarditis (SAIE) caused by methicillin-susceptible and methicillin-resistant strains."
5. Dosage Forms: injectable; 250 mg.vial and 500 mg/vial
6. Route of Administration: intravenous following reconstitution with 0.9% sodium chloride for injection
7. Chemical Structure:



8. Chemical Formula: $C_{72}H_{101}N_{17}O_{26}$
9. Chemical Name: 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
10. Molecular Weight: 1620.67

2.2 Currently Available Treatment for Indications

FDA-approved Indication for Daptomyccin:

- **Complicated skin and skin structure infections** caused by susceptible strains of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae* subsp. *equisimilis,* and *Enterococcus faecalis* (vancomycin-susceptible strains only).
- **D**aptomycin is not indicated in the treatment of pneumonia.

Currently, six drugs are labeled for the indications of bacteremia or bacterial endocarditis: cefazolin (Ancef™), gentamicin (Garamycin™ injectable), vancomycin (Vancocin™ HCL), and imipenem-cilastatin (Primaxin™), nafcillin, and oxacillin.

2.3 Availability of Proposed Active Ingredient in the United States

Daptomycin is a lipopeptide antibiotic derived from the fermentation product of *Streptomyces roseosporus*. It was manufactured as an investigational agent for clinical use. In the US, the product was distributed on behalf of the Sponsor by (b) (4) In Europe, daptomycin was shipped by (b) (4) to (b) (4) where it was labeled by country. It was then transferred to (b) (4) for distribution to investigative sites. All study drug shipment requests were processed and approved by the Sponsor. In the US, each investigative site was responsible for obtaining vancomycin, SSP, and gentamicin from commercial sources. In Europe, comparator agents were purchased, labeled, and distributed by (b) (4)

Daptomycin was approved for the single indication of complicated skin and skin structure infections in September, 2003. Daptomycin is not indicated in the treatment of pneumonia based on the results of two clinical studies: DAP-00-05, a comparative study of daptomycin with ceftriaxone in 661 subjects (Intent to Treat [ITT] population) for the

treatment of moderate to severe community-acquired pneumonia, and DAP-00-08, a comparative study of daptomycin with ceftriaxone in 173 subjects (ITT population) for the treatment of moderate to severe community-acquired pneumonia. In both clinical studies, the success rates for daptomycin were inferior to comparator. In Phase 3 studies of community-acquired pneumonia (CAP), the death rate and rates of serious cardiorespiratory adverse events were higher in daptomycin-treated patients than in comparator-treated patients. These differences were due to lack of therapeutic effectiveness of daptomycin in the treatment of CAP in patients experiencing these adverse events

The principal safety concerns from the current safety database for daptomycin include elevations in serum creatine phospokinase (CPK) and decreases in nerve conduction velocity. In Phase 3 complicated skin and skin structure infection (cSSSI) trials, elevations in serum creatine phosphokinase (CPK) were reported as clinical adverse events in 15/534 (2.8%) daptomycin-treated patients, compared to 10/558 (1.8%) comparator-treated patients. In a small number of patients in Phase 1 and Phase 2 studies, administration of daptomycin was associated with decreases in nerve conduction velocity and with adverse events (e.g., paresthesias, Bell's palsy) possibly reflective of peripheral or cranial neuropathy. Nerve conduction deficits were also detected in a similar number of comparator subjects in these studies. In Phase 3 cSSSI and CAP studies 7/989 (0.7%) daptomycin-treated patients and 7/1018 (0.7%) comparator-treated patients experienced paresthesias. Additional adverse events that occurred in 1-2% of patients in either daptomycin or comparator treatment groups in the cSSSI studies are as follows: edema, cellulitis, hypoglycemia, elevated alkaline phosphatase, cough, back pain, abdominal pain, hypokalemia, hyperglycemia, decreased appetite, anxiety, chest pain, sore throat, cardiac failure, confusion and Candida infections.

More recently, a labeling supplement was approved that cited post-marketing reports of rhabdomyolysis and hypersensitivity received following marketing of the drug in 2003.

2.4 Important Issues With Pharmacologically Related Products

At present, the only antibiotics that are FDA-approved for the treatment of S. aureus bacteremia and infective endocarditis are cefazolin, imipenem-cilastatin, vamcomycin, gentamicin, nafcillin, and oxacillin. There have been no recent revisions of the labels of the above products for efficacy or safety concerns.

2.5 Presubmission Regulatory Activity

Regulatory History of the Bacteremia Indication:
This is the first NDA submission for the labeled indication of *S. aureus* bacteremia and endocarditis in over twenty years, and it is the first such submission to include a randomized controlled clinical trial as the pivotal study for the indication. Prior to 1992, varying terminology had been used for antimicrobial labeling, including bacteremia,

septicemia, bacteremia/septicemia, bacterial septicemia, and septicemia (including bacteremia). Data to support labeling for such indications involved pooling of bacteremia cases from the following sources: clinical trials involving different primary sites of infection (such as lung or urinary tract), transient bacteremias, bacteremias secondary to an identified focus, and bacteremias of unknown origin. In 1992, the FDA published the Guidance to Industry on Clinical Development and Labeling of Anti-Infective Drug Products (also known as the "Points to Consider" document.) In relation to that document, a labeled indication referred to the treatment of an infection at a specific body site due to a specified pathogen.

The appropriateness of the bacteremia indication was the focus on a meeting of the Anti-Infective Drug Advisory Committee (AIDAC) in 1993. The Committee discussed a new proposed anti-infective drug indication, "bacteremic sepsis". The proposed indication was defined based on the published American College of Chest Physicians/Society of Critical Care Medicine Consensus Definitions of infection, bacteremia, and systemic inflammatory response syndrome (SIRS). However, following extensive discussion concerning issues such as the specificity of the definition, whether it is clinically relevant, and the heterogeneity of the patient populations, the Committee recommended that "bacteremic sepsis" be eliminated as an indication. The Committee's opinion was that the site of the infection was more important than the presence or absence of bacteremia. Product labeling should include bacteremia only in the context of a site-specific indication (such as community-acquired pneumonia with bacteremia).

In the ensuing years, bacteremia as a labeled indication was discussed at two AIDAC Meetings. At the 1998 AIDAC, consideration was given to primary bacteremia as a new indication and catheter-related bloodstream infections as a focus for future study. In 1999, the FDA/DAIDP Working Group issued a Draft Guidance for Industry on the Development of Antimicrobial Drugs for the Treatment of Catheter-related Bloodstream Infections (CRBSI), which was discussed at the 1999 Meeting of the AIDAC. No antimicrobial agents were approved for the bacteremia indication during those intervening years.

In April 2004, a joint workshop was conducted involving representatives of the US Food and Drug Administration (FDA), Infectious Disease Society of America (IDSA), and International Society of Antimicrobial Pharmacologists (ISAP) to address issues in study design and feasibility for the proposed indication of primary bacteremia due to *S. aureus* (PBSA). Among the issues discussed were that bacteremia is a laboratory finding and not a disease entity and that drug efficacy is most often related to the underlying source of the disease. Thus, drug efficacy may be different in pneumonia compared to complicated skin infections, although bacteremia may accompany both diseases. Participants discussed that disease with a primary focus and concomitant *S. aureus* bacteremia should be considered under the indication for the primary focus (such as pneumonia). They cited the need for clinical data from a serious disease indication as well as appropriate pre-clinical information before proceeding with clinical trials in PBSA due to the seriousness of the PBSA indication and high mortality rate in untreated disease.

In October 2004, the AIDAC discussed the feasibility of PBSA as an indication. During the meeting, there was considerable discussion about the difficulties encountered by some Sponsors in an effort to enroll a sufficient number of subjects due to the restrictive inclusion and exclusion criteria described in the Draft Guidance on CRBSI. The committee members concluded that PBSA was an acceptable indication and defined PBSA as referring to patients with *S. aureus* bacteremia without an obvious portal of entry. Patients with indwelling intravascular catheters could be included in the PBSA studies.

On March 6, 2006, a meeting of the AIDAC was convened regarding this application. Please refer to section 8.5 of this document for additional details.

2.6 Other Relevant Background Information

There are several relevant background issues in relation to the development of daptomycin as an anti-infective agent. First, daptomycin is a large molecule of high molecular weight compared to some of the other approved parenteral antistaphylococcal agents (such as vancomycin, MW 1485.73). As a consequence of its molecular size, the penetration of daptomycin into dysvascular cardiac valve vegetations and into biofilms could be hindered. Further studies are needed to investigate the interaction of daptomycin with biofilms. Second, daptomycin is a calcium-dependent molecule. Calcium induces conformational changes in its structure that augments the drug's interaction with bacterial membranes (2). As cardiac vegetations are relatively devoid of free calcium, additional studies should be performed to further characterize the interaction of daptomycin and calcium in relation to the drug's ability to penetrate into vegetations and sterilize bacteria residing there. Third, prior to Cubist' acquisition of the IND for daptomycin, Eli Lilly & Company conducted a phase 2 study of the drug in the treatment of subjects with Gram-positive bacteremia and endocarditis. In that study, the clinical efficacy of daptomycin at 3 mg/kg every 12 hours for the treatment of *S. aureus* infective endocarditis was lower than that of comparator (nafcillin and gentamicin, primarily). Further development of the drug was abandoned by Lilly shortly thereafter. However, following acquisition by Cubist Pharmaceuticals, it was postulated that the lower efficacy rate observed for daptomycin in the treatment of *S. aureus* endocarditis in that study was possibly due to the low daptomycin serum levels associated with the 3 mg/kg dose administered every 12 hours. The shortcomings of that dosage could be alleviated conceptually by administration of the drug in a 6 mg/kg once daily regimen, which was the dosage studied in the pivotal trial DAP-IE-01-02 in this supplement. Finally, daptomycin is not effective in the treatment of pneumonia. As described in section 2.3 of this document, Cubist conducted two controlled clinical trials of essentially identical design to evaluate daptomycin in the treatment of moderate to severe community-acquired pneumonia (CAP) due to *Streptococcus pneumoniae*, including penicillin-resistant strains. Each study was a randomized, multicenter, multinational, double-blinded, parallel group, active-treatment controlled trial using a dosage of 4 mg/kg q24h. The comparator in each trial was ceftriaxone 2 g q24h. In both trials, non-inferiority of daptomycin to comparator was not demonstrated. Subsequent research demonstrated that daptomycin interacts *in*

vitro with pulmonary surfactant (3), and this interaction was the possible mechanism for the drug's poor performance in the pneumonia studies.

3. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Please review to the original NDA submission for findings related to CMC issues. Please refer to the report of Dr. Peter Coderre for review of the Microbiology issues.

3.2 Animal Pharmacology/Toxicology

Please review to the report of Dr. Wendy Schmidt for findings related to animal pharmacology/toxicology.

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The Sponsor submitted materials electronically for the review of Study DAP-IE-01-02, including the study protocol, study report, multiple datasets, and multiple amendments (review aids) in response to various inquiries posed by the Division to the Sponsor during the review process. The integrated summary of efficacy relates to other clinical studies conducted in adults by Eli Lilly & Company and by Cubist, including studies B8B-MC-AVAE/B8B-EW-AVAG, B8B-MC-AVAM, DAP-BAC-9803, DAP-RRC-9804, DAP-SST-9801, and DAP-SST-9901.

4.2 Tables of Clinical Studies

Table 1: Summary Table of Clinical Studies

Study	Sponsor	Dates	Purpose	Control Group	Size (ITT)
B8B-MC-AVAE/ B8B-EW-AVAG	Lilly	1987-1988	Gram (+) skin/soft tissue infections	Conventional therapy	161
B8B-MC-AVAM	Lilly	1989-1990	Gram (+) bacteremia and endocarditis	Conventional therapy	124
DAP-BAC-9803	Cubist	1999-2001	Bacteremia due to Gram (+) bacteria	Vancomycin or semisynthetic penicillin	67
DAP-RRC-9804	Cubist	1999-2001	Hospitalized patients with Gram (+) infections that are refractory to or for which current therapy is contraindicated	Non-comparative	51
DAP-SST-9801	Cubist	1999-2001	Complicated skin and soft tissue infections	Vancomycin or semisynthetic penicillin	517
DAP-SST-9901	Cubist	2000	Complicated skin and soft tissue infections	Vancomycin or semisynthetic penicillin	562
DAP-IE-01-02	Cubist	2002-2005	Gram (+) bacteremia and endocarditis	Vancomycin or semisynthetic penicillin	235

Clinical study DAP-IE-01-02 is the pivotal study for the efficacy and safety review of this NDA efficacy supplement. The other studies in the table above provide limited additional efficacy data based on previous trials conducted by Eli Lilly and Company and Cubist Pharmaceuticals. Assessment of the efficacy results of study DAP-IE-01-02 will constitute the principal focus of this review document.

Studies B8B-MC-AVAE/B8B-EW-AVAG, B8B-MC-AVAM, DAP-BAC-9803, and DAP-RRC-9804 were phase 2 studies, whereas DAP-SST-9801 and DAP-SST-9901 were phase 3 studies. The Phase 2 Lilly studies demonstrated that daptomycin administered at a dose of 2 mg/kg q24h (Study B8B-MC-AVAE/B8B-EW-AVAG, designated AVAE/AVAG) and 3 mg/kg q12h (Study B8B-MC-AVAM) is active in treating Gram-positive skin and skin structure infections and is as safe and well tolerated as standard of care. Cubist subsequently conducted studies of daptomycin at 3 different doses for bacteremia (Study DAP-BAC-9803) and a variety of Gram-positive infections (Study DAP-RRC-9804). The goals of these studies were to further explore the safety, efficacy and dose-response relationship of the 4 mg/kg and 6 mg/kg q24h doses and the 3 mg/kg q12h dosage regimen. Further, Cubist studied daptomycin at 4 mg/kg q24h for complicated skin and skin structure infections. Two separate randomized controlled

clinical trials (Studies DAP-SST-9801, DAPSST- 9901) demonstrated that daptomycin is as effective as standard therapy and led to the licensing of daptomycin for complicated skin and skin structure infections. Although bacteremic patients were excluded from these trials, 24 patients were diagnosed with Gram positive bacteremia following enrollment, 12 of whom had *S. aureus* bacteremia.

4.3 Review Strategy

The FDA Medical Officer conducted an independent review of a random sample of 118 individual subject case report forms and patient profiles, which constituted 50% of the ITT population of 235 subjects. The case reports and patient profiles were assessed for the following information: case-id number, IEAC Entry Diagnosis, IEAC Outcome at EOT, IEAC Outcome at TOC, IEAC Final Diagnosis, baseline pathogen, risk factors, local and central Duke echocardiography reports, duration of bacteremia, persistence or relapse of bacteremia, disk susceptibility and MIC pattern of *S. aureus* isolates from the blood and other body sites (where provided), potentially effective non-study antibiotic use, procedures and diagnostic tests, adverse events, medical history and physical examination findings at study visits, investigator comments, duration of study medication, investigator assessment at EOT, inclusion and exclusion criteria violations, and reasons for early termination from study participation and premature discontinuation of study medication, and compliance with the procedures, definitions, and provisions of conduct according to the study protocol. During the course of the FDA review, the FDA Medical Officer reviewed the remaining 117 case report forms and patient profiles in order to gain a better understanding of the totality of the clinical experience, the IEAC and Investigators' diagnoses and outcome assessments, and the duration of study medication administered.

4.4 Data Quality and Integrity

For purposes of the FDA review of this submission, the Sponsor provided electronic versions of the all of the case report forms and patient profiles for purposes of verifying the data submitted as evidence. The Sponsor conducted the study in accordance with good clinical practices (see below).

4.5 Compliance with Good Clinical Practices

According to the Sponsor, the study was conducted in accordance with the ethical principles articulated in the Declaration of Helsinki and its amendments; with the Harmonized Tripartite Guidelines for Good Clinical Practices (GCP) issued by the International Conference on Harmonization (ICH); and with the local laws and regulations for the use of investigational therapeutic agents. These practices included:

IRB/IEC procedures, informed consent, protocol adherence, administrative documents, drug supply accountability, data collection, patient records (source documents), adverse event recording and reporting, inspection and audit preparation, and records retention. The Investigator was made aware that regulatory authorities and representatives of the Sponsor could inspect the documents and patient records at any time. All patient identities were kept confidential. Each patient was assigned a unique patient number, which in turn was used on the case report form (CRF) in place of the patient's name.

4.6 Financial Disclosures

The sponsor submitted financial disclosures for Study Dap-IE-01-02, including Form 3454 for the study investigators and Form 3455 for three investigators for services unrelated to the execution of the study. There were no financial disclosures that would cast doubt on the study findings.

5. CLINICAL PHARMACOLOGY

Please refer to the report of Dr. Charles Bonapace for review of the Clinical Pharmacology issues.

5.1 Pharmacokinetics

5.2 Pharmacodynamics

5.3 Exposure-Response Relationships

6. INTEGRATED REVIEW OF EFFICACY

6.1 Indication

This efficacy supplement was submitted to the FDA in support of the proposed indication of "*Staphylococcus aureus* bacteremia (SAB) including those with known or suspected endocarditis (SAIE) caused by methicillin-susceptible and methicillin-resistant strains".

6.1.1 Methods

Study DAP-IE-01-02 is the pivotal study in relation to the efficacy and safety of daptomycin in the treatment of staphylococcal bacteremia and endocarditis. Additional supportive data was provided in the integrated summary of efficacy regarding the clinical studies conducted by Eli Lilly & Company and Cubist Pharmaceuticals as described in Section 4.2 of this report.

6.1.2 General Discussion of Endpoints

The primary efficacy endpoint for study DAP-IE-01-02 to determine the success of the trial is the IEAC Outcome assessment at the TOC visit in the ITT and per-protocol (PP) populations. This is a composite endpoint that incorporates both clinical and microbiological outcomes in determining success. Based on discussion with the Agency, analyses were to be performed on the ITT and PP populations and were to be considered co-primary for this study. Because the size of the study was not powered for the PP population, the lower bound of the confidence interval (CI) in the PP population did not have to meet the guidelines established for the ITT population. However, the findings in the PP population were anticipated to be logically consistent with the findings in the ITT population in order for the outcome of this study to be considered as positive; clinical judgment would need to be applied in interpreting the study results. Thus, the outcome of a positive study was to be determined by consideration of the totality of the data, which would include evaluation of supportive sensitivity analyses.

Due to the open-label nature of the trial, the heterogeneity of the population, and the complexity of diagnosis and treatment outcome assessments in patients with *S. aureus* bacteremia and IE, an Independent External Adjudication Committee (IEAC) was convened to conduct a clinical review of the data from this trial in order to make independent assessments of Entry and Final diagnoses and outcome at selected time points (EOT and TOC). The committee was composed of five infectious disease experts, including one chairperson and four members as follows: (b) (4)

The IEAC was chartered to conduct a clinical review of final, locked patient data in a blinded fashion to establish:

- Diagnosis at study entry, based on the Modified Duke Criteria (Definite IE, Possible IE, Not IE).
- Diagnosis at EOT and Final Diagnosis, according to the diagnostic subgroups (LIE, Complicated RIE, Uncomplicated RIE, Complicated Bacteremia, Uncomplicated Bacteremia).
- Outcome at EOT (Success, Failure, Non-evaluable).
- Outcome at TOC (Success, Failure, Non-evaluable [carried forward from EOT]).
- Presence of polymicrobial bacteremia.

A chairperson was designated (b) (4) and the remaining f members were divided into 2 reviewing teams. All cases that the IEAC reviewed were blinded to study drug treatment. The chairperson was to review all cases and the 2 teams each reviewed 50% of cases. The members received their cases approximately 2 to 3 weeks prior to each IEAC meeting. During the meeting, each case was presented by a reviewing team member to his or her partner. In the event of a disagreement, the case was to be reviewed by the other team. If the other team also disagreed, the case was referred to the chairperson. IEAC members who were also study Investigators were not to review data from their site. The chairperson was to review results from each team for all cases and confirm all diagnoses and outcomes. To ensure consistency of results between the two teams, randomly selected cases were to be reviewed by both teams and concordance was to be assessed. IEAC meetings were held on 4 July 2004, 9 November 2004, 4 April 2005 and 18 May 2005. At each meeting, the IEAC reviewed individual patient data, blinded to study drug treatment, that had undergone final lock procedures at the CRO; any changes made to these data after this time were presented to the IEAC Chair to determine if re-adjudication of a case was necessary due to the data changes. IEAC-determined diagnoses and outcomes were recorded on the IEAC case report form (CRF) and entered into a database that was kept separate from the clinical database by (b) (4). Copies of each patient casebook reviewed by the IEAC, including the completed IEAC CRF, were included with the electronic submission.

Based on the review of the submission by the FDA team, major limitations of the Sponsor's primary endpoint and the planned endpoint analyses were identified including the following: (1) Conceptually, the primary endpoint attempts to bridge outcome assessments derived from an all-comers, pathogen-driven entry population of subjects to five different protocol-specified clinical disease subgroups that encompass the clinical spectrum of complicated and uncomplicated bacteremia and endocarditis due to *S. aureus* in a retrospective manner using post-randomization data. The generalizability of the results of the all-comers data and the ability to use such data to draw inferences about drug efficacy in the five clinical subgroups is problematic. Classifying all study subjects by clinical disease subgroup at study entry and then randomizing them within each clinical subgroup would have been preferred, as it would have relied solely upon pre-randomization data and would have ensured that the clinical subgroup distribution between the two main treatment arms would be virtually identical eliminating confounding from post-randomization variables. (2) The study was sized and powered for statistical analysis of the all-comers population and not in relation to analysis of the final diagnosis subgroups. Thus, it was not possible to make meaningful statistical inferences in relation to study drug efficacy in each of the final diagnosis clinical subgroups (particularly with respect to infective endocarditis).

In addition, it should be noted that, in general, the IEAC did not consider the recovery of both MSSA and MRSA from baseline blood cultures as a polymicrobial infection. In the FDA analysis, they were considered as separate pathogens when recovered simultaneously from the baseline cultures.

6.1.3 Study Design

Study DAP-IE-01-02 was the pivotal trial submitted in support of this efficacy supplement for the indication of *Staphylococcus aureus* bacteremia (SAB) including those with known or suspected endocarditis (SAIE) caused by methicillin-susceptible and methicillin-resistant strains. This was a multicenter study conducted in the United States (US) and Europe. Seventy-six (76) study sites were initiated for the study in the US, Belgium, France, Germany, Italy, and Spain and patients were enrolled at a total of 48 sites, including sites in the US, Belgium, France and Germany. The study was randomized (1:1) and open-label comparing i.v. daptomycin with conventional i.v. therapy [SSP (nafcillin, oxacillin, cloxacillin, or flucloxacillin) or vancomycin] in patients with IE or bacteremia due to *S. aureus*. Daptomycin was to be administered at 6 mg/kg q24h and the SSPs at 2 g q4h. In patients with normal renal function, vancomycin was to be administered 1 g q12h; vancomycin dosing was to be adjusted based on renal function and plasma levels according to the Investigator's standard practice and manufacturer's guidelines. All patients randomized to conventional treatment and patients with LIE randomized to daptomycin were to receive synergistic gentamicin for the first 4 days (or until blood cultures had been negative for 48 hours); patients with uncomplicated RIE due to a methicillin-susceptible isolate were to receive gentamicin for the entire 14-day course if short course therapy was deemed appropriate by the principal Investigator/treating physician. Loading doses of gentamicin may have been used with prior approval of the medical monitor; dosing of gentamicin also was to be adjusted based on renal function.

Objectives of the Study

The primary objective of the study was to demonstrate that daptomycin is not inferior to comparator in the treatment of *S. aureus* bacteremia and IE as assessed by the Independent External Adjudication Committee (IEAC) outcome at Test of Cure (TOC) in the Intent-to-Treat (ITT) population.

The secondary objectives of the study were as follows:

- To compare clinical success rates between daptomycin and comparator in the treatment of *S. aureus* bacteremia and IE as assessed by the IEAC outcome at End of Treatment (EOT) in the ITT population.
- To compare clinical success rates between daptomycin and comparator in the treatment of *S. aureus* bacteremia and IE as assessed by the IEAC outcome at EOT and TOC in the Per Protocol (PP) population.
- To compare clinical success rates between daptomycin and comparator in the treatment of *S. aureus* bacteremia and IE as assessed by the IEAC outcome at EOT for each of the diagnoses defined by the IEAC in the ITT population.
- To compare clinical success rates between daptomycin and comparator in the treatment of *S. aureus* bacteremia and IE as assessed by the IEAC outcome at EOT for each of the diagnoses defined by the Investigator in the ITT population.

- To compare microbiologic eradication rates between daptomycin and comparator.
- To demonstrate that survival rates are similar between daptomycin and comparator in the ITT population.
- To evaluate the safety of daptomycin as compared to comparator in the safety population.
- To assess the pharmacokinetics of daptomycin.
- To compare the pharmacoeconomic impact of daptomycin with that of comparator.

(Medical Officer Comments: As an open-label study, it is subject to investigator bias in terms of patient selection, duration of study drug, attribution of adverse effects to study drug, and outcome assessments. The use of an IEAC was one approach to achieving blinded assessment of outcome, but it also introduced additional subjective clinical perspectives, was performed retrospectively, and involved post-randomization data that was not accessible to the investigators in prospectively managing each study subject.)

Treatments Administered

Daptomycin

Patients randomized to the daptomycin treatment group were to receive daptomycin at a dose of 6 mg/kg administered every 24 hours as an i.v. infusion over 30 minutes. Daptomycin was to be reconstituted in the vial with 10 mL (500 mg vials) 0.9% sodium chloride (normal saline, NS) such that the concentration of the reconstituted daptomycin solution was 50 mg/mL and further diluted in 50 mL 0.9% sodium chloride (NS). The actual dose administered was to be determined based on the patient's actual body weight and could be adjusted on a weekly basis if there was a fluctuation of >5% in the patient's weight.

Conventional Therapy: Vancomycin or SSP

Patients randomized to receive conventional therapy were to receive vancomycin or semi-synthetic penicillin (SSP) (nafcillin, oxacillin, cloxacillin, or flucloxacillin). Patients for whom susceptibility results were unknown at the time of randomization were to receive vancomycin as the comparator medication. Patients whose isolates were reported as MRSA or who had a history of allergy to SSP, were to remain on vancomycin as comparator. At the discretion of the Investigator, patients with a history of allergy to other β-lactam antibiotics may have been designated as allergic to SSP. Patients who were not designated as allergic to SSP and whose isolates were reported as MSSA were to receive SSP as comparator. Vancomycin and SSP could have been administered on the same day, if required.

Patients treated with vancomycin were to receive a dose of 1 g, reconstituted with 20 mL of sterile water for injection (or 5% Dextrose or 0.9% Sodium Chloride), diluted with 200 mL of diluent (5% Dextrose or 0.9% Sodium Chloride), administered as an i.v. infusion over 60 minutes every 12 hours. Vancomycin dosing was to be adjusted based on renal function and plasma levels according to the Investigator's standard practice and local hospital guidelines.

Patients treated with one of the SSPs were to receive the medication at a dose of 2 g, reconstituted in 15 mL of sterile water for injection USP or 0.9% sodium chloride injection USP, administered as an i.v. infusion over 15 minutes every 4 hours.

(Medical Officer Comment: It is notable that some comparator-treated patients received SSP by continuous infusion rather than the intermittent infusion as described above. The potential effect of continuous infusion on serum drug levels and ultimately on drug efficacy was not elucidated.)

Gentamicin

Gentamicin (1 mg/kg actual body weight) was to be reconstituted in 2 mL of sterile 0.9% Sodium Chloride for injection, diluted with 50 mL of sterile 0.9% Sodium Chloride for injection, and administered as an i.v. infusion over 30 minutes every 8 hours. All patients randomized to conventional treatment and patients with LIE randomized to daptomycin were to receive synergistic gentamicin for the first 4 days (or until blood cultures had been
negative for 48 hours); patients with uncomplicated RIE due to a methicillin-susceptible isolate were to receive gentamicin for the entire 14-day course if short course therapy was deemed appropriate by the principal Investigator/treating physician. Loading doses of gentamicin may have been used with prior approval of the medical monitor. Gentamicin dosing was to be adjusted based on renal function according to the Investigator's standard practice and manufacturer's guidelines.

Randomization and Assignment of Subjects to Treatment Groups

Patients were randomized to treatment, daptomycin or conventional therapy (vancomycin or SSP), based on a centralized computer-generated randomization schedule designed to achieve a 1:1 ratio of patients, stratified by investigative site. With implementation of Amendment 4A, the study was opened to enrollment of LIE patients. Because of the late admission of LIE patients to the study and the small number of patients expected to be available for enrollment, a separate, centralized randomization, without stratification by investigative site, was implemented for patients with a high-likelihood of LIE at the time of enrollment. When a patient met all eligibility requirements, study site personnel were to contact an interactive voice response system (IVRS) to obtain a patient number and treatment assignment. Following randomization, a fax was to be sent to the site indicating that the patient had been randomized and the patient number and treatment assigned. Once a patient number and treatment were assigned to a given patient, that number could not be reused, even if the patient withdrew from the study prior to receiving any study medication.

Patients may have been randomized and study medication initiated on the basis of a single positive peripheral blood culture for *S. aureus*. Prior to Amendment 4A, patients whom the Investigator believed to have a high-likelihood of LIE were excluded. Subsequent to this amendment, patients with LIE were permitted enrollment and were separately randomized to ensure an equal distribution of these patients in the 2 treatment groups. If susceptibility results were unknown at the time of randomization, patients assigned to conventional therapy were to receive vancomycin. If the organism proved to

be MSSA, therapy was to be changed to SSP, unless contraindicated by a documented prior history of penicillin or β-lactam drug allergy.
(Medical Officer Notes: Randomizing subjects based on only a single positive blood culture without complete characterization of their underlying illness created uncertainties for the FDA review team with respect to the following: (1) the patient attribute(s) that led to the onset of the S. aureus bacteremia, (2) were there differences in the presence or absence of the attribute(s) that ultimately impacted prognosis and treatment outcome, (3) did inequities in site-specific disease distribution contribute to imbalances in terms of the overall outcome, variations in use of adjunctive surgical interventions, and different prognoses. It would have been preferable to have characterized the study population fully at study entry in terms of the underlying disease and any other identifiable attributes that could have led to onset of the S. aureus bacteremia or complicated response to study drug therapy prior to randomization even if this involved a delay of several days before randomization to complete diagnostic testing.)

Blinding
In spite of its open-label design, the Sponsor implemented procedures to enhance the rigor of the trial by keeping Sponsor's employees, other than those identified below, blinded to the treatment assignment of individual patients.

- Sponsor physicians directly involved in discussions with sites regarding individual patient safety were in some instances unblinded to study drug treatment for the specific patients being discussed.
- Pharmacovigilance personnel were unblinded to study drug treatment for patients with SAEs.
- Three Sponsor employees had access to study drug listings. These listings were not accessed during data review to ensure an unbiased data cleaning process. It was necessary, however, to review the medication listings as part of the data quality control process. This review occurred at a separate time and place from the remaining blinded study data review.
- The Director of Pharmacokinetics had access to the identity of patients who received daptomycin in order to prepare blinded PK data for DMC review; he was not involved in reviewing any of the clinical data.
- The Manager of Data Management had access to unblinded data in order to:
    - verify the accuracy of the PK data files, and
    - prepare and blind local microbiology data for reconciliation with central microbiology laboratory data by the Sponsor's Clinical Microbiology Department.
- The Sponsor physician who reviewed study medication listings to determine individual patient adherence to study medication was not involved in the conduct of the study.
- Two Sponsor employees from the Quality Assurance department had access to unblinded data when auditing CRF data and the database.

At no time did any Sponsor employee have access to summaries of unblinded aggregated

study data, nor was unblinded information on any given patient ever discussed between those few individuals within the company who had access to individual drug assignments and those individuals responsible either for the study design, for the study analysis, or for communications with the FDA or the public

Evaluations

Baseline evaluations were to be performed within 2 calendar days prior to first dose and included medical, antibiotic and medication history, physical examination, blood cultures, chest x-ray, electrocardiogram (ECG), and clinical laboratory tests (including hematology, clinical chemistry, coagulation, urinalysis, pregnancy test and CPK). All patients were to undergo transesophageal echocardiography (TEE) for the diagnosis of IE by the end of Day 5. During study treatment, daily and weekly assessments were to be performed including blood cultures, physical examinations, vital signs, ECGs, and clinical laboratory tests, as well as appropriate tests to rule-out metastatic foci of infection. An EOT evaluation was to be performed on the day of, or within 3 days after, study treatment completion or early termination.

Transesophageal echocardiography

All patients were to have a transesophageal echocardiography (TEE) performed by the end of Day 5. The site results of the TEE were to be used by the Investigator to determine the presence or absence of IE, as defined by the Modified Duke Criteria[1], to include Definite IE, Possible IE and Not IE. In addition, the study site was to send a copy of the echocardiogram to the central echocardiography laboratory, the Duke CORE Echo laboratory, Durham, NC, for blinded, independent evaluation. The assessment by the Duke CORE Echo laboratory was used by the IEAC for determination of Entry and Final diagnoses; these results were not used by the Investigator. The IEAC used the local echocardiography results in assigning the diagnosis at EOT, as their goal was to understand how the duration of therapy was selected. If the patient had a transthoracic echocardiogram (TTE) considered by the Investigator to be diagnostic for IE; that study may have been submitted in place of a TEE.

(Medical Officer Notes: The use of post-randomization central echocardiography by the IEAC in making final diagnosis assessments without providing the same information to investigators managing the patients' care prospectively limited the overall effects of randomization. The discrepancies between local and central echocardiographic interpretations may have underscored differences in assessment of the correct diagnosis by the IEAC and investigators, which also has implications in terms of the duration of study drug therapy and overall prognosis.)

Investigator's Assessment of Clinical Response

For patients who completed study treatment, the Investigator was to determine the patient's
clinical response at the EOT, TOC, and PS evaluations using the following categories:

- Cure: Resolution of clinically significant signs and symptoms associated with admission infection (i.e., return to pre-infection baseline). No further antibiotic therapy required for the primary infection under study.

- Improvement: Partial resolution of clinical signs or symptoms of infection such that no further antibiotic therapy was required for the primary infection under study.
- Failure: Inadequate clinical response to therapy - additional antibiotic therapy required for primary infection under study.
- Not seen: Patient was not available to be examined and assessed.

For patients who terminated study medication early, the Investigator was to determine the patient's response at the time of early termination of study medication using the following categories:

- Excellent: Complete resolution of signs and symptoms of *S. aureus* infection.
- Satisfactory: Partial resolution of signs and symptoms of *S. aureus* infection consistent with effective therapy (signs and/or symptoms present were to be specified).
- Unsatisfactory: Resolution of signs and symptoms of *S. aureus* infection substantially less than expected at this stage of treatment (signs and/or symptoms were to be specified).

IEAC Assessment of Diagnosis and Outcome

The IEAC was to conduct a clinical review of final patient data, blinded to treatment to determine diagnoses, assess outcome and determine the presence of polymicrobial bacteremia as detailed below:

1). Determination of IEAC diagnoses:

- Establish Entry Diagnosis based on the Modified Duke Criteria at Baseline (Definite IE, Possible IE or Not IE).
- Establish EOT and Final diagnoses (LIE, complicated RIE, uncomplicated RIE, complicated bacteremia, uncomplicated bacteremia).

  For EOT diagnosis, the IEAC used all available clinical, microbiological and safety data, as well as the local echocardiography reading, through the time of the EOT visit to determine the patient's "most severe diagnosis" while on therapy. This diagnosis was made in order to understand how the duration of therapy was selected.

- For Final Diagnosis, the IEAC used all data through the last visit (including the core echocardiography reading and the Investigator's assessment at the TOC visit) to determine the patient's "most severe diagnosis" over the course of the study. While the IEAC reviewed all available data, including that from the PS visit, if applicable, only data obtained through the TOC visit was used to determine Final Diagnosis.

  (Medical Officer Notes: The assignment of an Entry and Final diagnosis by the IEAC was problematic in this study, because the assignments were performed post-randomization and were based in part on post-randomization data (such as

echocardiography). The use of the "most severe diagnosis" by the IEAC could be a potential source of misclassification in assessment of the subject's diagnosis and could contribute to disparities between the Investigator and IEAC diagnosis assessments at EOT. As a consequence of the disparities in diagnosis assessments, the duration of study medication employed by the Investigators may not be aligned with the protocol-specified minimum treatment regimens as described below in Table XXX.)

2). Determination of IEAC outcomes of Success, Failure and Non-evaluable at EOT and TOC visits:

Definitions for Success, Failure and Non-evaluable at EOT:

Patients were to be classified by the IEAC as "Success" at EOT if they met all of the following criteria:

- Were judged as cured or improved by the IEAC at EOT.
- Had a negative blood culture at EOT.
- Did not receive a potentially effective non-study (PENS) antibiotic that could have altered the therapeutic outcome at EOT (as defined by the IEAC).
- Received at least the minimum amount of study medication.

Patients were to be classified by the IEAC as "Failure" at EOT if they met any one of the following criteria:

- Were judged a clinical failure by the IEAC at EOT.
- Had persisting or relapsing bacteremia or no blood culture at EOT.
- Died.
- Received a PENS antibiotic that influenced therapeutic outcome (as defined by the IEAC).
- Discontinued study medication prematurely according to the Investigator for one or more of the following reasons:
    - Adverse event.
    - Microbiological failure.
    - Clinical failure.

Patients were to be classified by by the IEAC as "Non-evaluable" at EOT if they were neither a success nor a failure and discontinued study medication prematurely according to the Investigator for one or more of the following reasons:

- Patient's care transferred to another physician.
- Patient withdrew consent, continued with alternative i.v. antibiotic treatment.
- Patient discontinued all i.v. therapy for the current infection against medical advice.
- Patient was lost to follow-up.
- Other administrative reason (reason is specified by the IEAC).

Definitions for Success, Failure and Non-evaluable at TOC:

Patients were to be classified by the IEAC as "Success" at TOC if they met all of the

following criteria:

- Were a success as determined by the IEAC outcome at EOT.
- Were judged as cured or improved by the IEAC at TOC.
- Had a negative blood culture at TOC.
- Did not receive a PENS antibiotic that could have altered the therapeutic outcome at TOC (as defined by the IEAC).
- Received at least the minimum amount of study medication.

Patients were to be classified by the IEAC as "Failure" at TOC if they met any one of the following criteria:

- Were judged a clinical failure by the IEAC at EOT or TOC.
- Had persisting or relapsing bacteremia or no blood culture at TOC.
- Died.
- Received a PENS antibiotic that influenced therapeutic outcome (as defined by the IEAC).
- Discontinued study medication prematurely.

Patients who were classified by the IEAC as "Non-evaluable" at EOT were considered "Non-evaluable" by the IEAC at TOC. Patients who were determined by the IEAC to be "Failures" at EOT were considered "Failures" at TOC; i.e., "Failures" were carried forward.

(Medical Officer Comments: The IEAC outcomes at EOT and TOC were a composite of clinical and microbiology data. Although the protocol requires that subjects without a blood culture at EOT be deemed as a failure, the IEAC imputed a successful EOT outcome for subjects who had negative blood cultures at TOC and no obvious use of PENS antibiotics. An identical approach was applied by the IEAC for subjects who had no blood culture at TOC but had a negative post-study blood culture, stable clinical examination, and no record of PENS use. Although this approach is reasonable in terms of clinical medical practice, it is a significant deviation from the original study design and tends to make the two treatment groups appear equivalent when applied in the setting of a clinical trial to assess the efficacy of a drug. In addition, the use of such imputed data could potentially be biased if applied on a non-random basis by the IEAC.

The IEAC did not articulate a clear definition of what specific antibiotics constituted PENS, the relationship of the PENS antibiotics to pre-enrollment, on study, or post-EOT time periods, or the duration of PENS that would be considered sufficient to confound assessment of the treatment effect of the study drug. It is apparent that many of the PENS determinations by the IEAC were made on an individual case-by-case basis using subjective clinical perspectives and without a pre-specified algorithm.)

3). Review of blood culture data to determine the presence of polymicrobial bacteremia at Baseline.

(Medical Officer Comments: The FDA considered recovery of MRSA and MSSA from the same blood culture(s) as polymicrobial infections, although they are the same species of Stpahylococci.)

Microbiological Evaluations

The microbiological response was to be ascertained from information obtained at the local laboratory reported on the CRF, from data provided by the central microbiology laboratory, and from data generated through supplemental microbiological testing. This information was to be evaluated as described below. Microbiological outcomes by patient were part of the IEAC outcome.

The study treatment regimen was to be based on the patient's diagnosis and the susceptibility of the *S. aureus* isolate. Baseline diagnosis was based on the Modified Duke Criteria[1] and included the following categories:

Definite IE.
Possible IE.
Not IE.

(Medical Officer Comments: As originally designed, the modified Duke criteria were developed to increase the sensitivity of assessing patients for the likelihood of having infective endocarditis (4). Although this approach is reasonable when applied in clinical medical practice in order to avoid missing a potential case of IE, the Duke criteria are not specific enough to ensure that all individuals classified as possible IE actually have endocarditis. The assessment of subjects at entry using only the Duke criteria overestimates the true number of subjects with IE in the study population and provides no anatomical characterization of potential portal(s) of entry for staphylococcal infection or evidence of concomitant metastatic infection complications.)

Diagnosis at EOT was defined as follows and reflected the Investigator's chosen duration of therapy:

S. aureus LIE
: Definite or possible IE according to the Modified Duke Criteria[1]; and echocardiographic evidence of involvement or predisposing pathology of the mitral or aortic valve.

Complicated *S. aureus* RIE
: Definite or possible IE according to the Modified Duke Criteria[1]; and echocardiographic evidence indicating no predisposing pathology or active involvement of either the mitral valve or the aortic valve; and any of the following additional criteria:
  - patient was not an IVDU,
  - evidence of extrapulmonary sites of infection,
  - serum creatinine ≥2.5 mg/dL,
  - blood cultures yielded MRSA.

Uncomplicated *S. aureus* RIE

Definite or possible IE according to the Modified Duke Criteria[1]; and echocardiographic evidence indicating no predisposing pathology or active involvement of either the mitral valve or the aortic valve; and

- history of intravenous drug use; and
- no evidence of extrapulmonary sites of infection; and
- serum creatinine <2.5 mg/dL; and
- blood cultures yielded only MSSA.

Complicated *S. aureus* bacteremia

Patient did not have IE according to the Modified Duke Criteria[1]; and *S. aureus* was isolated from blood cultures obtained on at least two different calendar days up through Day 5 (one blood culture must have been obtained from a fresh venipuncture site and one blood culture must have been obtained on the calendar day of or the day immediately preceding the first dose of study medication (Day –1 or Day 1); and/or metastatic foci of infection (deep tissue involvement) was present including, for example, septic arthritis, deep tissue abscess, or infection involving prosthetic material including intravascular foreign material not removed by Day 4.

Uncomplicated *S. aureus* bacteremia

Patient did not have IE according to the Modified Duke Criteria}; and *S. aureus* was isolated from blood culture(s) obtained on a single calendar day within 2 calendar days preceding the first dose of study medication (Day –2 or Day –1); and no metastatic foci of infection was present; and no infection of prosthetic material was present (not including intravascular foreign material removed by Day 4).

(Medical Officer Comments: The definitions for the five final diagnosis subgroups involved use of post-randomization data. In addition, the definitions are not based on a uniform set of validated criteria that are accepted as standard within the medical profession currently. In relation to specific definitions are the following comments: (1) The definitions of RIE above do not require echocardiographic evidence of tricuspid or pulmonic valve involvement, whereas the definition of LIE requires echocardiographic evidence of left-sided heart valve (mitral or aortic) involvement. In the absence of echocardiographic evidence of valvular vegetations or perforations for the diagnosis of RIE, the specificity of that diagnosis is decreased and the applicable clinical subgroups of patients with RIE may include subjects who do not actually have the disease. (2) The definitions above of complicated and uncomplicated S. aureus RIE involve evidence of extrapulmonary sites of infection, and the definitions of complicated and uncomplicated bacteremia refer to evidence of metastatic foci of infection. It is noteworthy that there is no requirement for all study subjects to have a standardized radiologic imaging evaluation for metastatic extrapuulmonary infections. The decision as to the intensity and scope of such a diagnostic evaluation was left solely to the discretion of the individual Investigators. Thus, the magnitude of subjects with evidence of extrapulmonary metastatic sites of infection as described in the sponsor's study report is likely an underestimate due to the lack of a systematic requirement for such diagnostic imaging for all study participants.

(3) The use of the criteria of two calendar days to define complicated bacteremias rather than more specific criteria of two blood cultures separated by ≥24 hours in time could lead to an overestimate of the number of subjects with a complicated bacteremia. It is possible to have positive blood cultures over two calendar days that are not separated by 24 hours in time frame yet still be considered as a complicated bacteremia according to the definition above. This approach could lead to subject misclassification, especially in instances where the Investigator has treated a study subject for uncomplicated bacteremia with a short course of study drug therapy on clinical grounds, but the same patient is later reclassified as having complicated bacteremia by the IEAC due only to the number of positive blood cultures as above.)

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Minimum Study Treatment Regimen and Duration

The duration of study treatment was to be based on the patient's diagnosis as determined by the Investigator and the susceptibility of the *S. aureus* isolate. The protocol-defined treatment regimens are outlined in the following table which is based on the Modified Duke Criteria.[1] Treatment may have been extended at the request of the Investigator, with the concurrence of the medical monitor, based on the diagnosis and clinical status of the patient. During the conduct of the study, actual treatment duration was based on Investigator discretion.

Table 2: Protocol-Specified Minimum Treatment Regimens for Specific Diagnoses

Diagnosis Organism	Daptomycin	Conventional Therapy
LIE		
MSSA	28 to 42 days plus gentamicin first 4 days (or until blood cultures had been negative for 48 hours)	28 to 42 days SSP plus gentamicin first 4 days (or until blood cultures had been negative for 48 hours)
MRSA	28 to 42 days plus gentamicin first 4 days (or until blood cultures had been negative for 48 hours)	28 to 42 days vancomycin plus gentamicin first 4 days (or until blood cultures had been negative for 48 hours)
Complicated RIE		
MSSA	28 to 42 days	28 to 42 days SSP plus gentamicin first 4 days (or until blood cultures had been negative for 48 hours)
MRSA	28 to 42 days; or 14 to 28 days if only complicating factor was MRSA	28 to 42 days vancomycin plus gentamicin first 4 days (or until blood cultures had been negative for 48 hours)
Uncomplicated RIE		
MSSA	14 to 28 days	14 days SSP and gentamicin; or 28 to 42 days SSP plus gentamicin first 4 days (or until blood cultures had been negative for 48 hours)
Complicated *S. aureus* bacteremia without IE		
MSSA	28 to 42 days	28 to 42 days SSP plus gentamicin first 4 days (until blood cultures had been negative for 48 hours)
MRSA	28 to 42 days	28 to 42 days vancomycin plus gentamicin first 4 days (until blood cultures had been negative for 48 hours)
Uncomplicated *S. aureus* bacteremia without IEa		
MSSA	10 to 14 days	10 to 14 days SSP plus gentamicin first 4 days (or until blood cultures had been negative for 48 hours)
MRSA	10 to 14 days	10 to 14 days vancomycin plus gentamicin first 4 days (or until blood cultures had been negative for 48 hours)

a Patients with uncomplicated bacteremia may have been treated for 10 days at the discretion of the Investigator if they were clinicall stable and had no evidence of active infection at the time.

(Medical Officer Comments: Actual treatment duration was based on the Investigator's discretion and, frequently, did not correspond with the minimum treatment durations as specified in the table above. This discrepancy was further compounded by the reclassification of subjects by the IEAC in making assessments of the patient's final diagnosis post-randomization. In the case of complicated bacteremias, there were

multiple instances in which the IEAC reclassified a patient from an assessment of uncomplicated bacteremia (per the Investigator at EOT) to complicated bacteremia as the final diagnosis based solely on the criteria of S. aureus isolated from blood cultures obtained on at least two different calendar days. As there was no differentiation of subjects who had blood cultures collected on two consecutive calendar days that were separated by ≥24 hours compared to those whose blood cultures were collected in <24 hours, there is likely an overestimation of the number of complicated bacteremias in the final diagnosis assessments by the IEAC. In addition, although evidence of a metastatic focus was part of the criteria for a complicated bacteremia, there was no prospective systematic assessment of all subjects for evidence of a metastatic focus, making that criterion ineffective as the basis for classifying subjects.)

The IEAC also determined Entry, EOT and Final Diagnoses using these same definitions. Specifically, they used Modified Duke criteria for Entry Diagnosis and Definitions above for EOT and Final Diagnoses. Patients with LIE or complicated RIE were to receive inpatient parenteral antibiotic therapy (IPAT) for at least 28 days. If conditions required outpatient parenteral antibiotic therapy (OPAT), these patients were to have had at least 5 days of documented clearance of bacteremia, had a stable ECG, and been free of systemic symptoms prior to switch to OPAT. Patients with uncomplicated RIE, or complicated or uncomplicated bacteremia without IE were to receive at least 5 days of IPAT. Prior to OPAT, these patients were to have had at least 3 days of documented clearance of bacteremia, had a stable ECG, and been free of systemic symptoms. If a patient needed to complete treatment using OPAT, the Investigator was to provide a written plan to the medical monitor and obtain approval in advance.

Patients completing the minimum duration of study treatment who had a successful clinical outcome (Cured, Improved) at EOT were to have a follow-up evaluation performed 42 days (TOC) after completion of study medication; similarly, patients who completed the minimum duration of study treatment and who had a successful clinical outcome (Cured, Improved) at TOC were to have a follow-up evaluation performed 84 days (PS) after completion of study medication to assess for relapse. Most patients who completed therapy and had an unsuccessful outcome at EOT (Failure) had a follow-up safety visit conducted 42 days after completion of study medication. Patients prematurely terminating treatment with study medication who were continued on alternate therapy were to be followed weekly through completion of their alternate therapy or to a maximum of 12 weeks from discontinuation. All patients who prematurely terminated treatment with study medication were to have a posttherapy safety visit 42 days after the last dose of study medication.

The Investigator was responsible for assuring that all protocol requirements were met, including administration of all study medications and performance of all scheduled assessments.

As described in Section 6.1.2 of this document, the Sponsor convened two separate committees, a DMC to review blinded interim composite data broken down by treatment

group A vs. B, and an IEAC to review blinded, individual patient data. The DMC was chartered to undertake an ongoing review of safety and efficacy (as related to safety) data during the course of the study. The IEAC was charged with confirming patient's diagnoses and determining outcomes via a post study review of blinded data using standard definitions.

The Sponsor established a Data Monitoring Committee (DMC) whose main purpose was to monitor the safety data from the study on a regular basis, review and assess the performance of the study, and make appropriate recommendations to the Sponsor with respect to the continuation of the study based on safety and efficacy (as it related to safety). The DMC was comprised of the following 3 members who were not otherwise involved in the conduct of the study: (b) (4)

Six DMC meetings were convened in a timely manner. The first DMC meeting was scheduled following completion of approximately the first 30 patients (29 September 2003). Subsequent meetings were scheduled following completion of approximately an additional 20 to 50 patients (26 March 2004, 9 July 2004, 29 September 2004, 28 January 2005 and 29 April 2005). The DMC reviewed blinded patient listings and partially blinded tables prepared by the CRO, where treatment groups were blinded as "A" and "B" as well as pharmacokinetic (PK) reports including de-identified individual patient data. The blinded patient profiles included data from physical examinations, medical history, echocardiogram results, all adverse events, SAEs, clinical evaluations, microbiologic evaluations, procedures, medications, etc.

Clinical and Microbiological Endpoints:
Primary Efficacy Endpoint: IEAC Outcome at TOC
The primary efficacy endpoint is the IEAC Outcome at TOC.
Success:
Subjects are classified as "Success" at TOC if they meet **all** of the following criteria:

- Were a "Success" as determined by the IEAC Outcome at EOT; and
- Were judged "Cure" or "Improved" by the IEAC at TOC; and
- Had a negative blood culture at TOC; and
- Did not receive a potentially effective non-study (PENS) antibiotic that could alter the therapeutic outcome at TOC (as defined by the IEAC); and
- Received at least the minimum amount of study medication as defined in above on Minimum Study Treatment Regimen and Duration

(Medical Officer Comments: The actual duration of study drug as prescribed by the Investigator was frequently not aligned with the pre-specified minimum study treatment regimen and duration guidelines in the protocol. Thus, it was problematic to consider subjects treated with shorter courses of therapy than outlined in the guidelines as true successes in circumstances where the minimum duration was specified to be significantly longer for a particular final diagnosis subgroup. This was a frequent finding among subjects with complicated bacteremia who were treated for 14 days by Investigators, but

for whom the minimum study treatment duration specified a 28-42 day course. The study was not designed to assess whether short courses of antibiotic therapy would have comparable efficacy to longer courses per the protocol guidelines.)

Failure:
Subjects are classified as a "Failure" at TOC if they meet any one of the following criteria:

- Were a "Failure" as determined by the IEAC outcome at EOT[a]; or
- Were judged "Failure" or "Not seen"[a] by the IEAC at TOC; or
- Had persisting or relapsing bacteremia, positive blood cultures or no blood culture[a] at TOC; or
- Died; or
- Received PENS antibiotics that influenced therapeutic outcome (as defined by the IEAC); or
- Discontinued study medication prematurely.
    - In the ITT analysis:
      Subjects who discontinue study medication prematurely for any reason are defined as "Failures".
    - In the PP analysis:
      Subjects who discontinue study medication prematurely due to the following reasons are defined as "Failures":
      - Adverse Event;
      - Microbiologic Failure;
      - Clinical Response unsatisfactory.

      Subjects who discontinue study medication prematurely due to the following reasons are defined as "Non-evaluable" and will be excluded from the PP analysis
      -Subject's care transferred to different physician;
      - Subject withdrew consent for study medication treatment; continued with alternative i.v. antibiotic treatment;
      -Subject discontinued all i.v. treatment for current infection against medical advice;
      - Other.

  Subjects who were "Not seen" (with the exception of Deaths) or who did not have blood cultures at EOT or TOC are included in the ITT population, but are excluded from the PP analysis population.

<u>Secondary Efficacy Endpoint: IEAC Outcome at EOT</u>
A secondary efficacy endpoint is the IEAC Outcome at EOT

Success:
Subjects are classified as "Success" at EOT if they meet **all** of the following criteria:
Were judged "Cure" or "Improved" by the IEAC at EOT; and
Had a negative blood culture at EOT; and

Did not receive a PENS antibiotic that could alter the therapeutic outcome at EOT (as defined by the IEAC); and

Received at least the minimum amount of study medication as defined in the section above on Minimum Study Treatment Regimen and Duration.

Failure:

Subjects are classified as a "Failure" at EOT if they meet any one of the following criteria:

Were judged "Failure" or "Not seen"[a] by the IEAC at EOT; or

Had persisting or relapsing bacteremia (Section 9.4.3) positive blood cultures or no blood culture[a] at EOT; or

Died; or

Received PENS antibiotics that influenced therapeutic outcome (as defined by the IEAC); or

- Discontinued study medication prematurely.
    - In the ITT analysis:
        - Subjects who discontinue study medication prematurely for any reason are defined as "Failures".
    - In the PP analysis:
        - Subjects who discontinue study medication prematurely due to the following reasons are defined as "Failures":
          - Adverse Event;
          - Microbiologic Failure;
          - Clinical Response unsatisfactory.
        - Subjects who discontinue study medication prematurely due to the following reasons are defined as "Non-evaluable" and will be excluded from the PP analysis:
          - Subject's care transferred to different physician;
          - Subject withdrew consent for study medication treatment; continued with alternative i.v. antibiotic treatment;
          - Subject discontinued all i.v. treatment for current infection against medical advice;
          - Other.

Subjects who were "Not seen" (with the exception of Deaths) or who did not have blood cultures at EOT are included in the ITT population, but are excluded from the PP analysis population.

Investigator's Assessment of Clinical Response

At End-of-Therapy, Test-of-Cure, and Post-Study Evaluations, the Investigator will determine the subject's clinical response using the following categories:

- **Cure:** Resolution of clinically significant signs and symptoms associated with admission infection (ie, return to pre-infection Baseline). No further antibiotic therapy required for the primary infection under study.
- **Improvement:** Partial resolution of clinical signs or symptoms of infection such that no further antibiotic therapy is required for the primary infection under study.
- **Failure:** Inadequate clinical response to therapy – additional antibiotic therapy required for primary infection under study.

- **Not seen:** Subject was not available to be examined and assessed.

Microbiologic Endpoints
Microbiologic responses will be ascertained from information collected on CRFs and from data provided by the Central Microbiology Laboratory. This information will be evaluated as described below. Determination of microbiologic outcomes by pathogen will be made before the study blind is broken. Microbiologic outcome by subject is evaluated by the sponsor as part of the IEAC Outcome.

Standardization of Organism Identification
The Local Microbiology Laboratories will culture specimens and will send isolates to the Central Microbiology Laboratory for re-identification and for susceptibility testing. The Sponsor will review a list of all unique isolates reported by both the Local and Central Microbiology Laboratories and will assign an organism code and an organism name to each using a standard vocabulary. Based on testing at the Central Microbiology Laboratories, isolates will further be categorized, where appropriate, based on vancomycin (ie VRE) and methicillin (ie MRSA) susceptibilities using the currently accepted interpretative criteria (National Committee for Clinical Laboratory Standards, M100-S13 document, January 2003). These isolates will have their organism code and standard name modified to indicate the appropriate susceptibility categorization (ie MRSA, VRE). The susceptibility results of the Local Microbiology Laboratories will be listed, but will not be used for study analyses.
Isolates will be considered to represent the "same bacterial strain" if they are the same genus, species, susceptibility type (ie MRSA or VRE), and molecular strain type. Molecular strain typing will be performed at the discretion of the Sponsor.

(Medical Officer Comments: The IEAC made the final determination about whether a subject had a polymicrobial infection. Despite the guidelines above, the IEAC did not consider subjects infected concurrently with MSSA and MRSA to have polymicrobial infections. This is noteworthy, because patients with a polymicrobial bacteremia at Baseline, as determined by the IEAC, were to be excluded from the PP population.)

Baseline Infecting Pathogen
A Gram-positive pathogen reported by either the Local or Central Microbiology Laboratories cultured from a valid source for bacteremia or IE within the two days prior to and including the first day of study drug administration (Day -2 through Day 1).
Non-pathogen:

- a non-Gram-positive isolate; or
- a Gram-positive isolate
- not considered to be pathogenic;
- not associated with emergence or worsening of clinical signs and symptoms; and
- not requiring antimicrobial therapy.
-

Negative Baseline Culture:
Subjects who do not have a Baseline Infecting Pathogen identified subsequent to enrollment will be assigned an organism code and organism name that reflect the

category "Negative Baseline Culture". Enrollment into the study is dependent upon a diagnosis of *S. aureus* bacteremia. Therefore, there is no requirement that all subjects have a confirmed Baseline Infecting Pathogen identified prior to study enrollment.

Isolates cultured from Study Day 2 through the Test-of-Cure (TOC) visit, inclusive

The Sponsor will classify all reported isolates cultured from Study Day 2 through the TOC visit, inclusive, into one of the following three categories:

Persisting Pathogen:

A Gram-positive pathogen that

- represents the same bacterial strain as a Baseline Infecting Pathogen;
- is cultured from an appropriate specimen obtained any time while on-therapy (Study Day 2) through to and including the TOC visit; and
- is reported by either the Local or the Central Microbiology Laboratories.

Superinfecting Pathogen:

A Gram-positive pathogen other than a Baseline Infecting Pathogen that

- is cultured from any site on Study Day 6 through to and including the TOC visit;
- is associated with emergence or worsening of clinical signs and symptoms;
- requires antimicrobial treatment; and
- is reported by either the Local or the Central Microbiology Laboratories.

Non-pathogen:

- a non-Gram-positive isolate; or
- a Gram-positive isolate
    - not considered to be pathogenic;
    - not associated with emergence or worsening of clinical signs and symptoms; and
    - not requiring antimicrobial therapy.

Not Classified:

A Gram-positive pathogen other than a Baseline Infecting Pathogen that

- is cultured from any site on Study Day 2 through to and including Study Day 5;
- is associated with emergence or worsening of clinical signs and symptoms;
- requires antimicrobial treatment; and
- is reported by either the Local or the Central Microbiology Laboratories.

Isolates cultured after the Test-of-Cure (TOC) visit through to and including the Post-Study (PS) visit

The Sponsor will classify all reported isolates after the TOC visit through to and including the PS visit into one of the following three categories:

Relapsing Pathogen:

A Gram-positive pathogen that

- represents the same bacterial strain as a Baseline Infecting Pathogen;
- is cultured from an appropriate specimen after the TOC visit through to and including the PS visit; and

- is reported by either the Local or the Central Microbiology Laboratories.

Superinfecting Pathogen:
A Gram-positive pathogen other than a Baseline Infecting Pathogen that

- is cultured from any site after the TOC visit through to and including the PS visit;
- is associated with emergence or worsening of clinical signs and symptoms;
- requires antimicrobial treatment; and
- is reported by either the Local or the Central Microbiology Laboratories.

Non-pathogen:

- a non-Gram-positive isolate; or
- a Gram-positive isolate
- not considered to be pathogenic;
- not associated with emergence or worsening of clinical signs and symptoms; and
- not requiring antimicrobial therapy.

Pathogen-Level Microbiologic Response at the TOC Visit
For subjects with one or more Baseline Infecting Pathogens, the Sponsor will assign each Baseline Infecting Pathogen to a microbiologic response category according to the criteria
below. The criteria are hierarchical and mutually exclusive.

- **Documented Persistent:** The Baseline Infecting Pathogen was present at the TOC visit as determined by an isolate classified as "Persisting Pathogen".
- **Presumed Persistent:** The Baseline Infecting Pathogen was presumed present at the TOC visit as determined by the lack of a negative culture result.
- **Documented Eradicated:** The Baseline Infecting Pathogen was absent at the TOC visit as determined by a negative culture result from an appropriate specimen.
- **No Baseline Pathogen:** Subjects who do not have any Baseline Infecting Pathogen
  identified will be assigned to this category for purposes of display and analyses.

Patients with *S. aureus* IE have substantial risk for serious complications, including relapsing infection and death. Patients with *S. aureus* bacteremia without IE are also at risk,
particularly if the bacteremia is sustained or high grade, i.e., documented to extend over 2 or more days or if metastatic foci of infection are present. At the initial presentation, it is typically difficult to determine the nature of the bacteremia on clinical grounds. Therefore, this study enrolled patients in whom *S. aureus* bacteremia had been documented, but additional evaluation was pending to determine the presence of IE and the severity of the bacteremia. The Investigator was to evaluate the patient daily for any evidence of metastatic sites of infection. If metastatic sites of infection were suspected, the Investigator was to perform appropriate investigations such as computed tomography (CT) scans, magnetic resonance images (MRI), and/or bone scans. Final diagnostic categories and treatment regimens were to be based

(Medical Officer Comments: There was no specific requirement for investigators to perform systematic diagnostic evaluations and imaging tests on all study subjects for evidence of metastatic infections. The workup for metastatic sites of infection was left to the individual investigator's discretion and clinical suspicion; any metatstatic foci subsequently identified on imaging tests were to be reported as adverse events. In view of the lack of systematic radiologic imaging of all patients, the number of metastatic infections reported in the study are likely underestimated. Clinical follow-up is limited to the post-study visit (80-88 days following EOT), which may not be long enough following treatment for some occult metastatic infections to become clinically apparent.)

The study was designed to facilitate enrollment of patients early in the course of infection while providing appropriate intensity and duration of treatment for patients with varying severity of infection.

(Medical Officer Comments: Bacteremia and endocarditis are not part of a continuum of the same illness, but represent distinct clinical entities with differing pathophysiologies, varied portals of entry, different anticipated response rates, and different requirements for adjunctive surgical interventions that can confound assessment of the treatment effect of the study drug. Failure to fully characterize the all-comers study population prior to randomization makes it problematic to assess if the two study drug treatments had comparable effects.)

Inclusion Criteria

A patient was eligible for inclusion in the study if he/she met the following criteria:

1. Provided signed and dated informed consent.
2. Was ≥18 years of age.
3. If female of childbearing potential, was willing to practice barrier methods of birth control (e.g., condoms or diaphragms together with spermicidal foam or gel) during treatment and for at least 28 days after treatment with study medication.
4. Had documented *S. aureus* bacteremia defined as at least one positive blood culture for *S. aureus* obtained within 2 calendar days prior to the first dose of study medication (Day –2 or Day –1).

(Medical Officer Comments: As the target population in the study was defined based on a common pathogen (S. aureus) in the baseline blood cultures, data was not collected prospectively with regard to other variables that would portray the heterogeneity of the patients in terms of specific baseline disease entities. The primary efficacy endpoint provided an assessment of study drug efficacy in this all-comers population. However, the generalizability of the all-comers efficacy data to the final diagnosis subgroups was limited due to the absence of statistical power and adequate sample size in the final diagnosis subgroups. In addition, the final diagnosis determinations were made using post-randomization data, which further complicates efficacy assessment.)

Exclusion Criteria

The following presents the exclusion criteria as outlined in the final protocol; several of the
criteria were modified by protocol amendment .

A patient was to be excluded from the study if he/she met any of the following criteria:

1. Was anticipated to require non-study systemic antibiotics that were potentially effective against *S. aureus* for another reason after the time of randomization.
2. Weighed >150 kg or <50 kg.
3. Had intravascular foreign material at the time a positive blood culture was drawn (e.g., intracardiac pacemaker wires, percutaneous or implanted venous catheters, vascular grafts), unless the Investigator intended to have the material removed within 4 days after the first dose of study medication (exception: vascular stents that had been in place >6 months or permanent pacemaker attached via epicardial leads).
4. Had a prosthetic heart valve.
5. Had cardiac decompensation and/or valve damage such that there was a high likelihood of requiring valve replacement surgery in the 3 days after randomization.
6. Had a moribund clinical condition (i.e., high likelihood of death during the 3 days after randomization).
7. Had shock or hypotension (supine systolic blood pressure <80 mmHg) or oliguria (urine output <20 mL/hour) unresponsive to fluids or pressors within 4 hours.
8. Had received an investigational drug within 30 days of study entry.
9. Had a documented history of significant allergy or intolerance to both SSPs and vancomycin, or if known to be infected with MRSA, to vancomycin.
10. Had an infecting pathogen with confirmed reduced susceptibility to vancomycin (MIC >4 μg/mL).
11. Had a creatinine clearance (CL_{cr}) < 30 mL/minute (calculated using the Cockcroft-Gault equation using actual body weight).
12. Had an alanine aminotransferase (ALT) >5 · upper limit of normal (ULN).
13. Had an aspartate aminotransferase (AST) >5 · ULN.
14. Had a total bilirubin ε3.0 mg/dL.
15. Was severely lymphopenic (i.e., CD_4 lymphocytes $<0.200 \cdot 10^3$/ μL).
16. Was severely neutropenic (absolute neutrophil count $<0.500 \cdot 10^3$/ μL).
17. Was anticipated to develop severe neutropenia (absolute neutrophil count $<0.500 \times 10^3$/μL) during the study treatment period due to prior or planned chemotherapy.
18. Was considered unlikely to comply with study procedures or to return for scheduled posttreatment evaluations.
19. Was pregnant, nursing or lactating.
20. Had known osteomyelitis.
21. Had a polymicrobial blood infection.
22. Had pneumonia.

(Medical Officer Comments: Despite specific exclusions, there were several patients enrolled who had radiographic evidence of pneumonia and five subjects had a creatinine clearance (CL_{cr}) < 30 mL/minute at baseline.)

Efficacy Populations

Efficacy analyses were to be performed on the ITT and PP populations. The ITT population included all patients who were randomized and received at least one dose of study medication. Patients enrolled prior to Amendment 4A who were considered by the Investigator to have a high likelihood of LIE were to be excluded from the ITT population and all efficacy analyses. All efficacy data collected for these patients are presented in the data listings, thus the listings of efficacy data are based on the Safety population. Patients in the ITT population were to be analyzed according to their randomized treatment group. The PP population includes those patients in the ITT population with documented adherence to the protocol.

Patients in the PP population were to be analyzed according to their randomized treatment group. The following considerations were to be made in a hierarchical manner when determining the composition of the PP population:
1). Patients were to be excluded from the PP population if they violated inclusion/exclusion criteria that could have had an impact on the assessment of efficacy.

- The following criteria were to be evaluated on a per-patient basis. If it was felt that the extent of the violation would impact the assessment of efficacy, then the patient was to be excluded from the PP population. This evaluation was to be performed by a manual Sponsor review of the clinical relevance of these violations prior to unblinding of the data.

  Inclusion Criteria
  - .≥18 years of age.
  - adequate birth control for females

  Exclusion Criteria
  - weight >150 kg or <50 kg.
  - investigational drug within 30 days.
  - CL_{cr} <30 mL/min.
  - ALT >5·ULN.
  - AST >5·ULN.
  - total bilirubin ε3.0 mg/dL.
  - CD_4 lymphocytes $<0.200 \cdot 10^3/\infty L$.
  - absolute neutrophil count $<0.500 \cdot 10^3/\infty L$.
  - absolute neutrophil count $<0.500 \cdot 10^3/\infty L$ anticipated due to chemotherapy.
  - considered unlikely to comply.
  - pregnant, nursing, or lactating.
- Patients expected to receive HMG CoA Reductase Inhibitors were not to be excluded from the PP population.
- Patients with a polymicrobial bacteremia at Baseline, as determined by the IEAC, were to be excluded from the PP population.
- The inclusion criterion for the blood culture window was to be determined programmatically. All patients assigned a Baseline Infecting Pathogen of

S. aureus
were to be considered to have met this inclusion criterion.

- Patients in violation of any of the inclusion/exclusion criteria not specifically mentioned above were to be excluded from the PP population.

2). Patients were to be excluded from the PP population if their duration of treatment with study drug was less than 4 days.
3). Patients not excluded from the PP population based on Items 1 and 2 above were to be included in the PP population if, according to the Investigator, they terminated early from study medication because of an adverse event, microbiologic failure, or clinical response of unsatisfactory.
4). With the exception of those patients identified in Item 3 (who are included in the PP population), the remaining patients were to be excluded from the PP population if they satisfied any of the following criteria:

- Did not receive the correct study drug per randomization.
- Received <80% of the minimum expected total daily doses for the duration of study drug treatment as determined by a manual Sponsor review of the data by a non-study physician who was not otherwise involved in the conduct of the study on a by-patient basis prior to unblinding.
- Did not have evaluations performed at major specified time points (Baseline, EOT, and TOC [if required]). At Baseline, these evaluations include the Investigator's Entry Diagnosis and a blood culture; at EOT and TOC these evaluations each included the Investigator's assessment of clinical response and a blood culture.
- Were determined to be "Non-evaluable" per the IEAC.

(Medical Officer Comments: In this non-inferiority study, permitting reassignment of subjects who would have been excluded from the PP population if they violated inclusion/exclusion criteria to be included in the PP population if it was felt that the violation(s) did not have had an impact on the assessment of efficacy could make it easier to show non-inferiority of the treatment groups and mask any true treatment efficacy differences.)

Patients may have been withdrawn from the study and treatment with study medication may have been terminated under the following circumstances (Investigators were to indicate <u>one</u> primary reason for early termination):

- Adverse event (AE), regardless of whether the event was considered serious or drug-related. Patients who withdrew because of an AE were to have follow-up until the AE resolved or stabilized.
- Microbiologic failure - persistent positive cultures from blood or other site, such that the Investigator considered the response to study medication inadequate.
- Clinical (symptomatic) response unsatisfactory - inadequate response to study medication based on evaluation of clinical signs and symptoms of infection.
- Patient's care transferred to a different physician unwilling to continue study medication as randomized.
- Patient withdrew consent for study medication treatment.

- Patient discontinued all i.v. treatment for current infection against medical advice.
- Other.

All patients who terminated study medication early were to have an Early Termination evaluation performed between the last day study medication was administered and the third post-treatment day, inclusive. These patients were also to be followed for safety weekly through completion of alternative treatment (if applicable) or to a maximum of 12 weeks from discontinuation. Patients prematurely terminating treatment also were to have a posttherapy safety visit 42 days after the last dose of study medication.

Prior and Concomitant Therapy

Clinically indicated non-study medications may have been administered as required except as noted below. Patients were prohibited from receiving potentially effective non-study anti-staphylococcal antibiotics (e.g., rifampin) during the study (i.e., from enrollment to completion of follow-up) unless administered for study treatment failure. With the approval of the study medical monitor, patients requiring treatment for an intercurrent infection may have received aztreonam for Gram-negative organisms or metronidazole for anaerobic organisms or both.

(Medical Officer Comments: The use of potentially effective non-study antibiotics (PENS) was of critical importance in the assessment of patient outcomes at EOT and TOC by the IEAC and the FDA. Based on the FDA review of the source documents, the IEAC was inconsistent in re-adjudicating cases for use of PENS and did not provide a pre-specified algorithm to describe PENS in terms of susceptibility of the baseline pathogen, duration of PENS therapy, use of PENS to the pre-enrollment period, on-study period, and in the time interval following completion of study drug. Many IEAC decisions regarding PENS were subjective and were conducted on a case-by-case basis.)

Treatment Compliance

Treatment compliance was assured using quality control systems established at the clinical study site. Measures taken to ensure compliance included recording of dose and timing on the appropriate CRF, recording of study drug dispensing on the appropriate drug accountability forms, and verification of the accurate accounting of study drug by the clinical monitor at the completion of the study. In addition, the Investigator maintained records that adequately documented that the patients were provided the doses specified in the protocol (date, time, regimen, route and total dose) and that all study drug provided by the Sponsor was fully reconciled. The records included dates, quantities, lot numbers, and any unique code numbers assigned to the investigational product and/or patients.

Efficacy and Safety Measurements Assessed and Flow Charts

In addition to daily monitoring for adverse events and concomitant medications, each patient was to have the following evaluation visits:

- Baseline - within 2 calendar days prior to the first infusion of study medication (designated as Day -2 to Day 1 prior to treatment).
- Treatment period - Day 1 to the last day of therapy (designated as #L, where # is the last study day of therapy).
- EOT - within 3 days after the last day study medication was administered for patients who completed the minimum duration of treatment (Day 3P, where the day after the last day of therapy is designated as Day 1P).
- TOC - 38 to 46 days after completion of study medication for all patients who completed the minimum duration of study treatment and who were considered to have a successful outcome at the EOT evaluation (Cured or Improved). For patients who completed treatment but did not have a successful outcome at EOT or discontinued treatment prematurely, an evaluation of safety was to be performed at this visit.
- PS - 80 to 88 days after completion of study medication for all patients who completed the minimum duration of study medication and who were considered to have a successful outcome at the TOC (Cured or Improved). If the patient was unable to return to the site for follow-up, a clinical assessment may have been done via telephone contact. Patients reporting signs or symptoms of infection were to be seen for full evaluation.

Table 3: (Sponsor Table 9-3) Schedule of Assessments - Patients who Completed Study Medication

	Baseline	Treatment										Follow-up	
Day[a]	-2, -1,or 1	1	2	3	4	5	6	7	Daily to EOT[b]	Weekly to EOT	EOT	TOC 42P	PS 84P
Informed Consent	X												
Demographics and Medical History	X												
Antibiotic / Medication History	X												
Investigator's Assessment of Clinical Response											X	X	X
Clinical Assessment	X	X	X	X	X	X	X	X	X		X	X	X
Vital Signs	X	X	X[c]	X[c]	X[c]	X[c]	X[c]	X	X[c]	X	X	X	X
Physical Examination	X							X		X	X	X	X
Blood Culture	X[d]	X[e]	X[e]	X[e]							X	X	X
Hematology, Chemistry, Coagulation, Urinalysis[f]	X	X[g]			X			X		X	X	X	
CPK Monitoring[h]	X	X			X			X	X[i]		X		
Pregnancy Test[j]	X											X	
PK Sampling		X[k]				X[l]							
Chest X-ray	X												
ECG	X							X		X	X	X	
TEE[m]	X												
SF-12v2□Health Survey	X							X		X	X	X	
Randomization		X											
Study Medication Administration		X	X	X	X	X	X	X	X		X		
Concomitant Antibiotics/Significant Procedures		X	X	X	X	X	X	X	X		X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X		X		
AE Monitoring		X	X	X	X	X	X	X	X		X	X	X

a. Study days were numbered relative to the day of the first dose of study medication, which was designated Day 1. The preceding day was Day -1, the day before that was Day –2, etc. The last day of study medication per protocol was designated Day #L and subsequent days were designated Day 1P, Day 2P", etc.
b. EOT = End-of-Treatment;
c. Temperature only
d. Patients were to have at least one blood culture positive for *S. aureus* that was obtained on Day -2 or Day -1.
e. Blood cultures were to be repeated daily until all cultures obtained within the past 48 hours had remained negative.
f. Any clinically significant abnormal laboratory value considered probably or possibly related to study medication was to be repeated until it returned to the baseline value.
g. Laboratory tests on Day 1 were to be obtained prior to the first dose of study medication.
h. CPK was to be monitored using local laboratory; if the value exceeded 4.0 x ULN the medical monitor was to be contacted and additional CPK evaluations were required.
i. CPK was to be obtained every other day (after Day 7) during the treatment period or a minimum of 3 days per week.
j. Pregnancy test was required only for females of childbearing potential.
k. To be obtained within 24 hours prior to the first dose of study medication

l. To be obtained 0.5 hours before and at 4 additional time points after the end of infusion
m. TEE was to be performed by the end of Day 5.

Table 4: (Sponsor Table 9-4) Schedule of Assessments - Patient who Did Not Complete Study Medication

	Baseline	Treatment										Follow-up	
Day[a]	-2, -1, or 1	1	2	3	4	5	6	7	Daily to ET	Weekly to ET	ET[b]	Wkly FU	Safety 38P - 46P
Informed Consent	X												
Demographics and Medical History	X												
Antibiotic / Medication History	X												
Assessment of Premature Termination											X		
Clinical Assessment	X	X	X	X	X	X	X	X	X		X		X
Vital Signs	X	X	X[c]	X[c]	X[c]	X[c]	X[c]	X	X[c]	X	X		X
Physical Examination	X							X		X	X		X
Blood Culture	X[d]	X[e]	X[e]	X[e]							X		X
Hematology, Chemistry, Coagulation, Urinalysis[f]	X	X[g]			X			X		X	X		X
CPK Monitoring[h]	X	X			X			X	X[i]				
Pregnancy Test[j]	X										X		X
PK sampling		X[k]				X[l]							
Chest X-ray	X												
ECG	X							X		X	X		X
TEE[m]		X											
SF-12v2□Health Survey	X							X		X	X		X
Randomization		X											
Study Medication Administration		X	X	X	X	X	X	X	X		X		
Concomitant Antibiotics/Significant Procedures		X	X	X	X	X	X	X	X		X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X		X		
AE Monitoring		X	X	X	X	X	X	X	X		X	X	X
Survival Data												X	X

a. Study days were numbered relative to the day of the first dose of study medication, which was designated Day 1. The preceding day was Day -1, the day before that was Day –2, etc. The last day of study medication per protocol was designated Day #L and subsequent days were designated Day 1P, Day 2P, etc.
b. ET = Early Termination
c. Temperature only
d. Patients were to have at least one blood culture positive for *S. aureus* that was obtained on Day -2 or Day -1.
e. Blood cultures were to be repeated daily until all cultures obtained within the past 48 hours had remained negative.
f. Any clinically significant abnormal laboratory value considered probably or possibly related to study medication was to
be repeated until it returned to the baseline value.

g. Laboratory tests on Day 1 were to be obtained prior to the first dose of study medication.
h. CPK was to be monitored using local laboratory; if the value exceeded 4.0 x ULN the medical monitor was to be contacted and additional CPK evaluations were required.
i. CPK was to be obtained every other day (after Day 7) during the treatment period or a minimum of 3 days per week.
j. Pregnancy test was required only for females of childbearing potential.
k. To be obtained within 24 hours prior to the first dose of study medication.
l. To be obtained 0.5 hours before and at 4 additional time points after the end of infusion.
m. TEE was to be performed by the end of Day 5.

All patients who terminated study medication early were to have an Early Termination evaluation performed within 3 days after the last day study medication was administered. Patients prematurely terminating study medication who continued on alternative antibiotic therapy were to be followed weekly for safety through completion of their alternative therapy, or to a maximum of 12 weeks from discontinuation. Patients who prematurely discontinued study treatment were to return for a follow-up safety visit 42 days after discontinuation of study medication. Efficacy was to be assessed based on evaluations of the clinical signs and symptoms of the infection and by bacteriologic cultures conducted at the above scheduled visits. The pharmacokinetic profile was to be determined based on blood samples obtained on Day 1 and Day 5 of the treatment period. Safety was to be assessed by monitoring for treatment-emergent adverse events and for use of concomitant medications and by analyzing changes in clinical laboratory data, physical examination findings, ECGs, and vital signs.

Changes in the Conduct of the Study

The original protocol, dated 8 November 2001, was amended 4 times as detailed below. No patients were enrolled under the original protocol or Amendment 1. Fifty-two patients were enrolled under Amendment 2, 104 patients were enrolled under Amendment 3, 26 patients were enrolled under Amendment 3-EU, and 64 patients were enrolled under Amendment 4A.

Amendment 1, dated 21 February 2002, changed the original protocol as follows:

- Patients with uncomplicated bacteremia were allowed to remain in the study.
- A Data Monitoring Committee was implemented to review the ongoing safety data and efficacy data (as it related to safety) on a periodic basis.
- Pharmacoeconomic endpoints were added.
- Background information correlating the animal pharmacokinetic and pharmacodynamic endocarditis data with the proposed human dose was added as was background information relating to Eli Lilly's previously conducted endocarditis study with daptomycin.
- Minor administrative changes were made.

Amendment 2, dated 3 May 2002, included the following changes to the protocol:

- Exclusion of patients with a high likelihood of LIE at enrollment. Patients who were enrolled and subsequently found by TEE to have left-sided involvement may have been continued or discontinued from the study at that time based upon the Investigator's judgment.
- The timing for convening the DMC was changed to after the completion of every 30 patients (originally after every 50 patients).

Amendment 3 (US only, dated 24 March 2003) and Amendment 3A-EU (Europe only,

dated 07 May 2003) made the following changes to the protocol:

- The qualifying blood culture window was extended from Day -1 to Day -2 for bacteremia patients because of the time constraints of reporting blood culture results.
- The microbiologic profile of daptomycin and Phase 2 and 3 Clinical Trial Safety Experience were updated.
- The use of conventional therapy was broadened due to the lack of nafcillin use in European countries. SSPs that could be used as comparator was to include nafcillin, oxacillin, cloxacillin or flucloxacillin.
- Additional administrative clarifications were made to the protocol.
- Changes from Administrative Letter #1 dated 01 August 2002 were incorporated. Specifically, exclusion criterion No. 12 was revised to incorporate the use of actual body weight rather than ideal body weight and LIE patients were excluded from the ITT population based upon discussion with the FDA.
- The frequency of the DMC meetings was modified to occur after the first 30 IE patients with subsequent meetings occurring after every 50 IE patients.
- Changes from Administrative Letter #2 dated 31 October 2002 were incorporated. Specifically, this allowed for the patient's legally authorized representative to provide asigned informed consent for the patient; clarified the expectations for discharge to outpatient antibiotic therapy; modified the stability of daptomycin based upon recent data that indicated reconstituted daptomycin product is stable longer than previously stated;incorporated minor clarifications to study drug receipt, accountability and dose adjustments; and clarified the susceptibility testing, shipment and storage of isolates.

Amendment 4A, dated 1 April 2004, made the following changes to the protocol:

- Allowed for enrollment of patients with LIE in order to expand the patient population for enrollment of sufficient numbers of patients.
- The definition of catheter-associated bacteremia was deleted from the protocol.

(Medical Officer Notes: There were considerable changes in the statistical analysis plan for the study over the course of the amendments that are not described in this report. Please refer to the report of Dr. Scott Komo, Statistical Reviewer, for further details.)

Disposition of Patients

A total of 246 patients were randomized into the study. Ten of these patients, including 4 randomized to receive daptomycin and 6 randomized to receive the comparator agent, were
not dosed. Thus, a total of 236 of the 246 randomized patients received at least one dose of study drug, including 120 who received daptomycin and 116 who received the comparator agent. These 236 patients, who were treated at 44 study sites in the US (38) and Europe (6), comprise the Safety Population. Among the 116 comparator patients in the Safety population, 53 received only vancomycin and 63 received SSP with or without initial vancomycin therapy of δ3 days duration, with the exception of 4 patients who received a longer duration of vancomycin therapy. These 4 patients included Patients (b) (6) and (b) (6) who received 5, 4 and 8 days of vancomycin prior to switching to nafcillin. All 3 of these patients had MSSA isolated at baseline. The fourth

patient, Patient (b) (6) received 9 days of nafcillin prior to switching to vancomycin, which the patient received through Day 35; MRSA was isolated at baseline in this patient but was not recognized until Day 9. The 63 patients who received SSP with or without initial therapy with vancomycin are reported as the 'SSP treatment group' in all in text tables.

Table 5: Sponsor Table of Subject Disposition:

Patient Disposition

Disposition	Daptomycin n (%)	Comparator n (%)	Total n (%)
Randomized	124	122	246
Randomized but not treated	4	6	10
Safety population	120	116	236
Completed therapy	80 (66.7%)	78 (67.2%)	158 (66.9%)
Prematurely discontinued therapy	40 (33.3%)	38 (32.8%)	78 (33.1%)
Reason for discontinuation of study treatmenta			
Adverse event	20 (16.7%)	21 (18.1%)	41 (17.4%)
Microbiologic failure	9 (7.5%)	3 (2.6%)	12 (5.1%)
Withdrew consent	1 (<1%)	2 (1.7%)	3 (1.3%)
Discontinued therapy against medical advice	1 (<1%)	2 (1.7%)	3 (1.3%)
Unsatisfactory clinical response	1 (<1%)	1 (<1%)	2 (<1%)
Care transferred to another physician	1 (<1%)	1 (<1%)	2 (<1%)
Other	7 (5.8%)	8 (6.9%)	15 (6.4%)
Completed therapy and study	54 (45.0%)	50 (43.1%)	104 (44.1%)
Completed therapy, prematurely discontinued study	26 (21.7%)	28 (24.1%)	54 (22.9%)
Reason for discontinuation of studyb			
Lost to follow-up	7 (5.8%)	9 (7.8%)	16 (6.8%)
Adverse event	6 (5.0%)	5 (4.3%)	11 (4.7%)
Withdrew consent	1 (<1%)	0	1 (<1%)
Other	12 (10.0%)	14 (12.1%)	26 (11.0%)

Note: percents are based on the number of patients in the Safety population.
a Primary reason for discontinuation from treatment as reported by the Investigators; only one reason could be given.
b Primary reason for premature discontinuation for patients who completed therapy.

Based on the table above, approximately 44% of all study subjects both completed therapy and completed study participation, whereas 33% discontinued therapy prematurely. Adverse events and microbiologic failures were the most frequently cited reasons for discontinuation of study drug.

Table 6: Sponsor Table of Protocol Deviations

Table 10-2: Major and Minor Protocol Violations (Safety Population)

Violation	Daptomycin (N=120) n (%)	Comparator (N=116) n (%)	Total (N=236) n (%)
At least one violation	19 (15.8%)	35 (30.2%)	54 (22.9%)
At least one major violationa	18 (15.0%)	27 (23.3%)	45 (19.1%)
Did not have evaluations at major time point(s)	7 (5.8%)	6 (5.2%)	13 (5.5%)
Polymicrobial blood infection (Exclusion 23)b	6 (5.0%)	4 (3.4%)	10 (4.2%)
Intravascular foreign material not intended to be removed within 4 days of 1st dose (Exclusion 3)	3 (2.5%)	6 (5.2%)	9 (3.8%)
Not adherent to study drug	0	8 (6.9%)	8 (3.4%)
Blood culture negative for S. aureus (Inclusion 3)	1 (<1%)	1 (<1%)	2 (<1%)
Known osteomyelitis (Exclusion 22)	1 (<1%)	1 (<1%)	2 (<1%)
Pneumonia at baseline (Exclusion 24)	1 (<1%)	1 (<1%)	2 (<1%)
Anticipated to require non-study antibiotics (Exclusion 1)	1 (<1%)	0	1 (<1%)
High likelihood of LIE (prior to Amendment 4A) (Exclusion 21)	0	1 (<1%)	1 (<1%)
Creatinine clearance <30 mL/min (Exclusion 12)c	0	1 (<1%)	1 (<1%)
At least one minor violationa	2 (1.7%)	8 (6.9%)	10 (4.2%)
Expected to receive HMGCoA reductase inhibitor (Exclusion 9)	1 (<1%)	3 (2.6%)	4 (1.7%)
Creatinine clearance <30 mL/min (Exclusion 12)c	1 (<1%)	2 (1.7%)	3 (1.3%)
Total bilirubin ≥3 mg/dL (Exclusion 15)	0	3 (2.6%)	3 (1.3%)

a More than one violation could have occurred per patient.

b As reported by the IEAC

c The patient with a major violation (Patient (b) (6) had a creatinine of 210 µmol/L and a calculated CLcr of 23.0 mL/min; patients with minor violations had CLcr of 27.0 (Patient (b) (6) 27.3 (Patient (b) (6) and 29.7 mL/min (Patient (b) (6) These data were based on site-reported creatinine clearance values (see

Based on the table above, more comparator-treated patients had at least one violation and at least one major violation compared to daptomycin-treated patients. There was one subject with high likelihood of left IE who was enrolled in the comparator-treatment group prior to amendment 4A. Eight comparator-treated subjects were non-adherent to study drug compared to none in the daptomycin group.

6.1.4 Efficacy Findings

Baseline Demographics of the Overall Study Population for Study DAP-IE-01-02:
The baseline characteristics of the study population are summarized in the following table:

Table 7: FDA MO summary of subject demographics for Study DAP-IE-01-02

		Daptomycin	Combined Comparator	Vancomycin	SSP+/-Vanco
		N=120	N = 116	N=53	N=63
Baseline Demographics	Age				
	Median	50	56	53	58
	Mean ±sd	52.6 ±17.55	56.47 ±15.6	54.9 ±15.96	57.76 ±15.24
	<65 years	90	78	37	41
	≥65 – 74 years	11	22	11	11
	≥75 years	19	15	5	10
	Gender				
	Male	70 (58.3)	72 (62.1)	31 (58.5)	41 (65.1)
	Female	50 (41.7)	44 (37.9)	22 (41.5)	22 (34.9)
	Race				
	Caucasian	75 (62.5)	82 (70.7)	35	47
	Black	32 (26.6)	23 (19.8)	12	11
	Hispanic	8 (6.7)	5 (4.3)	2	3
	Asian	1 (0.8)	2 (1.7)	0	2
	Other	4 (3.3)	4 (3.4)	4	0
	Diabetes Mellitus	44 (36.7)	42 (36.2)	21	21
	Prior Endocarditis	7 (5.8)	6 (5.2)	3	3
	Shock	1 (0.8)	0 (0)	0	0
	SIRS	89 (74)	87 (75.6)	39	48
	HIV (+)	8 (6.7)	1 (0.9)	0	1
	IVDA	25 (20.8)	25 (21.7)	11	14
Study Populations	ITT (n =235)	120 (100)	115 (99.1)	53 (100)	62 (98.4)
	PP (n =139)	79 (65.8)	60 (51.7)	22 (41.5)	38 (60.3)
	Safety Population*	120 (100)	116 (100)	53 (100)	63 (100)
	Non-evaluable by IEAC	9 (7.5)	14 (12)	8 (15)	6 (9.5)
Baseline Pathogen	MSSA	74 (61.7)	71 (61.2)	10	61
	MRSA	45 (37.5)	44 (37.9)	43	1
	No BLP	1 (0.8)	1 (0.9)	0	1
IEAC Entry Dx	Definite IE	17 (14)	20 (17)	7 (13)	13 (21)
	Possible IE	73 (61)	72 (62)	37 (70)	35 (55)
	Not IE	30 (25)	24 (21)	9 (17)	15 (24)
IEAC Final Dx (ITT)	Uncomp Bacteremia	32 (26.7)	29 (25)	15 (28.3)	14 (22.2)
	Uncomp RIE	6 (5.0)	4 (3.4)	0 (0)	4 (6.4)
	Left IE	9 (7.5)	10 (8.6)	4 (7.6)	6 (9.5)
	Comp Bacteremia	60 (50)	61 (52.6)	28 (52.8)	33 (52.4)
	Comp RIE	13 (10.8)	12 (10.3)	6 (11.3)	6 (9.5)
Patient Disposition	Deaths	18 (15)	19 (16)		
	D/C due to an Adverse Event	17 (14)	15 (13)		
	Lost to follow-up	9 (7.5)	10 (8.6)		
	Withdrew consent	2 (1.7)	3 (2.3)		
	Transferred Care	1	0		
	Other	13 (11)	17 (15)		

- 10 subjects were not treated and were not included in the safety population.

As depicted in the table above, both treatment groups had more men than women, more Caucasians than non-Caucasian subjects, and similar percentages of intravenous drug users (IVDU), diabetics, and subjects with previous endocarditis. Of note, there were more HIV-seropositive subjects and fewer subjects older than age 65 in the daptomycin group. Approximately 75% of the subjects in both groups had systemic inflammatory response syndrome (SIRS), but only one patient had frank shock.

The overall intent-to-treat (ITT) population consisted of 235 subjects, including 120 in the daptomycin group and 115 in the comparator group. The per-protocol (PP) population was considerably smaller in size and disparate by subgroup, as there were 79 patients in the daptomycin group and 60 patients in the comparator group. Methicillin-susceptible *S. aureus* was the predominant pathogen in both groups accounting for 61% of the infected subjects compared to methicillin-resistant *S. aureus* (MRSA). In terms of entry diagnosis based on modified Duke criteria, approximately 75% of both groups had definite or possible endocarditis. Complicated bacteremia was the largest clinical subgroup final diagnosis accounting for 50% of the subjects in both treatment groups. Subjects with infective endocarditis due to *S. aureus* accounted for almost 22% of both groups.

In addition to the data depicted in the table, 30 study subjects had only one positive blood culture for *S. aureus* (16 in the daptomycin group and 14 in the comparator group), and 202 patients had two or more positive blood cultures (103 in the daptomycin group and 99 in the comparator group).

IEAC Entry Diagnosis and modified Duke Criteria for IE:

The use of the modified Duke criteria by the IEAC to classify study subjects at study entry for their likelihood of having IE uses post-randomization data (central echocardiography) and overestimates the true number of subjects with IE in the study population. The table below illustrates the incomplete correspondence between the IEAC Entry Diagnosis (based on modified Duke criteria) and the IEAC Final Diagnosis (based on the IEAC's retrospective assessment of all study data):

Table 8: FDA analysis of Correspondence between IEAC Entry and IEAC Final Diagnosis Subgroups

IEAC Entry Diagnosis Subgroups	Daptomycin (n=120)		Comparator (n=115)	
	Bacteremias*	IE**	Bacteremias*	IE**
Definite IE (n=37)	0	17	0	20
Possible IE (n=144)	63	10	66	5
Not IE (n=54)	29	1	24	0
Totals	*92*	*28*	*90*	*25*

*includes complicated and uncomplicated bacteremia;
**includes complicated RIE, uncomplicated RIE, left IE

Of note, 63/73 (86.3%) of the patients classified as "Possible IE" in the daptomycin group had an IEAC Final Diagnosis of Bacteremia (complicated or uncomplicated), and 66/71 (92.9%) of the patients classified as "Possible IE" in the comparator group had an IEAC Final Diagnosis of Bacteremia. The substantial overestimate of the number of

subjects with infective endocarditis reflects the poor specificity of the modified Duke criteria and the lack of anatomical correlation between using this methodology to assess likelihood of IE and the true underlying disease process for study patients. It is evident that using the modified Duke criteria at study entry does not permit the all-comers population to be characterized in terms of critical predisposing factors and patient attributes that could lead to the onset of *S. aureus* bacteremia (such as portals of entry) nor does it reflect differences in pathophysiology between primary bacteremias, secondary bacteremias, and IE and their inherent differences in prognosis.

Strict application of the modified Duke criteria revealed some subjects who were misclassified by the IEAC. The cross-tabulation of IEAC entry diagnosis subgroups and IE according to the modified Duke criteria are summarized in the following two tables:

Table 9: Comparator-Treated Subjects with IEAC Final Diagnosis of IE

	IE according to modified Duke Criteria						
	Possible IE		Definite IE				
IEAC Entry Diagnosis	1,1*	1,2	1,3	2,1	2,2	2,3	2,4
Definite IE	0	1	4	2	7	4	2
Possible IE	2	1	1	1	0	0	0

*The number pairs provide the number of major, minor Duke criteria that are applicable for the diagnosis category

Misclassified subjects in the Comparator group: Two subjects with findings compatible with definite IE by modified Duke criteria were miscategorized as possible IE, and one subject with findings compatible with possible IE was miscategorized as definite IE.

Table 10: Daptomycin-Treated Subjects with IEAC Final Diagnosis of IE

	IE according to modified Duke Criteria									
	Not IE	Possible IE			Definite IE					
IEAC Entry Diagnosis	1,0*	0,3	1,1	1,2	1,3	1,4	2,1	2,2	2,3	2,4
Definite IE	1	0	1	0	4	1	4	2	3	1
Possible IE	0	2	1	7	0	0	0	0	0	0
Not IE	1	0	0	0	0	0	0	0	0	0

*The number pairs provide the number of major, minor Duke criteria that are applicable for the diagnosis category

Misclassified subjects in the Daptomycin group: One subject with findings compatible with not IE by modified Duke criteria was miscategorized as definite IE, and one subject with findings compatible with possible IE was miscategorized as definite IE

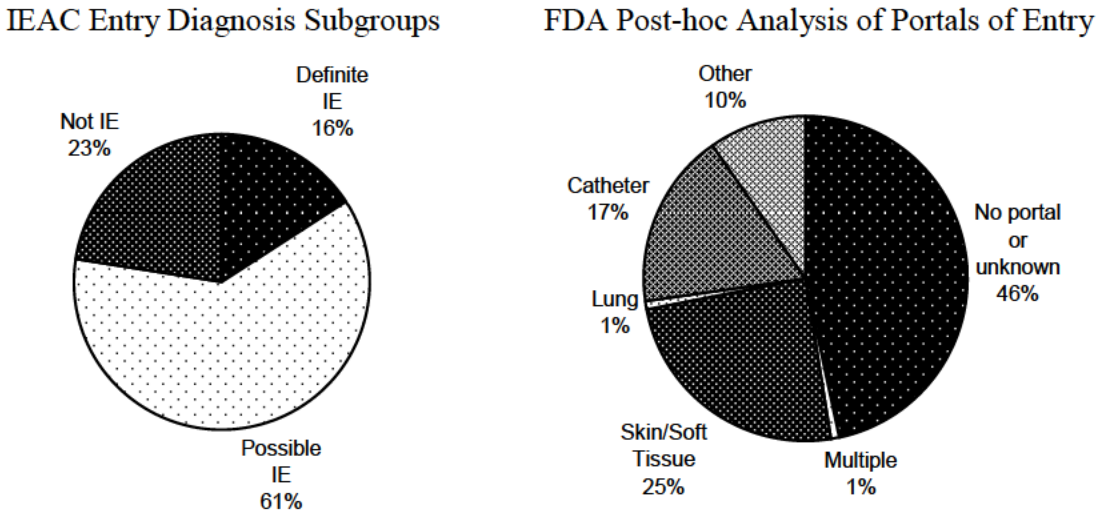
Portals of Entry

According to the Sponsor's data, 73.3% of the daptomycin-treated and 74.8% of the comparator-treated patients had an infection within 30 days of onset of *S. aureus* bacteremia; additionally, 40.8% of the daptomycin-treated patients and 31.3% of the comparator-treated patients had undergone surgery within 30 days of onset of *S. aureus* bacteremia. However, despite the striking frequency of infections and surgeries prior to

the onset of bacteremia in a considerable number of study subjects, discrete data relevant to potential portals of entry was not collected prospectively as part of the study design. Patients with bacteremias that develop secondary to an identifiable portal of entry frequently need adjunctive treatment (such as incision and drainage procedures, surgical debridement, etc.) which can confound assessment of the treatment effect of the study drug. Primary staphylococcal bacteremias, in contrast, have no identifiable source; hence, treatment relies much more substantially on the efficacy of the study drug for successful eradication.

The FDA conducted a post-hoc review of all the case report forms and patient profiles in order to compile data relevant to potential portals of entry. The following figure contrasts the relative homogeneity of the all-comers study population as assessed based on IEAC Entry Diagnosis subgroups using the modified Duke criteria compared to the underlying heterogeneity of the same population that is evident when characterized by potential portals of entry. Of note, approximately 25% of the patients with staphylococcal bacteremias in the study had a probable skin/soft tissue portal of entry and 17% were likely catheter-related. In the remaining 46% of subjects, either no portal of entry was identified or there was insufficient information to determine the existence of a portal of entry.

Figure 1: IEAC Entry Diagnosis versus Possible Portals of Entry



In summary, the study population was quite heterogeneous at enrollment. Sufficient data was not compiled prospectively to completely characterize the study subjects, although careful characterization was clearly warranted. Patients with bacteremias of varied sites of origin were pooled in the all-comers population, such that it was not possible to understand the underlying heterogeneity and its impact on outcome. As some subgroups of the overall population would have secondary bacteremias with inherently favorable prognoses, enhanced efforts by the Sponsor to completely characterize the study population would have provided better clarification of the overall clinical experience in the study and would have improved our understanding of the results of the primary and

clinical subgroup analyses.

Inclusion and Exclusion Criteria pertinent to the efficacy analysis:
As described in the previous section of this report on Efficacy Populations, the sponsor intended to make a blinded assessment of the extent of inclusion/exclusion criteria violations on a per-subject basis to assess if the violation could impact assessment of drug efficacy. If it was felt that the extent of the violation could impact the assessment of efficacy, then the subject would be excluded from the PP population. However, if the extent of the violation did not impact on efficacy assessment, the subject could be included in the PP population even though such violation(s) would have disqualified the subject under the original criteria. By modifying the original exclusion criteria post-randomization in this manner so that subjects that would have been excluded from the PP population could later be included in the PP, there is the risk of minimizing any differences between the treatment groups and making the two study groups appear non-inferior.

In Sections 5.3.1 and 6.10.1.8 of the final statistical analysis plan (SAP), the Sponsor clarified that subjects enrolled prior to Amendment 4a who were considered by the Investigator to have a high likelihood of LIE will be excluded from the ITT and PP populations and all efficacy analyses. There was one subject in the comparator arm with Left IE and no subjects in the daptomycin group who were enrolled prior to Amendment 4a and were subsequently excluded form the ITT and PP populations.

Analysis Windows (according to the Final Statistical Analysis Plan):
The strictest data analysis windows were defined as follows:

- Baseline: Day -02 to 1
- EOT: LDD-2 to Day 03P
- TOC: 38 P to 46P
- Post-study: 80P to 88P

However, it is noteworthy that the analysis windows could be extended as follows within the provisions of the SAP:

- Baseline: Day -05 to Day 1
- EOT: either LDD to 03P or 04P to 29P
- TOC: 04P or EOT+1 to 60P
- Post-study: 61P to 88P or 89P to last culture.

The implications of using the broader windows are that more subject data is included from time points that are outliers from the strict data analysis windows (i.e., subjects who missed study visits within the strict analysis windows would be included in the broader defined windows). The result of this approach is that there is significant overlap between the analysis windows of EOT, TOC, and Post-study, which blurs the distinctions between them in terms of assessing endpoint outcome data.

Based on the FDA review of the random sample of 118 case reports, only 50% of subjects had a post-study visit due to deaths, withdrawals, and lost-to-followup. Thus, conclusions about long-term study drug efficacy (to Day 88P) and inferences regarding

the frequency of relapses and metastatic complications of *S. aureus* bacteremia are limited.

Efficacy Data: All-comers Study Population

The following table summarizes the Sponsor's data for the all-comers population:
Table 11: Summary of Sponsor's Efficacy Data for All-comers Population (ITT and PP)

	Daptomycin (N,%)	Comparator (N,%)	Difference in success rates (95% CI)
Intent to Treat (ITT)			
Total	120	115	
Success	53 (44.2)	48 (41.7)	2.4% (-10.2, 15.1)
Failure	58 (48.3)	53 (46.1)	
Non-evaluable	9 (7.5)	14 (12.2)	
Per Protocol (PP)			
Total	79	60	
Success	43 (54.4)	32 (53.3)	1.1% (-15.6, 17.8)
Failure	36 (45.6)	28 (46.7)	

The results of study DAP-IE-01-02 satisfied the primary endpoint of non-inferiority in the all-comers ITT population having at least one positive blood culture for *S. aureus* based on the IEAC outcome at TOC.

Table 12: Summary of Sponsor's Efficacy Data for All-comers Population (ITT) stratified by IEAC Final Diagnosis Subgroups

Intent to Treat (ITT)	n	Daptomycin	Comparator	Diff (D-C) (95% CI)
Total Bacteremia	182	44/92 (47.8%)	39/90 (43.3%)	-4.5 (-19.0, 10.0)
Complicated bacteremia	121	26/60 (43%)	23/61 (37.7%)	5.6% (-11.8, 23.1)
Uncomplicated bacteremia	61	18/32 (56.3%)	16/29 (55.2%)	1.1% (-23.9, 26.0)
Total IE	53	9/28 (32.1%)	9/25 (36%)	-3.9 (-29.4, 21.7)
Complicated RIE	25	5/13 (38.5%)	6/12 (50%)	-11.5% (-50.3, 27.2)
Uncomplicated RIE	10	3/6 (50%)	1 /4 (25%)	25.0% (-33.3, 83.3)
Left IE	18	1/9 (11%)	2/9 (22%)	-11.1% (-45.2, 22.9)
Total Bacteremia and IE	235	53/120 (44.2%)	48/115 (41.7%)	2.4% (-10.2, 15.1)

The results of study DAP-IE-01-02 satisfied the primary endpoint of non-inferiority in the all-comers ITT population having at least one positive blood culture for *S. aureus* based on the IEAC outcome at TOC. However, it is noteworthy that the study was statistically powered for the all-comers analysis, but was of insufficient power to make any statistically meaningful inferences with respect to the final diagnosis subgroups (particularly endocarditis). The delta for the difference in success rates between the treatment groups of 20% is based on the all-comers experience and cannot not be applied uniformly to the final diagnosis subgroups as well. In the subjects with left IE, the extremely low success rates in both treatment groups with the comparator group having the higher efficacy rate of only 22% raises concerns that the study is unable to distinguish between active and inactive treatments (assay sensitivity) for this entity.

The predominant study subgroup involved subjects with *S. aureus* bacteremia, which constituted approximately 77% of the total population, whereas subjects with IE constituted approximately 23% of the study experience. Despite comparability with respect to outcomes in the all-comers population, the point estimates in all IEAC Final Diagnosis subgroups of complicated and uncomplicated bacteremia and endocarditis were low compared to the anticipated efficacy rates. The reasons for the low overall efficacy rates are uncertain, but may be related to idiosyncrasies in the design and conduct of the study, the method for selection of study subjects, and the inherent variability among the study investigators in terms of aggressive diagnostic evaluation, adjunctive interventions, and follow-up care. In addition, the final diagnosis subgroups are defined only at end of study using post-randomization data rather than being delineated at study entry and thereby assuring that the mix of subgroup cases within any one treatment arm was unbalanced and potentially confounded the study results.

Table 13: Summary of Sponsor's Efficacy Data for All-comers Population (ITT) stratified by Baseline Pathogen and IEAC Final Diagnosis Subgroups

ITT	n	Daptomycin (n = 120)			Comparator (n = 115)		
		Total	MSSA	MRSA	*Total*	MSSA	MRSA
Comp RIE	25	5/13 (38.5%)	1/5 (20%)	4/8 (50%)	6/12 (50%)	3/5 (60%)	3/7 (43%)
Uncomp RIE	10	3/6 (50%)	3/6 (50%)	0 (0%)	1 /4 (25%)	1 /4 (25%)	0 (0%)
Composite RIE	*35*	*8/19 (42%)*	*4/11 (36%)*	*4/8 (50%)*	*7/16 (43.8%)*	*4/9 (44%)*	*3/7 (43%)*
LIE	18	1/9 (11%)	1 /4 (25%)	0/5 (0%)	2/9 (22%)	2/5 (40%)	0/4 (0%)
Comp bacteremia	121	26/60 (43%)	16/38 (42%)	10/22 (45%)	23/61 (37.7%)	17/39 (44%)	6/22 (27%)
Uncomp bacteremia	61	18/32 (56.3%)	12/21 (57%)	6/10 (60%)	16/29 (55.2%)	11/17 (65%)	5/11 (45%)
Total	235	53/120 (44.2%)*	33/74 (45%)	20/45 (44%)	48/115 (41.7%)*	34/70 (48.6%)	14/44 (32%)

* one subject has no baseline pathogen

In terms of baseline pathogen, the two treatment groups had comparable efficacy against MSSA in the all-comers population with a trend of increased efficacy for daptomycin compared to the comparator for MRSA infections. However, due to the small sample size of MRSA infections in each of the IEAC Final Diagnosis subgroups, no statistically meaningful inferences could be made.

Table 14: Summary of Sponsor's Efficacy Data for All-comers Population (PP) stratified by IEAC Final Diagnosis Subgroups

Per Protocol (PP)	n	Daptomycin	Comparator	Diff (D-C) (95% CI)
Total Bacteremia	106	36/60 (60%)	26/46 (57%)	3.5% (-15.5, 22.4)
Complicated bacteremia	68	19/39 (49%)	14/29 (48%)	0.4% (-23.6, 24.5)
Uncomplicated bacteremia	38	17/21 (81%)	12/17 (71%)	10.4% (-17.0, 37.8)
Total IE	33	7/19 (37%)	6/14 (43%)	-6.0% (-39.8, 27.8)
Complicated RIE	16	5/10 (50%)	4/6 (67%)	-16.7% (-65.5, 32.2)
Uncomplicated RIE	4	1 /2 (50%)	0/2 (0%)	50.0% (-19.3, 119.3)
Composite RIE	*20*	*6/12 (50%)*	*4/8 (50%)*	*0% (-44.7, 44.7)*
Left IE	13	1/7 (14%)	2/6 (33%)	-19.0% (-64.8, 26.7)
Overall Total	139	43/79 (54%)	32/60 (53%)	1.1% (-15.6, 17.8)

The study was not powered for a per-protocol analysis as originally designed. However, the (ADD 95% CI to the TABLE) results of DAP-IE-01-02 in the PP population analysis were consistent with the ITT analysis in satisfying the primary endpoint of non-inferiority

in the all-comers PP population (ADD 95% CI to the TABLE) having at least one positive blood culture for *S. aureus* based on the IEAC outcome at TOC. The size of the PP population overall is considerably smaller than the ITT population. With respect to the treatment groups, the PP subpopulation is 52% of the ITT population for the comparator arm and is 65.8% of the ITT for the daptomycin arm. Due to the small sample size and inadequate power, no statistically meaningful inferences could be made with respect to the final diagnosis subgroups.

Table 15: Summary of Sponsor's Efficacy Data for All-comers Population (PP) stratified by Baseline Pathogen and IEAC Final Diagnosis Subgroups

PP	n	Daptomycin (n = 79)			Comparator (n = 60)		
		Total	MSSA	MRSA	*Total*	MSSA	MRSA
Comp RIE	16	5/10 (50%)	1 /4 (25%)	4/6 (67%)	4/6 (67%)	2/3 (67%)	2/3 (67%)
Uncomp RIE	4	1 /2 (50%)	1 /2 (50%)	0 (0%)	0/2 (0%)	0/2 (0%)	0 (0%)
Composite RIE	*20*	*6/12 (50%)*	*2/6 (33%)*	*4/6 (67%)*	*4/8 (50%)*	*2/5 (40%)*	*2/3 (67%)*
LIE	13	1/7 (14%)	1 /2 (50%)	0/5 (0%)	2/6 (33%)	2/3 (67%)	0/3 (0%)
Comp bacteremia	68	19/39 (49%)	11/24 (46%)	8/15 (53%)	14/29 (48%)	12/23 (52%)	2/6 (33%)
Uncomp bacteremia	38	17/21 (81%)	11/13 (85%)	6/8 (75%)	12/17 (71%)	8/11 (73%)	4/6 (67%)
Total	139	43/79 (54%)	25/45 (55.5%)	18/34 (53%)	32/60 (53%)	24/42 (57%)	8/18 (44%)

As was observed in the ITT analysis of efficacy with respect to baseline pathogen, the two treatment groups had comparable efficacy against MSSA in the all-comers population with a trend of increased efficacy for daptomycin compared to the comparator for MRSA infections. However, due to the small sample size of MRSA infections in each of the IEAC Final Diagnosis subgroups, no statistically meaningful inferences could be made.

Table 16: Comparative Success Rates for IEAC Outcome at EOT and Investigator Outcome at EOT (ITT)

IEAC Final Diagnosis	IEAC Outcome at EOT		Investigator Outcome at EOT	
	Comparator	Daptomycin	Comparator	Daptomycin
Complicated RIE	9/12 (75)	6/13 (46.2)	6/11 (54.5)	5/10 (50)
Uncomplicated RIE	1 /4 (25)	3/6 (50)	1/5 (20)	3/ 4 (75)
Left IE	3/9 (33.3)	4/9 (44.4)	2/8 (25)	1/5 (20)
Complicated Bacteremia	35/61 (57.4)	36/60 (60)	20/44 (45.5)	19/45 (42.2)
Uncomplicated Bacteremia	22/29 (76)	25/32 (78.1)	26/45 (57.8)	34/55 (61.8)
Composite: Bacteremia & IE	70/115 (60.9)	74/120 (61.7)	55/113 (48.7)	62/119 (52.1)

Note: The Investigator Outcome at TOC was not used for data analysis by the Sponsor.

The IEAC success rates at EOT were higher for both treatment groups compared to the IEAC success rates at TOC (discussed previously). In relation to the Investigator success rates at EOT, the IEAC success rates were higher for the composite of bacteremia/IE and within the subgroups of left IE, uncomplicated bacteremia, and complicated bacteremia.

There were disparities in the total number of subjects in the IEAC Final Diagnosis subgroups of complicated and uncomplicated bacteremia compared to the same subgroups as classified by the Investigators. In that regard, there are 16 more subjects (45 vs 29) in the daptomycin arm and 13 more subjects (55 vs 32) in the comparator arm classified as having uncomplicated bacteremia by the Investigators compared to the IEAC. In contrast, there are more subjects (61 vs 44) in the daptomycin arm and 15 more subjects (60 vs 45) in the comparator arm classified as having complicated bacteremia by the IEAC compared to the Investigators. The FDA review of the individual case report forms revealed most of the classification discrepancies between the IEAC and the Investigators are related to the criterion of two or more positive blood cultures collected on successive days as being indicative of a complicated bacteremia. There are important implications of shifting a substantial number of patients in both treatment arms with uncomplicated bacteremia as assessed and managed clinically by the Investigators into a category of more severe disease (complicated bacteremia for which they were not treated) by the IEAC. The overall effect of such shifting of patients is to erroneously enhance the success rates in the IEAC final diagnosis subgroups of complicated bacteremia by inclusion of subjects with uncomplicated disease, who had less severe disease, better prognoses, were managed clinically for uncomplicated bacteremia, and responded to treatment regimens appropriate for uncomplicated disease.

Table 17: Discordance between IEAC Outcomes and Investigator Outcomes at TOC

	IEAC OC	INV OC	N	Daptomycin	Comparator
EOT	Success	Failure	1	0	1
	Failure	Cure	7	5	2
TOC	Failure	Cure	22	13	9

* IEAC: PRSA at TOC; EOT success…Investigator:

There was discordance between the IEAC and the Investigator outcomes involving 8 subjects at EOT and 22 subjects at TOC. In all but one case, the IEAC outcome was failure for the corresponding Investigator outcome of cure. There was one patient with an Investigator outcome of failure at EOT that was adjudicated to success by the IEAC.

Efficacy Analysis and Baseline Demographic Parameters

The efficacy of the study drugs stratified by specific baseline characteristics of the study population was investigated by the FDA Medical Officer. The following series of tables summarizes the IEAC success rates at the primary efficacy endpoint (TOC) in relation to the following baseline characteristics: creatinine clearance, age, gender, and race.

Table 18: IEAC Success Rates at TOC stratified by Baseline creatinine clearance

Baseline CrCL	Daptomycin		Comparator	
	All-comers	IE	All-comers	IE
>80	38/67 (56.7)	8/17 (47)	25/59 (42.3)	6/17 (35)
50-80	13/34 (38.2)	1/8 (12.5)	14/34 (41.2)	1/3 (33.3)
30-50	2/17 (11.8)	0/3 (0)	9/19 (47.4)	2/2 (100)
<30*	0/2 (0)	0/0 (0)	0/3 (0)	0/3 (0)

*Subjects with creatinine clearance of <30 mL/min were to be excluded from the study.

As depicted in the table above, there is a dramatic decline in the efficacy of daptomycin in the all-comers population and in subjects with IE subjects who have progressive renal insufficiency from >80 mL/min to 30-50 mL/min. This trend is in sharp contrast to the relatively stable efficacy rate of the comparator in the all-comers and IE patients with similar degrees of renal dysfunction. The reason(s) for the disparate efficacy trends is uncertain due to insufficient data in terms of characterizing the underlying heterogeneity of the study population, lack of death certificate data to explain mortality rates, and identification of other potential confounders.

Table 19: IEAC Success Rates at TOC stratified by Age

Age Category	Daptomycin		Comparator	
	All-comers	IE	All-comers	IE
<65 years	47/90 (52.2)	9/23 (39)	35/78 (44.9)	8/18 (44.4)
≥65 – 74	4/11 (36.4)	0/2 (0)	8/22 (36.4)	0/5 (0)
≥75	2/19 (10.5)	0/3 (0)	5/15 (33.3)	1 /2 (50)

As depicted in the table above, there is a dramatic decline in efficacy of daptomycin in the all-comers population and in subjects with IE who are older than age 65. This trend is in sharp contrast to the efficacy rates of the comparator in the all-comers population and in subjects with IE who are elderly. The reason(s) for the disparate efficacy trends is uncertain due to insufficient data in terms of characterizing the underlying heterogeneity of the study population, lack of death certificate data to explain mortality rates, and identification of other potential confounders.

Table 20: IEAC Success Rates at TOC (all-comers) stratified by Sex (gender)

Gender	Daptomycin	Comparator
Male	35/70 (50)	30/71 (42.3)
Female	18/50 (36)	18/44 (40.9)

The table above depicts the IEAC success rates in the all-comers population stratified by gender. Overall, the efficacy rates appear similar between the two treatment arms when analyzed by gender.

Table 21: IEAC Success Rates at TOC (all-comers) stratified by Race

Race	Daptomycin	Comparator
Caucasian	27/75 (36)	35/81 (43.2)
Black	21/32 (65.6)	10/23 (43.5)
Others	5/13 (38.5)	3/11 (27.3)

The table above depicts the IEAC success rates in the all-comers population stratified by race. Overall, the efficacy rates appear similar between the two treatment arms when analyzed by race.

Efficacy Analysis: All-comers with SIRS

Table 22: Subjects with SIRS (ITT and PP)

	ITT with SIRS (n=176)			PP with SIRS (n=110)		
	MSSA	MRSA	Total ITT	MSSA	MRSA	Total PP
Daptomycin	54	35	89	35	29	64
Comparator	54	33	87	33	13	46
Totals	108	68	176	68	42	110

Evidence of systemic inflammatory response syndrome (SIRS) was used as a marker of disease severity in the conduct of the study. Approximately 75% of the subjects (176/235) in the ITT population had evidence of SIRS, indicating that most of the study population had severe illnesses as a consequence of *S. aureus* bloodstream infections. Among the 176 patients with SIRS, 108 (61.3%) were infected with MSSA and 68 (38.6%) were infected with MRSA. In the PP population, approximately 79% of the subjects (110/139) had SIRS with similar percentages infected with MSSA and MRSA as observed in the ITT.

Table 23: IEAC Success Rates at TOC among Subjects with SIRS

	ITT		PP	
	Daptomycin n/N (%)	Comparator n/N (%)	Daptomycin n/N (%)	Comparator n/N (%)
All-comers	38/89 (46.7)	37/87 (42.5)	33/64 (51.6)	24/46 (52.2)
Complicated RIE	4/11 (36.4)	6/10 (60.0)	4/9 (44.4)	4/6 (66.7)
Uncomplicated RIE	1/4 (25.0)	1/4 (25.0)	0/1 (0.0)	0/2 (0.0)
Left IE	1/7 (14.3)	1/7 (14.3)	1/6 (16.7)	1/4 (25.0)
Complicated Bacteremia	19/47 (40.4)	17/43 (39.5)	15/32 (46.9)	9/13 (69.2)
Uncomplicated Bacteremia	13/20 (65.0)	12/23 (52.2)	13/16 (81.2)	10/21 (47.6)

The table above reveals the overall IEAC success rates for subjects with SIRS stratified by IEAC final diagnosis subgroups compared to the overall all-comers data. The efficacy rates for the two treatment groups were comparable in the subjects in the all-comers population who had systemic inflammatory response syndrome (SIRS). Among the IEAC final diagnosis subgroups, the efficacy of the two treatment groups was comparable, although there were trends indicative of better performance of daptomycin in subjects with uncomplicated bacteremia with SIRS, whereas there was better performance of the comparator in subjects with complicated RIE with SIRS. However, due to the small sample size in each of the IEAC Final Diagnosis subgroups, no statistically meaningful inferences could be made.

Table 24: Synopsis of IEAC Success Rates at TOC in ITT and PP Populations in Patients with SIRS who have MSSA as Baseline Pathogen

MSSA/SIRS	Daptomycin		Comparator	
	ITT	PP	ITT	PP
	N=54	N=35	N=54	N=33
All-comers	22/54 (40.7%)	18/35 (51.4%)	27/54 (50%)	19/33 (57.6%)
Complicated RIE	1 /4 (25%)	1 /4 (25%)	3/5 (60%)	2/3 (66.7%)
Uncomplicated RIE	1 /4 (25%)	0/1 (0%)	1 /4 (25%)	0/2 (0%)
Left IE	1 /3 (33.3%)	1 /2 (50%)	1 /3 (33.3%)	1/1 (100%)
Complicated Bacteremia	11/30 (36.7%)	8/19 (42.1%)	13/27 (48.2%)	9/17 (52.9%)
Uncomplicated Bacteremia	8/13 (61.5%)	8/9 (88.9%)	9/15 (60%)	7/10 (70%)

In terms of baseline pathogen, the comparator group had better overall success rates for MSSA infections associated with SIRS than did daptomycin-treated subjects in the all-comers population (ITT and PP). This discrepancy was most noteworthy for patients with complicated RIE and complicated bacteremia in the ITT and PP populations. However, due to the small sample size in each of the IEAC Final Diagnosis subgroups, no statistically meaningful inferences could be made.

Table 25: Synopsis of IEAC Success Rates at TOC in ITT and PP Populations in Patients with SIRS who have MRSA as Baseline Pathogen

MRSA/SIRS	Daptomycin		Comparator	
	ITT	PP	ITT	PP
	N=35	N=29	N=33	N=13
All-comers	16/35 (45.7%)	15/29 (51.7%)	10/33 (30.3%)	5/13 (38.5%)
Complicated RIE	3/7 (42.8%)	3/5 (60%)	3/5 (60%)	2/3 (66.7%)
Uncomplicated RIE	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Left IE	0/4 (0%)	0/4 (0%)	0/4 (0%)	0/3 (0%)
Complicated Bacteremia	8/17 (47%)	7/13 (53.8%)	4/16 (25%)	1 /4 (25%)
Uncomplicated Bacteremia	5/7 (71.4%)	5/7 (71.4%)	3/8 (37.5%)	2/3 (66.7%)

Among subjects infected with MRSA who had evidence of SIRS, the daptomycin group had better overall success rates than did comparator-treated subjects in the ITT and PP populations. This discrepancy was most noteworthy for patients with uncomplicated and complicated bacteremia in the ITT and PP populations. However, due to the small sample size in each of the IEAC Final Diagnosis subgroups, no statistically meaningful inferences could be made.

Efficacy Analysis: Infectious Endocarditis (IE) due to *S. aureus*

Table 26: Summary of selected demographic characteristics of subjects with IE

ITT Population		**Daptomycin (N = 28)**	**Comparator (N = 25)**
Characteristic	**Age: Mean ± S.D.**	**46.7 ± 15.7**	**49.6 ± 18.9**
	Male: Female	**14 (50): 14 (50)**	**11 (44): 14 (56)**
	Diabetes Mellitus	**4 (14.2)**	**5 (20)**
	Prior Endocarditis	**4 (14.2)**	**5 (20)**
	SIRS	**22 (78.6)**	**21 (84)**
	IVDU	**17 (60.7)**	**14 (56)**
Oxacillin susceptibility	**MSSA**	**15 (53.6)**	**14 (56)**
	MRSA	**13 (46.4)**	**11 (44)**
IEAC Entry Diagnosis	**Definite IE**	**17 (60.7)**	**20 (80)**
	Possible IE	**10 (35.7)**	**5 (20)**
	Not IE	**1(3.6)**	**0**
IEAC Final Diagnosis	**Complicated RIE**	**13**	**12**
	Uncomplicated RIE	**6**	**4**
	LIE	**9**	**9**

The table above summarizes selected demographic data regarding the 53 study subjects with an IEAC Final Diagnosis of IE. There were nine subjects with left IE in each treatment group. There were 19 subjects in the daptomycin group and 16 in the comparator group who were identified as having right-sided IE. The proportion of subjects with MSSA and MRSA infections was comparable in each treatment group. In addition, a greater percentage of subjects in the comparator group had evidence of SIRS compared to the daptomycin group. There were similar numbers of intravenous drug users (IVDU) in each treatment group.

Table 27: Summary of IEAC Efficacy Rates at TOC for subjects classified at Entry using modified Duke criteria:

	Intent to Treat (ITT)			Per Protocol (PP)		
Modified Duke Classification at Entry (IEAC)	# Subjects (n)	Daptomycin n=28	Comparator n=25	# Subjects (n)	Daptomycin n=19	Comparator n=14
Definite IE	**37**	**7/17 (41.2)**	**8/20 (40)**	**24**	**5/13 (38.5)**	**5/11 (45.4)**
Possible IE	15	2/10 (20)	1/5 (20)	9	2/6 (30)	1/3 (33.3)
Not IE	1	0/1 (0)	0/0 (0)	0	0/0 (0)	0/0 (0)
Total	53	9/28 (32.1)	9/25 (36)	33	7/19 (36.8)	6/14 (42.9)

Based on IEAC Entry Diagnoses (using modified Duke criteria), there were 37 subjects identified with findings compatible with definite endocarditis and 15 with possible endocarditis of the 53 subjects in the ITT with the IEAC final diagnosis of IE. There were more patients in the daptomycin group with findings compatible with possible endocarditis, whereas there were more subjects with definite endocarditis in the comparator group. This disparity raised concern among the FDA review team of the poor specificity of the diagnosis of endocarditis that is attainable using the modified Duke criteria; Study drug efficacy relevant to IE is best assessed among subjects clearly identified as having IE as the underlying diagnosis.

Table 28: Summary of Sponsor Data on IEAC Efficacy Rates at TOC for Subjects with **Definite IE** at Entry by Modified Duke Criteria

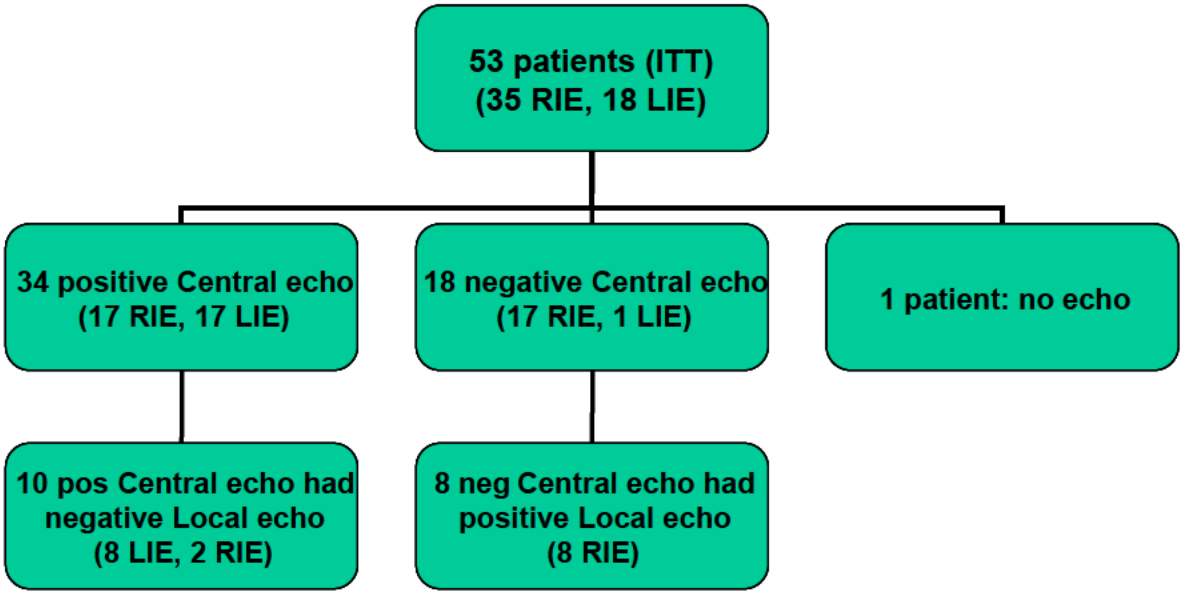
	Intent to Treat (ITT)			Per Protocol (PP)		
IEAC Final Diagnosis	# Subjects (n)	Daptomycin n=17	Comparator n=20	# Subjects (n)	Daptomycin n=13	Comparator n=11
Complicated RIE	18	4/8 (50)	6/10 (60)	12	4/7 (57)	4/5 (80)
Uncomplicated RIE	7	2/3 (67)	1 /4 (25)	3	0/1 (0)	0/2 (0)
Left IE	12	1/6 (16.7)	1/6 (16.7)	9	1/5 (20)	1 /4 (25)
Total	**37**	**7/17 (41.2)**	**8/20 (40)**	**24**	**5/13 (38.5)**	**5/11 (45.4)**

Among the subjects with definite endocarditis as identified using modified Duke criteria, it is noteworthy that the success rates are very low in all relevant IEAC Final Diagnosis subgroups. In the table above, there is only one cell with greater than 5 observations of success. The small sample size hampers interpretation of comparative drug efficacy, and no meaningful statistical inferences can be made. The very low success rates in subjects with left IE raise concerns about assay sensitivity and they do not provide substantial evidence of daptomycin efficacy as required by current federal regulations (21 CFR 314.126).

Echocardiography

Echocardiography (primarily transesophageal) was performed in all but one study subject with IE. It is noteworthy that the protocol-defined criteria for left and right IE differ with respect to the requirement for echocardiographic evidence of endocarditis. The definition of left IE (SECTION OF PROTOCOL) requires echocardiographic evidence of involvement or predisposing pathology of the mitral or aortic valve in order to make the diagnosis, whereas there is no comparable requirement for echicardiographic evidence of involvement of the tricuspid or pulmonic valves in right-sided endocarditis. This disparity in echocardiographic evidence of disease combined with the limitations of the modified Duke criteria as discussed above raised concern among the FDA review team about the specificity of the diagnosis of endocarditis among many of the subjects identified as having IE by the IEAC.

Figure 1: FDA Synopsis of Echocardiographic Interpretations derived from the Local and Central (Duke) Echolabs



The schematic diagram in the figure above provides an algorithm to track the local and central echolab interpretations. Among the 18 subjects with left IE, 94% (17/18) had positive Central echocardiogram interpretations, although 47% (8/17) of subjects with positive Central echocardiograms had negative local interpretations for the same echocardiogram. Of the 35 subjects with right IE, only 49% (17/35) had positive Central or local echocardiogram interpretations. Thus, although one approach to improving the specificity of the diagnosis was to analyze the efficacy of the study drugs in the subset of patients who had echocardiographically-demonstrable evidence of endocarditis (valve vegetations or valve perforations) within the IEAC-identified IE population, it was quite problematic to identify a consistent subgroup. The table below summarizes the efficacy success rates for daptomycin and comparator stratified by echocardiographic evidence of the disease.

Table 29: Echocardiography: IEAC Success Rates at TOC based on Central and Local Echocardiographic Evidence of IE*

IE Population	N	Comparator	Daptomycin
ITT	53	9/25 (36)	9/28 (32.1)
All pos Central plus all pos Local	42	9/24 (37.5)	6/18 (33.3)
All positive Central echo (regardless of Local)	34	7/20 (35)	4/14 (28.6)
Positive Local echo (regardless of Central)	32	7/19 (36.8)	6/13 (46.1)
Positive Central who have positive Local	24	5/15 (33.3)	4/9 (44.4)
All negative Central echo (regardless of Local)	18	2/5 (40)	5/13 (38.5)
Negative Central but positive Local	8	2/4 (50)	2/4 (50)

*one subject with RIE did not have an echocardiogram

It s evident from the above table that the efficacy rates for each study drug group vary considerably depending on whether the local or the Central echocardiogram interpretations are considered valid indicators of IE. Using the subgroup of patients with IE as identified by the IEAC, the efficacy rate for the comparator is greater than that of daptomycin (36% vs. 32.1%). Limiting analysis only to those subjects with positive Central echocardiography irrespective of local echocardiography, the total number of IE subjects identified decreases to 34 with the comparator having greater efficacy than daptomycin (35% vs. 28.6%). However, when limited only to those subjects with positive local echocardiography irrespective of Central echocardiography, the number of IE subjects identified decreases to 32 with daptomycin having greater efficacy than comparator (46.1% vs. 36.8%). It is the contrasting conclusions that can be drawn as a consequence of the marked disparities in interpretation of the echocardiograms that confounds attempts to clearly identify a subgroup of study subjects with confidence that actually have IE and then to assess study drug efficacy within that subgroup with defined disease. Due to small sample size and insufficient power as well as concern about assay sensitivity in the left IE subgroup (as described previously), there are no statistically meaningful inferences that can be deduced about study drug performance from the endocarditis experience in this study.

Kappa was calculated as a measure of inter-observer agreement between the central and local echolabs with respect to the echocardiographic interpretations. The kappa value was 0.2548 [95% CI (-0.0142, 0.5238)], indicating that there is not much consistency of agreement between the two echolab interpretations.

Efficacy Analysis: Metastatic Complications of *S. aureus* Bacteremia and IE:

Table 30: Compilation of Metastatic Infections and Septic Complications reported as Serious Adverse Events (ITT)

	Comparator	Daptomycin	Total
Osteomyelitis	4	7	11
Epidural Abscess	0	2	2
Septic arthritis	2	0	2
Abdominal wall abscess	0	1	1
Exacerbation right lower back abscesses	1	0	1
Left inguinal abscess	0	1	1
Paraspinal abscess	1	0	1
Pulmonary Abscess (ruptured)	0	1	1
Intramural heart abscess	1	0	1
Perivalvular ring abscess	1	0	1
Total	10	12	22

The table above summarizes the septic complications observed among study patients, which were reported as adverse events. There was not a uniform requirement in the study protocol for investigators to perform a pre-specified series of diagnostic imaging tests for evidence of metastatic staphylococcal infections among all enrolled patients with *S. aureus* bacteremia. The Investigator was advised to evaluate the patient daily for any evidence of metastatic sites of infection. If metastatic sites of infection were suspected, the Investigator was to perform appropriate investigations, such as computed tomography (CT) scans, magnetic resonance images (MRI), and/or bone scans. If abnormalities were

noted on diagnostic imaging scans that suggested or confirmed the presence of a metastatic infection, the abnormal findings were reported as adverse events. Thus, the data depicted in the table is likely an underestimate of the actual number of septic and metastatic complications due to the lack of systematic metastatic infection evaluations in all enrolled subjects.

Osteomyelitis was the most frequently reported septic complication as a serious adverse event with seven cases noted among the daptomycin group compared to four cases in the comparator group. All of the patients with osteomyelitis had either complicated bacteremias or complicated RIE. There were no cases of osteomyelitis reported among subjects with left IE. Also noteworthy, there were no subjects with meningitis, prosthetic valve endocarditis, or deep organ abscess (brain, kidney, liver, spleen) as a consequence of the staphylococcal bacteremia.

FDA Reassessment of Individual Case Outcomes at EOT and TOC:

Based on a review of the case report forms, there were multiple subjects whose IEAC assessments at EOT and/or TOC were in question. The lack of a detailed narrative by the Investigators and the IEAC to explain their rationale for the diagnosis and outcome assessments that they assigned to individual subjects and the reason(s) for failure among those subjects greatly hampered our ability to gain an in-depth understanding of the performance of study drug in both treatment groups. It is noteworthy that the Investigator was limited to indicating only one reason for failure on the case report forms, whereas the IEAC often indicated multiple reasons for failure without establishing any hierarchial order among them. Thus, discerning the primary reason for failure became difficult.

In an effort to create to serve as a framework for reassessing outcome assessments, the FDA Medical Officer developed the following uniform guidelines:

1. PENS: use of a PENS agent for ≥4 days was assessed as a failure at TOC
2. Subjects with TOC blood cultures but missing EOT blood cultures could have the EOT assessment imputed based on the TOC culture results.
3. Subjects with missing TOC blood cultures were considered failures at TOC even if they had a Post-study blood culture. The TOC window was considered to extend up to Day 60P. Blood cultures obtained on Days 61P and later were considered Post-study blood cultures.
4. Subjects treated with <3 days of study med were considered non-evaluable

Table 31: Study Subjects with FDA Reassessment of Outcomes at EOT and TOC

CASE-ID	IEAC Final Diagnosis	Treatment	IEAC Outcome at EOT/TOC	FDA reassessed outcome at EOT/TOC	FDA Reason for Reassessment of Outcome
(b) (6)	Complicated bacteremia	Comparator	Non-eval	S/F	PENS: dicloxacillin from EOT x 20 days
	Complicated bacteremia	Comparator	S/S	S/F	No TOC BC; Day 92P in PS window (negative)
	Complicated bacteremia	Comparator	S/F[g]	F/F; Reclassify as persistent bacteremia	Persistent bacteremia: (+) EOT BC on day 03P
	Complicated bacteremia	Comparator	S/S	S/F	No TOC BC; Day 90P in PS window (negative)
	Complicated bacteremia	Comparator	S/F[i]	F/F	PENS: Vanco days -03 to 01 with (-) BC day 01 and later; only (+) BCs on Days -04, -02; Missing TOC BCs
	Complicated bacteremia	Comparator	S/F	S/F	PENS: Bactrim for 11 days for a UTI
	Uncomplicated bacteremia	Comparator	S/F[a]	F/F	PENS (Levofloxacin days -01 to 05 for pneumonia)
	Uncomplicated bacteremia	Comparator	S/S	S/F	No TOC BC; Day 66P in PS window (negative)
	Uncomplicated bacteremia	Comparator	F/F[f]	Noneval/noneval	Subject received only one day of study drug
	Complicated bacteremia	Daptomycin	S/S	F/F	AE: premature D/C study drug due to 2900 CPK with UE weakness
	Complicated bacteremia	Daptomycin	F/F[c]	F/F; Exclude PP	Polymicrobial bacteremia (MRSA, MSSA)
	Complicated bacteremia	Daptomycin	S/S	S/F	PENS: Bactrim days 07P to 15P
	Complicated bacteremia	Daptomycin	Non-eval	F/F	AE: (+) osteomyelitis of foot bone scan; PENS: change in Tx to broader coverage for osteo
	Complicated bacteremia	Daptomycin	F/F[e]	F,F; Reclassify as persistent bacteremia and micro failure	Investigator stopped study treatment due to persistent (+) BCs
	Complicated bacteremia	Daptomycin	S/S	S/F	No TOC BC; Day 85P in PS window (negative)
	Complicated bacteremia	Daptomycin	F/F[h]	Reclassify as not clinical failure	Study drug stopped due to concern that dapto was not indicated for SA pneumonia; Probably shouldn't have been enrolled; worsening respiratory status from Day 01; Study drug administered for only 3 days
	Complicated bacteremia	Daptomycin	Non-eval	F/F; reclassify as clinical failure	Study med terminated by investigator for unsatisfactory clinical response; (+) perinephric fluid
	Complicated bacteremia	Daptomycin	F/F[j]	F/F; Reclassify as clinical failure	Serial MRI reveals new development of epidural abscess/discitis; new pneumonia Day 03
	Complicated RIE	Daptomycin	S/S	F/F	PENS (Doxycycline days 12-19 for pneumonia); new pneumonia
	Complicated RIE	Daptomycin	S/S	S/S; Exclude PP	Polymicrobial bacteremia (MRSA, MSSA)
	Complicated RIE	Daptomycin	Non-eval	F/F	Missing BCs: NO EOT/TOC/PS BCs
	Complicated RIE	Daptomycin	S/S	F/F	PENS: Rifampin on Days -01 to Day 03; only (+)

					BCs on Days -02 and -01
(b) (6)	Uncomplicated bacteremia	Daptomycin	S/F[b]	F/F	PENS: cephalexin days -02 to 03; only (+) BC on Day -02; Missing TOC BC
	Uncomplicated bacteremia	Daptomycin	S/F	F/F	Missing BCs: No EOT/TOC/PS BCs
	Uncomplicated bacteremia	Daptomycin	F/F[d]	F/F; Exclude PP	Polymicrobial bacteremia (MSSA, staph species)
	Uncomplicated bacteremia	Daptomycin	S/S	F/F	PENS: Vanco on Days -01 to 02 (4 days) for line sepsis; only (+) BC on Day -02
	Uncomplicated RIE	Daptomycin	S/S	S/F	No TOC BC; 2 BCs done in PS analysis window and one had MSSA (RELAPSE)

*S=success, F=failure, BC=blood culture
[a]IEAC: PENS: vancomycin x 49 days for MRSA in blood on Day 30P
[b]IEAC: Missing TOC and Post-study BC
[c]IEAC: Persistent bacteremia
[d]IEAC: PENS for inguinal abscess
[e]IEAC: Discordance on IEAC assessment sheet (micro failure); RLL pneumonia on admission should not have been enrolled
[f]IEAC: PENS: cefazolin, levaquin, vanco; Other: physician preference for cefazolin
[g]IEAC: persistent bacteremia
[h]IEAC: Other: suspicion of staph pneumonia; Subject treated only 3 days; trach aspirate MRSA
[i]IEAC: Missing TOC BCs
[j]IEAC: PENS: meropenem, flucloxacillin, cefuroxime, rifampin

Table 32: Chart of Reasons for FDA Reassessment of Outcomes at EOT and TOC

	Comparator N = 9	Daptomycin N = 18	Totals N = 27
PENS	4	6	10
Missing TOC Blood culture	4	4	8
Pneumonia	1	2	3
Adverse Event	0	2	2
Reclassified as clinical failure	0	2	2
Persistent bacteremia	1	1	2
Reclassified as Micro failure	0	1	1
Relapse (post-study)	0	1	1
Reclassified as not clinical failure	0	1	1
Reclassified as non-evaluable	1	0	1

As depicted in the table above, the most common reason for reassessment of outcome was use of PENS antibiotics followed in frequency by missing blood cultures.

Table 33: IEAC Non-evaluable outcomes at TOC that were reassessed to Failure at TOC by FDA

CASE-ID	*IEAC Final Diagnosis*	*Study Drug*	*SMDUR (days)*	*IEAC Reason for Non-evaluable assessment*	*FDA Outcome at EOT/TOC*	*FDA Reason for re-assessment of outcome*
(b) (6)	Complicated Bacteremia	Comparator	15	Received 20 days of diclox subsequent to stopping study drug for neuropathic soft tissue ulcer	Success/Failure	PENS: dicloxacillin for 20 days from EOT
	Complicated RIE	Daptomycin	41	No (+) BC within 2 days of enrollment	Failure/Failure	(+) Blood culture Day -03 and Day -05; No EOT, TOC, PS blood culturess
	Complicated Bacteremia	Daptomycin	4	Patient required broad spectrum antibiotics per physician's opinion	Failure/Failure	AE: osteomyelitis (bone scan); PENS: change to broad spectrum antibiotics
	Complicated Bacteremia	Daptomycin	4	Withdrawn from study inappropriately	Failure/Failure	Study medication terminated by investigator for unsatisfactory clinical response

SMDUR = study medication duration; AE = adverse event; PENS = potentially effective non-study antibiotic; EOT = end of therapy; TOC = test of cure

Among the reassessed subject outcomes, there were four subjects with non-evaluable IEAC outcomes that were reassessed as failures by the FDA. The details of the four cases are summarized above.

Table 34: Subjects assessed as IEAC successes at TOC who had missing TOC blood cultures

CaseID	SMDUR	EOT BC	Next relevant post-EOT BC*	Notes
(b) (6)	14	Day 14L	Day 66P	
	14	Day 02P	Day 92P	
	28	Day 28L	Day 85P	
	14	Day 02P	Day 65P & 85P	Day 85P (+) BC
	28	Day 28L	Day 90P	

*PS Window: Day 61P to 88P (or last Cx)

In subjects with missing TOC blood cultures, the IEAC imputed successful outcomes at TOC based in part on negative blood cultures from the post-study visit as depicted in the table above. Of note, all of the post-study blood cultures were obtained beyond the Day 60P (60 days post-EOT) analysis window for TOC. The FDA review team felt that this approach was problematic as the primary efficacy endpoint for this study was the IEAC outcome at TOC. The FDA reviewers felt that imputing the outcome for this critical time point in the study was inappropriate. In addition, the IEAC's approach was in violation of the protocol which required that all subjects with missing EOT and/or TOC blood cultures be considered as failures. Consequently, the IEAC outcomes for the patients listed in the table above were reassessed as failures for the FDA efficacy analysis.

Table 35: FDA Efficacy Analysis in the All-comers Population (ITT and PP)

	Daptomycin (N,%)	Comparator (N,%)	Difference in success rates (95% CI)
ITT			
Total	120	115	
Success	46 (38.3)	44 (38.3)	0.1% (-12.4, 12.5)
Failure	68 (56.7)	57 (49.6)	
Non-evaluable	6 (5)	14 (12.2)	
PP			
Total	77	60	
Success	42 (54.5)	32 (53.3)	1.2% (-15.6, 18.0)
Failure	35 (45.6)	28 (46.7)	

The results of the FDA analysis indicated that daptomycin satisfied the primary endpoint of non-inferiority in the all-comers ITT and PP populations having at least one positive blood culture for *S. aureus* based on the IEAC outcome at TOC. This result was noted despite the overall decrease in success rates in both treatment groups following FDA case reassessments.

Table 36: Cases with FDA Reassessment of Outcomes: Comparative Success Rates in the All-comers Population (ITT)

ITT (all-comers)	Daptomycin		Comparator	
	Sponsor	FDA	Sponsor	FDA
Success	53/120 (44.2%)	46/120 (38.3)	48/115 (41.7%)	44/115 (38.3)
Failure	58/120 (48.3%)	68/120 (56.7%)	53/115 (46%)	57/115 (49.6%)
Non-evaluable	9/120 (7.5%)	6/120 (5%)	14/115 (12.2%)	14/115 (12.2%)

The table above summarizes comparative Sponsor (IEAC)-derived and FDA-derived outcomes at TOC in the all-comers population incorporating the case reassessments by the FDA. Using the FDA reassessment of patient outcomes, the success rates in the all-comers population was 38.3% for both treatment groups [95% CI for difference in success rates= 0.1% (-12.4, 12.5)], which represents a decline in efficacy assessments compared to the Sponsor (IEAC) outcome assessments.

Table 37: Cases with FDA Reassessment of Outcomes: Comparative Success rates at TOC by Disease Category in the All-comers Population (ITT)

ITT	N	Daptomycin		Comparator	
		Sponsor	FDA MO	Sponsor	FDA MO
Bacteremia*	182 (77.4)	44/92 (47.8)	40/92 (43.5)	39/90 (43.3)	35/90 (38.9)
IE**	53 (22.5)	9/28 (32.1)	6/28 (21.4)	9/25 (36)	9/25 (36)
Total	235 (100)	53/120 (44.2)	46/120 (38.3)	48/115 (41.7)	44/115 (38.3)

*complicated and uncomplicated; **Right IE and left IE

In terms of major disease category, the table above summarizes comparative Sponsor (IEAC)-derived and FDA-derived outcomes at TOC in the all-comers population incorporating the case reassessments by the FDA. Of note, the FDA-derived success rates revealed a decrease in both treatment arms for bacteremia and in the daptomycin arm for IE.

Table 38: Cases with FDA Reassessment of Outcomes: Comparative Success Rates at TOC by IEAC Final Diagnosis Subgroups

ITT	Daptomycin		Comparator	
	Sponsor	FDA MO	Sponsor	FDA MO
Complicated RIE	5 (38.5)	3 (23.1)	6 (50)	6 (50)
Uncomplicated RIE	3 (50)	2 (33.3)	1 (25)	1 (25)
Left IE	1 (11)	1 (11)	2 (22)	2 (22)
Complicated Bacteremia	26 (43)	23 (38.3)	23 (37.7)	20 (32.8)
Uncomplicated Bacteremia	18 (56.3)	17 (53.1)	16 (55.2)	15 (51.7)

*RIE = right IE

The table above summarizes the comparative Sponsor (IEAC) and FDA success rates in the patients with IE and bacteremia stratified by IEAC final diagnosis subgroups. Noteworthy is the decline in efficacy rates for daptomycin in subjects with complicated and uncomplicated RIE when assessed using FDA outcomes, whereas the corresponding comparator efficacy data remain unchanged. There were smaller decreases in drug efficacy in both treatment arms for subjects with bacteremia. Due to small sample size and insufficient power, no meaningful statistical inferences can be made regarding the performance of the study drugs in the endocarditis experience.

Synopsis of Sponsor and FDA Infective Endocarditis Efficacy Data

Table 39: Comparative Success Rates at TOC (Composite RIE and LIE)

	Sponsor		FDA	
	ITT	PP	ITT	PP
Daptomycin	9/28 (32.1)	7/19 (36.8)	6/28 (21.4)	4/18 (22.2)
Comparator	9/25 (36)	6/14 (42.8)	9/25 (36)	6/14 (42.8)

The table above depicts the comparative Sponsor (IEAC) and FDA outcomes at TOC for all patients with an IEAC final diagnosis of IE (composite right and left IE) in the ITT and PP populations. Of note, the efficacy rates for the daptomycin-treated patients with

IE are lower in the FDA analysis in both the ITT and PP populations compared to the corresponding Sponsor analysis and compared to the comparator-treated patients. However, due to small sample size and insufficient power, no meaningful statistical inferences can be made regarding the performance of the study drugs in the endocarditis experience.

Table 40: Comparative Success Rates at TOC stratified by IEAC Final Diagnosis, Study Treatment Group, and ITT/PP population

	Sponsor				FDA			
	Daptomycin		Comparator		Daptomycin		Comparator	
IEAC Final Diagnosis Category	ITT	PP	ITT	PP	ITT	PP	ITT	PP
Uncomplicated RIE	3/6 (50)	1 /2 (50)	1 /4 (25)	0/2 (0)	2/6 (33)	1 /2 (50)	1 /4 (25)	0/2 (0)
Complicated RIE	5/13 (38.5)	5/10 (50)	6/12 (50)	4/6 (66.7)	3/13 (23)	2/9 (22)	6/12 (50)	4/6 (66.7)
LIE*	1/9 (11)	1/7 (14.2)	2/9 (22)	2/6 (33.3)	1/9 (11)	1/7 (14.2)	2/9 (22)	2/6 (33.3)

* Two daptomycin- and one comparator-treated patient had valve replacement surgery for LIE. The comparator-treated patient was a failure at TOC; one daptomycin-treated patient was a failure at TOC and the other was non-evaluable at TOC.

In terms of the IEAC final diagnosis subgroups with IE, there are fewer successes in the daptomycin group with uncomplicated and complicated RIE in the FDA analysis compared to the Sponsor's analysis. However, due to small sample size and insufficient power, no meaningful statistical inferences can be made regarding the performance of the study drugs in the endocarditis experience.

Table 41: Comparative Success Rates at TOC stratified by Baseline Pathogen (ITT)

	Sponsor				FDA			
	Daptomycin		Comparator		Daptomycin		Comparator	
IEAC Final Diagnosis Category	MSSA	MRSA	MSSA	MRSA	MSSA	MRSA	MSSA	MRSA
Uncomplicated RIE	3/6 (50)	0/0 (0)	1 /4 (25)	0/0 (0)	2/6 (33.3)	0/0 (0)	1 /4 (25)	0/0 (0)
Complicated RIE	1/5 (20)	4/8 (50)	3/5 (60)	3/7 (42.9)	0/5 (0)	3/8 (37.5)	3/5 (60)	3/7 (42.8)
Left IE	1 /4 (25)	0/5 (0)	2/5 (40)	0/4 (0)	1 /4 (25)	0/5 (0)	2/5 (40)	0/4 (0)

Table 42: Comparative Success Rates at TOC stratified by Baseline Pathogen (PP)

	Sponsor				FDA			
	Daptomycin		Comparator		Daptomycin		Comparator	
IEAC Final Diagnosis Category	MSSA	MRSA	MSSA	MRSA	MSSA	MRSA	MSSA	MRSA
Uncomplicated RIE	1 /2 (50)	0/0 (0)	0/2 (0)	0/0 (0)	1 /2 (50)	0/0 (0)	0/2 (0)	0/0 (0)
Complicated RIE	1 /4 (25)	4/6 (66.7)	2/3 (66.7)	2/3 (66.7)	0/4 (0)	2/5 (40)	2/3 (66.7)	2/3 (66.7)
Left IE	1 /2 (50)	0/5 (0)	2/3 (66.7)	0/3 (0)	1 /2 (50)	0/5 (0)	2/3 (66.7)	0/3 (0)

The two tables above provide comparative success data stratified by baseline pathogen for the ITT and PP population. Due to small sample size and insufficient power, no meaningful statistical inferences can be made regarding the performance of the study drugs in the endocarditis experience.

FDA: Post-Hoc Analysis of Efficacy by Identifiable Focus

Table 43: Post-Hoc Analysis of Efficacy by Identifiable Focus (ITT)

Subgroup	IEAC Outcome at TOC	Daptomycin N=62	Comparator N=63
All-comers with identifiable focus, ITT	Success	31 (50)	33 (52.4)
	Failure	26	22
	Non-evaluable	5	8
Catheter-related	Success	13 (54.2)	13 (76.5)
	Failure	11	4
	Non-evaluable	0	0
Skin/skin structure	Success	10 (45.5)	16 (44.4)
	Failure	9	13
	Non-evaluable	3	7
Other	Success	8 (57.1)	3 (33)
	Failure	5	5
	Non-evaluable	1	1
Pneumonia	Success	0 (0)	1 (100)
	Failure	1	0
	Non-evaluable	0	0
Combined SSSI and Other	Success	0 (0)	0 (0)
	Failure	0	0
	Non-evaluable	1	0

Based on the FDA analysis of the all-comers population for potential portals of entry, a post-hoc efficacy analysis was conducted as summarized in the table above. The analysis is based on a total of 125 patients in the ITT population for which a potential portal of entry could be determined following review of the individual case report forms. The success rates at TOC, the primary efficacy endpoint, in the patients in the all-comers population who have an identifiable focus is comparable in the two treatment arms. In terms of the subgroups, the two treatment groups are comparable for patients with skin and skin structure infections. However, in patients with catheter-related infections, the comparator group had much better success rates compared to the daptomycin group. For the other subgroups, the analysis was extremely limited by the small sample size.

Table 44: FDA: Post-Hoc Efficacy analysis by Identifiable Focus (PP)

Subgroup	IEAC Outcome at TOC	Daptomycin	Comparator
		N=43	N=32
All-comers with identifiable focus, ITT	Success	26 (60.5)	22 (68.8)
	Failure	17	10
Catheter-related	Success	11 (61.1)	8 (88.9)
	Failure	7	1
Skin/skin structure	Success	9 (64.3)	12 (66.7)
	Failure	5	6
Other	Success	6 (60)	1 (25)
	Failure	4	3
Pneumonia	Success	0 (0)	1 (100)
	Failure	1	0

There were 75 subjects in the PP population for which an identifiable focus could be determined based on a review of individual case report forms. In alignment with the findings in the ITT population, the success rates in the PP population were comparable between the two treatment groups in the all-comers population. Among the subgroups, the efficacy rates were comparable in patients with skin and skin structure infections; however, among patients with catheter-related infections, the success rates among the comparator-treated group were much higher than in the daptomycin group. Due to small sample size and insufficient power, no statistically meaningful inferences about drug performance could be made.

Failure Analysis

Table 45: Compilation of IEAC Reasons for Failure: All-comers Population

IEAC Reasons for Failure	Daptomycin N = 58	Comparator N = 53	*Total* N= 111
Microbiologic Failure	28	23	51
Clinical Failure	21	14	35
PRSA	19	11	30
PENS	19	15	34
Death	13	13	26
Adverse Event	9	16	25
Missing Blood Culture	9	12	21
Other	4	3	7
Total	122	107	229

PRSA=persisting and relapsing *S. aureus* infections
PENS=potentially effective non-study antibiotics

The table above is a compilation of all of the reasons for failure as attributed by the IEAC for the 111 subjects in the all-comers with one or more positive blood cultures for *S. aureus* who were assessed as having failed their study drug treatment. There were 58 daptomycin failures and 53 comparator failures in the ITT population. Some patients had multiple reasons for failure; however, the IEAC did not have to designate a primary reason for failure among those subjects. In contrast, the Investigators were required to indicate the one principal cause for failure when completing the case report forms.

Microbiological and clinical failures were more frequently cited as the reasons for failure among the daptomycin-treated subjects. Persisting and relapsing staphylococcal bacteremias were observed more frequently among the daptomycin-treated subjects, whereas adverse events were more common among the comparator group. There were more missing blood cultures as a cause for failure in the comparator group, whereas potentially effective non-study antibiotics were a more frequent cause for failure in the daptomycin group.

Table 46: Compilation of IEAC Reasons for Failure: IE

IEAC Reasons for Failure	Daptomycin N = 15	Comparator N = 14	*Total* N=29
Microbiologic Failure	9	6	15
Clinical Failure	7	7	14
PRSA	7	5	12
PENS	3	5	8
Death	3	5	8
Adverse Event	3	4	7
Missing Blood Culture	2	1	3
Other	0	1	1
Total	34	34	68

Among subjects with infective endocarditis as identified by the IEAC, microbiological failures and persisting and relapsing bacteremias were more frequent causes for failure in the daptomycin group. In contrast, the use of PENS was a more common cause for failure in the comparator group. There were three deaths in the daptomycin group and five deaths in the comparator group to Day 42 post-EOT.

Table 47: FDA Persistent and Relapsing Bacteremias (including post-study relapses) and Persistent Infections

	Daptomycin N=120		Comparator N=115	
	MRSA	MSSA	MRSA	MSSA
Complicated RIE	-	1	2	1
Uncomplicated RIE	-	3	-	-
LIE	4	-	2	-
Subtotal: Endocarditis	8		5	
Complicated bacteremia	8	4	5	-
Uncomplicated Bacteremia	-	-	-	-
Subtotal: Bacteremias	*12*		*5*	
Persistent Infections (non-bacteremia)	-	1	-	1
Subtotal: Composite Bacteremia/IE/Persistent Infections	*12*	*9*	*9*	*2*
Overall Totals	21		11	

As a follow-up to the Sponsor's data on failures, the FDA review team conducted a separate analysis of failures due to PRSA in the All-comers population based on a review of the case report forms and patient profiles. A total of 21 subjects with PRSA were identified in the daptomycin arm, which includes two additional patients than the Sponsor's assessment, and 11 in the comparator arm.

The two additional subjects in the daptomycin included the following:
(1) A 27 year old Caucasian male with history of intravenous drug use who experienced a relapse at Day 85P. The subject had no TOC blood cultures and a blood culture at Day 65P was negative. Both of the Day 65P and 85P blood cultures are outside of the TOC analysis window. In addition, based on electrophoresis patterns, the baseline isolate and the Day 85P blood culture isolates were both of the same clone.
(2) A 54 year old Caucasian male who was deemed a clinical and micro failure by the Investigator after 6 days of persistent positive blood cultures. The IEAC did not identify this subject as having persistent positive blood cultures, but deemed him a micro failure with the comment that the patient had a right lower lobe pneumonia and should not have been enrolled in the first place.

There are several important trends that are evident in this data table:
(1) The total magnitude of PRSA infections in the daptomycin arm was about twice that of the comparator group.
(2) The frequency of PRSA infections by clinical subgroup revealed that among patients with endocarditis, there were more cases of PRSA in the daptomycin arm. Among patients with bacteremia, there were more cases of PRSA in the daptomycin group.
(3) When assessed in terms of oxacillin susceptibility, the frequency of PRSA in the daptomycin group was similar among subjects whose staphylococcal isolates were methicillin-susceptible and methicillin-resistant, whereas PRSA infections were predominantly confined to subjects with MRSA infections in the comparator group.

Table 48: FDA Table of Clinical Failures (non-microbiological failures)

	Daptomycin		Comparator	
	MRSA	MSSA	MRSA	MSSA
Complicated RIE	1	-	-	-
Uncomplicated RIE	-	-	-	-
LIE	-	-	1	1
Complicated bacteremia	1	3	-	2
Uncomplicated Bacteremia	1		-	-
Subtotals	*3*	*3*	*1*	*3*
Overall Total Clinical Failures (only)	*6*		*4*	

Based on FDA review of the case report forms, there were a total of six clinical failures in the daptomycin group and four in the comparator group.

Table 49: FDA Composite Persisting and Relapsing Bacteremias, PS Relapses, Persistent Infections, and Clinical Failures

	Daptomycin		Comparator	
	MRSA	MSSA	MRSA	MSSA
Complicated RIE	1	1	2	1
Uncomplicated RIE	0	3	0	0
LIE	4	0	3	1
Complicated bacteremia	9	7	5	2
Uncomplicated Bacteremia	1	0	0	0
Persistent Infections (non-bacteremia)	0	1	0	1
Subtotals	*15*	*12*	*10*	*5*
Overall Total Composite	*27*		*15*	

The total of clinical failures, persisting and relapsing bacteremias, and persisting infections in the daptomycin group was approximately 1.8-fold higher than in the comparator group. In terms of oxacillin susceptibility, there were comparable numbers of subjects with clinical and microbiolgical failures due to MRSA and MSSA infections among the daptomycin patients, whereas there were twice as many clinical and microbiological failures among comparator-treated patients with infections due to MRSA compared to MSSA.

Reduced Susceptibility to Daptomycin and Vancomycin

Table 50: IEAC Outcome at TOC for Subjects whose *S. aureus* blood culture isolates exhibited Increasing MICs from baseline during or immediately following study drug treatment

		n	IEAC Outcome at TOC	
			Success	Failure
Comparator N=96	Vancomycin MIC=2	3	2	1
	Daptomycin MIC ≥2	0	0	0
	Increased MICs to both drugs	1	1	0
	Total Subjects	4	3	1
Daptomycin N=113	Vancomycin MIC=2	3	1	2
	Daptomycin MIC ≥2	4	0	4
	Increased MICs to both drugs	2	0	2
	Total Subjects	9	1	8

Another issue of concern to the FDA review team involved subjects whose S. aureus isolates exhibited increasing MICs (from baseline) during the course of study drug therapy. The table above summarizes the patients in each treatment group with blood culture isolates that exhibited increasing MICs (based on central laboratory results) during therapy along with the IEAC outcome at TOC, the primary efficacy endpoint.

Of note are the following observations:

(1) Among 96 comparator-treated subjects for whom full MIC data was available, a total of 4 subjects had Staphylococcal isolates that exhibited increasing MICs to vancomycin or daptomycin: 3 subjects had a highest vancomycin MIC of 2 ug/ml and one subject had increasing MICs to both drugs. Of the 4 patients, there were 3 successes and 1 failure at TOC.

(2) Among 113 daptomycin-treated subjects for whom full MIC data was available, a total of 9 subjects had Staphylococcal isolates that exhibited increasing MICs to vancomycin or daptomycin: 3 exhibited increasing MICs to vancomycin only, 4 had isolates with increasing MICs only to daptomycin, and 2 subjects had isolates with increasing MICs to both drugs. Of the 9 patients, there was only 1 success and 8 failures at TOC (including all subjects whose isolates exhibited increasing MICs to daptomycin while receiving daaptomycin therapy).

Thus, among all subjects for which full MIC data was available and whose S. aureus blood culture isolates exhibited increasing MICs to vancomycin and daptomycin during study drug treatment, treatment failures at the primary efficacy endpoint of TOC were predominantly limited to patients treated with daptomycin (especially subjects who

developed increasing MICs to daptomycin during daptomycin therapy).

Table 51: PRSA and Deaths among Subjects whose *S. aureus* blood culture isolates exhibited Increasing MICs from baseline during or immediately following study drug treatment

		n	PRSA	Death
Comparator N=96	Vancomycin MIC=2	3	0	0
	Daptomycin MIC ≥2	0	0	0
	Increased MICs to both drugs	1	0	0
	Total Subjects	4	0	0
Daptomycin N=113	Vancomycin MIC=2	3	0	1
	Daptomycin MIC ≥2	4	4	1
	Increased MICs to both drugs	2	2	1
	Total Subjects	9	6	3

This table summarizes the number of deaths in relation to the covariates of increasing MICs during study drug treatment, PRSA, and treatment group. It is noteworthy that only among daptomycin-treated subjects whose staphylococcal blood culture isolates exhibit increasing MICs to daptomycin, vancomycin, or both drugs that we observe PRSA infections and deaths. Of the 6 daptomycin-treated subjects whose blood culture isolates exhibited increasing MICs to daptomycin or both drugs, all of them developed PRSA and 2 died.

In contrast, none of the comparator-treated subjects whose blood culture isolated exhibited increasing MICs to daptomycin, vancomycin, or both drugs developed PRSA and there were no deaths among those patients.

Table 52: Summary table of all subjects whose baseline S. aureus blood culture isolates exhibited reduced susceptibility to study drug during or immediately following treatment

		Case ID #	IEAC Final Diagnosis	IEAC Success*	IEAC Failure*	PRSA	Death
Comparator	Vancomycin MIC=2	(b) (6)	Complicated Bacteremia	X			
			Complicated Bacteremia	X			
			Uncomplicated Bacteremia		X		
	Increased MICs to both drugs		Complicated RIE	X			
Daptomycin	Vancomycin MIC=2		Complicated Bacteremia	X			
			Complicated Bacteremia		X		X
			Complicated Bacteremia		X		
	Daptomycin MIC ≥2		Complicated Bacteremia		X	X	
			Complicated Bacteremia		X	X	
			Left IE		X	X	X
			Complicated Bacteremia		X	X	
	Increased MICs to both drugs		Complicated RIE		X	X	
			Left IE		X	X	X

*at TOC; IE = infective endocarditis; RIE = right-sided infective endocarditis;
Case (b) (6) had highest Daptomycin MIC = 4 ug/ml

Table 53: Summary of Subjects whose baseline S. aureus blood culture isolates exhibited increasing MICs to Daptomycin of ≥2 µg/ml

Case ID #	Study Group	Baseline Pathogen	IEAC Final Diagnosis	IEAC Outcome at TOC	Study Day Daptomycin MIC ≥ 2
(b) (6)	Comparator	MRSA	Complicated RIE	Success	Day 11
(b) (6) - §	Daptomycin	MRSA	Complicated bacteremia	Failure	Day 09P
- §	Daptomycin	MSSA	Complicated RIE	Failure	Day 18
- §	Daptomycin	MRSA	Complicated bacteremia	Failure	Day 20P
- *§	Daptomycin	MRSA	Left IE	Failure	Day 4
- *§	Daptomycin	MRSA	Left IE	Failure	Day 7
(b) (6)	Daptomycin	MSSA	Complicated bacteremia	Success	Day 13
(b) (6) §	Daptomycin	MRSA	Complicated bacteremia	Failure	Day 7

*Patient death; §Subject with persistent or relapsing bacteremia

Of note among subjects whose baseline staphylococcal isolates developed rising MICs to ≥2 µg/ml, there was wide variability in relation to duration of study drug, ranging from as few as 4 days following study drug initiation to as long as 20 days following end of treatment.

Additional Analyses

Time to Clearance Analysis

Table 54: Clearance from Days 01 to TOC (ITT)

	Daptomycin	Comparator
All-comers	56/120 (46.6)	46/115 (40)
SIRS (all-comers)	42/89 (47.2)	38/87 (43.7)
No SIRS (all-comers)	14/31 (45.2)	8/28 (28.6)
Endocarditis	12/28 (42.9)	7/25 (28)
Complicated RIE (all-comers)	7/13 (53.8)	1/12 (8.3)
Uncomplicated RIE (all-comers)	2/6 (33.3)	3 /4 (75)
Left IE	3/9 (33.3)	3/9 (33.3)
Bacteremias	44/92 (47.8)	39/90 (43.3)
Complicated bacteremia (all-comers)	13/60 (21.7)	16/61 (26.2)
Uncomplicated bacteremia (all-comers)	31/32 (96.9)	23/29 (79.3)

In terms of clearance of bloodstream infection between the two treatment groups, there were comparable percentages of subjects in the overall all-comers population and in all-comers with SIRS who had negative blood cultures within the Day 01 to TOC time frame in both groups. In terms of the final diagnosis subgroups, there were more subjects in the daptomycin group with endocarditis who had clearance of their blood cultures within that timeframe compared to the comparator group. In addition, more daptomycin treated subjects without SIRS had clearance of their blood cultures within the Day 01 to TOC timeframe.

Table 55: Clearance from Days 01 to TOC by Baseline Pathogen (ITT)

	Daptomycin		Comparator	
	MRSA	MSSA	MRSA	MSSA
All-comers	22/45 (48.9)	34/74 (45.9)	17/44 (38.6)	29/70 (41.4)
SIRS	19/35 (54.3)	23/54 (42.6)	13/33 (39.3)	25/54 (46.3)
No SIRS	3/10 (30)	11/20 (55)	4/11 (36.3)	4/16 (25)
Endocarditis	6/13 (46.1)	6/15 (40)	3/11 (27.3)	4/14 (27.9)
Complicated RIE	6/8 (75)	1/5 (20)	1/7 (14.3)	0/5 (0)
Uncomplicated RIE	0 (0)	2/6 (33.3)	0 (0)	3/ 4 (75)
Left IE	0/5 (0)	3 /4 (75)	2/4 (50)	1/5 (20)
Bacteremia	16/32 (50)	9/44 (20.5)	14/33 (42.2)	25/56 (44.6)
Complicated bacteremia	6/22 (27.2)	7/38 (18.4)	6/22 (27.2)	10/39 (25.6)
Uncomplicated bacteremia	10/10 (100)	2/6 (33.3)	8/11 (72.7)	15/17 (88.2)

In terms of clearance of bloodstream infection between the two treatment groups by baseline pathogen, there was a higher percentages of subjects in the daptomycin-treated overall all-comers population with MRSA infections and in all-comers with SIRS with MRSA infections who had negative blood cultures within the Day 01 to TOC time frame.

In terms of the final diagnosis subgroups, there were more subjects in the daptomycin group with endocarditis due to MRSA and MSSA who had clearance of their blood cultures within that timeframe compared to the comparator group. In addition, more daptomycin treated subjects with MRSA bacteremia had clearance of their blood cultures within the Day 01 to TOC timeframe compared to comparator, whereas more comparator-treated subjects with MSSA bacteremia had negative blood cultures compared to the daptomycin-treated subjects.

Time to Defervescence Analysis

Table 56: Median Days to Defervescence (ITT)

	Daptomycin	Comparator
SIRS (all-comers)	3.0	3.0
No SIRS (all-comers)	2.0	2.5
Complicated RIE	2.0	4.0
Uncomplicated RIE	2.0	3.0
LIE	3.5	3.0
Complicated bacteremia	3.0	3.0
Uncomplicated bacteremia	2.0	2.0

In terms of time to defervescence, the median number of days is comparable between the two treatment groups when assessed by presence or absence of SIRS and when assessed by IEAC final diagnosis subgroups.

Table 57: Median Days to Defervescence by Baseline Pathogen (ITT)

	Daptomycin		Comparator	
	MRSA	MSSA	MRSA	MSSA
All-comers	3.0	2.0	2.5	3.0
SIRS (all-comers)	2.5	4.0	2.5	3.0
No SIRS (all-comers)	3.0	2.0	2.5	2.0
Complicated RIE	2.0	2.5	5.0	3.5
Uncomplicated RIE	-	2.0	-	3.0
LIE	7.0	3.0	3.0	3.0
Complicated bacteremia	3.0	2.0	2.0	3.0
Uncomplicated bacteremia	2.0	2.0	3.0	3.0

In terms of time to defervescence, the median number of days is comparable between the two treatment groups when assessed by presence or absence of SIRS and oxacillin susceptibility. When assessed by IEAC final diagnosis subgroups and stratified by oxacillin susceptibility, the median number of days to defervescence is higher in the comparator arm for subjects with complicated RIE and MRSA infections. However, the median number of days to defervescence is higher in the daptomycin arm for subjects with left IE and MRSA infections.

Duration of Study Medication:

Table 58: Comparison of median duration of study drug administration based on IEAC and Investigator Diagnoses

IEAC Final Diagnosis Subgroup	Median duration (days) based on IEAC assessment		Median duration (days) based on Investigator assessment	
	Comparator	Daptomycin	Comparator	Daptomycin
Complicated RIE	30	26	32	28
Uncomplicated RIE	15	14	18	14
Left IE	20	12	16.5	8
Complicated Bacteremia	15	14	24	14
Uncomplicated Bacteremia	14	14	14	14

The table above provides a summary of the median duration of study drug administration in each of the IEAC final diagnosis subgroups. Of note, Investigators treated subjects with complicated bacteremia and left IE in the comparator arm for longer median periods of time than those in the daptomycin arm. In addition, although there is a 28-42 day protocol-specified minimum treatment duration for subjects with complicated bacteremia, such patients received a median of only 14 days in most instances. Interpretation of outcome data becomes confusing in that setting as the definition of the IEAC outcome at TOC (primary efficacy endpoint) includes a provision regarding patients having received at least the minimum amount of study medication as defined in the Minimum Study Treatment Regimen and Duration guidelines. The study was not designed to determine if 14 days of treatment is comparable to 28-42 days of treatment for subjects with complicated bacteremias.

Table 59: Analysis of Median Duration of Study Medication (ITT)

IEAC Final Diagnosis Subgroup	Daptomycin			Comparator		
	Overall Median Duration (days)	IEAC Successes at TOC (days)	IEAC Failures at TOC (days)	Overall Median Duration (days)	IEAC Successes at TOC (days)	IEAC Failures at TOC (days)
Complicated RIE	26	28	17.5	30	30	24.5
Uncomplicated RIE	14	14	11.5	15	15	13.5
Left IE	12	42*	12	20	27**	16.5
Complicated Bacteremia	14	14	14	15	26	14
Uncomplicated Bacteremia	14	14	13	14	14	16.5

*n = 1; **n = 2

Based on an analysis of the median duration of study medication among patients assessed as successes and failures by the IEAC at TOC, it appears possible that the open-label nature of the study may have influenced the duration of study medication employed by the investigators. Overall, patients who ultimately failed treatment with the comparator

drug regimen received longer courses of treatment than the failures in the daptomycin group. Among patients with complicated RIE, subjects who ultimately failed treatment with the comparator received approximately 7 more days of study drug compared to daptomycin failures. Among patients who failed study therapy for uncomplicated RIE, Left IE, and uncomplicated bacteremia, comparator-treated patients received study medication for a longer duration (2 days, 4.5 days, and 3.5 days, respectively) compared to failures in the daptomycin group. In addition, among patients who were assessed as successes by the IEAC at TOC, comparator-treated patients with complicated bacteremia received approximately 12 more days of study medication than successes in the daptomycin group.

Mortality Data Analysis

Table 60: All-cause mortality data

	Daptomycin	Comparator
	N=120	N=116
Deaths up to day 42P	15 (12.5)	13 (11.2)
Bacteremia	12 (10)	8 (6.9)
Endocarditis	3 (2.5)	5 (4.3)
All deaths (to end of study)	18 (15)	19 (16.4)
Bacteremia	15 (12.5)	11 (9.5)
Endocarditis	3 (2.5)	8 (6.9)

This table depicts the all-cause mortality data for the All-comers population stratified by the timepoints of deaths to Day 42P and all deaths to end of study and stratified by the clinical subgroups.

Of note:

(1) The overall percentages of deaths at both timepoints are similar.
(2) Focusing on the clinical subgroups, there were more deaths in the daptomycin group at both timepoints in subjects with bacteremia, whereas there were more deaths in the comparator group at both timepoints in subjects with endocarditis.

Table 61: Case-Fatality Rates for Subjects with PRSA Infections

	Daptomycin N=19	Comparator N=11
Deaths to Day 42P	7/19 (36.8)	3/11 (27.3)
All deaths to end of study	8/19 (42.1)	7/11 (63.4)

*case-fatality rate = # deaths associated with PRSA/total # of subjects with PRSA

The case-fatality rates for subjects with PRSA infections for the two treatment groups are summarized in the table above. By Day 42P, there is a higher case-fatality rate among daptomycin-treated subjects, whereas there is a higher case-fatality rate for the comparator group at the end of the study. PRSA infections are more frequent in the daptomycin group, but the case-fatality rate is higher in the comparator group at the end of the study. This finding suggests that although the comparator group has fewer cases of PRSA, those who develop PRSA infections have more severe disease compared to their counterparts in the daptomycin group.

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Table 62: Details of Subjects with PRSA who Died up to Day 42P

Study Drug	Case ID	Final Diagnosis	Duration (Days)	Adverse Events and other noteworthy findings
Comparator (n = 3)	(b) (6)	Complicated RIE	3	Sepsis, Renal Failure
		Complicated bacteremia	3	Sepsis, Renal Failure
		Left IE	7	Cerebral embolus Septic shock
Daptomycin (n = 7)		Complicated bacteremia §	13	Vertebral osteomyelitis Psoas abscess MRSA Pneumonia (autopsy)
		Left IE† §	7	Worsening DIC, CHF
		Left IE†	8	Right CVA Multi-organ Failure
		Complicated bacteremia	3	Septic shock, Heart failure
		Complicated bacteremia	9	Mycotic aneurysm thoracic aorta
		Complicated bacteremia	3	Sepsis, Multi-organ Failure
		Complicated bacteremia	4	Persistent bacteremia Worsening sepsis

*All deaths involve MRSA baseline pathogen; †daptomycin MIC≥ 2; §vancomycin MIC=2

The table above lists the 10 subjects who developed PRSA infections and died by Day 42 P in both treatment groups. Half of the deaths occurred by Day 4 of study drug administration and were in the setting of sepsis or septic shock. All of the deaths involved subjects with either complicated bacteremia or IE and were due to MRSA infections. Three subjects in the daptomycin group and none in the comparator group who died up to Day 42P had baseline *S. aureus* blood isolates that exhibited increasing MICs to daptomycin and/or vancomycin during daptomycin therapy.

Table 63: Details of Subjects with PRSA who Died up to the end of study

Study Drug	Case ID	Final Diagnosis	Duration Study Med	Adverse Events and other noteworthy findings
Comparator (n = 4)	(b) (6) †	Complicated bacteremia	13	End stage cutaneous T cell lymphoma
	†	Complicated RIE	7	Congestive heart failure, chest pain, cardiac arrest
	*	Uncomplicated bacteremia	16	Progression of prostate cancer, pathologic femur fracture
	†	Left IE	27	Left subdural hematoma, intramural heart abscess
Daptomycin (n = 1)	*	Complicated bacteremia	5	Thrombopenia with coagulopathy, CLL

*baseline pathogen = MSSA; †baseline pathogen = MRSA

The table above lists the 5 subjects who developed PRSA infections and died to the end of the study in both treatment groups. Many of the deaths were related to underlying diseases rather than due to septic complications. Three subjects had MRSA infections and two had MSSA infections. No subjects had baseline *S. aureus* blood isolates that exhibited increasing MICs to daptomycin and/or vancomycin during daptomycin therapy.

Table 64: Proportionate Mortality associated with PRSA

	Daptomycin	Comparator
Deaths to Day 42P	7/15 (46.7)	3/13 (23)
All deaths to end of study	8/18 (44.4)	7/19 (36.8)

*Proportionate mortality = $\frac{\text{\# deaths associated with PRSA in time period}}{\text{total \# all-cause deaths in same time period}}$

As depicted in the table above, the proportionate mortality rate associated with PRSA was higher in the daptomycin group at Day 42P and at end of study. The proportionate mortality rate associated with PRSA in the comparator arm increased from Day 42P to end of therapy, but did not reach the same magnitude as observed in the daptomycin arm.

Table 65: Crude Mortality Rates

		Daptomycin	Comparator	Relative Risk of Death
Deaths to Day 42 P	All-cause MR	12.5%	11.2%	
	Proportionate MR associated with PRSA	46.7%	23%	
	MR associated with PRSA	5.84%	2.58%	2.26 95% CI (0.60, 8.51)
All deaths to end of study	All-cause MR	15.0%	16.4%	
	Proportionate MR associated with PRSA	44.4%	36.8%	
	MR associated with PRSA	6.66%	6.02%	1.10 95% CI (0.41, 2.95)

*Mortality Rate from PRSA = (all-cause mortality rate) X (proportionate mortality rate);
MR = mortality rate

The FDA review team conducted several exploratory analyses of mortality data to determine the risk for death among persons who failed study drug treatment due to PRSA. The table on this slide depicts the crude mortality rates for both treatment groups based on the all-cause mortality rates among the All-comers population and the proportionate mortality rates associated with PRSA in the two treatment groups.

Although the proportionate mortality rate associated with PRSA was higher in the daptomycin group, the risk of death at the end of study in terms of the mortality rate associated with PRSA in the entire population was similar to that of the comparator group. The relative risk of death was 1.10. A follow-up assessment using age-adjusted mortality rates revealed similar risks of death associated with PRSA in both groups.

More worrisome, however, is the higher risk of death in terms of the mortality rate associated with PRSA in the daptomycin group up to Day 42P. The relative risk of death for the daptomycin-treated patients with PRSA is over 2-fold greater than the risk of death for comparator-treated subjects. Unfortunately, there is insufficient information in terms of characterizing the underlying heterogeneity of the study population, lack of death certificate data to explain mortality rates, and identification of other potential confounders to explain the mortality rates.

Table 66: Summary of Study Subjects' Deaths (up to Day 42) in All-comers Population

	Daptomycin	Comparator
Total Deaths per subgroup	15 (100)	13 (100)
Complicated RIE	0	1 (8)
Uncomplicated RIE	0	0
Left IE	3 (20)	4 (30)
Complicated Bacteremia	7 (47)	8 (62)
Uncomplicated Bacteremia	5 (33)	0
Other Characteristics		
PRSA	7 (47)	3 (25)
MRSA	11 (73)	4 (33)
MSSA	4 (27)	8 (67)

As depicted in the table of study subject deaths up to Day 42P above, there were two more deaths among patients with IE in the comparator group. However, more striking, there were five deaths in the daptomycin group among subjects with uncomplicated bacteremia compared to none in the comparator group. The five deaths in subjects with uncomplicated bacteremia, included three subjects with cardiac-related problems, one subject with a candidemia, and one subject with a gangrenous dysvascular left lower extremity who refused amputation and subsequently died.

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6.1.5 Clinical Microbiology

Please refer to the report of Dr. Peter Coderre for full details on the Microbiology issues.

6.1.6 Efficacy Conclusions

Study DAP-IE-01-02 represented the first attempt by a Sponsor to conduct a sizable, randomized, controlled, pivotal clinical study to demonstrate the efficacy of an antibiotic in subjects with *S. aureus* bacteremia and infective endocarditis to support of an NDA supplement for the *S. aureus* bacteremia and endocarditis indications. However, various issues in relation to study design and conduct limited the ability to generalize the results from the all-comers population to each of the IEAC final diagnosis subgroups. The relevance of the findings in the all-comers target population to the reference population of all subjects with *S. aureus* bacteremia and various complications (including infective endocarditis) is limited. Based on the FDA assessment of the results of study DAP-IE-01-02, daptomycin was non-inferior to standard of care (SSP or vancomycin) in the treatment of *S. aureus* bacteremia due to methicillin-susceptible and methicillin-resistant strains in adults. However, the data was insufficient to demonstrate the efficacy of daptomycin in the treatment of *S. aureus* infective endocarditis.

The principal factors that limited assessment of the efficacy (treatment effect) of daptomycin as studied in DAP-IE-01-02 were the following: (1) As an open-label trial, the study was subject to bias in terms of patient selection, attribution of adverse events (such as renal insufficiency and CPK elevations) to study drug, and duration of study medication prior to premature discontinuation due to clinical or microbiological failure from the Investigators' perspectives. (2) The study lacked appropriate size and power to make statistically meaningful inferences about the performance of study drug in each of the IEAC final diagnosis subgroups. There was inconsistency of study drug efficacy across the IEAC final diagnosis subgroups. As a consequence, there is statistical uncertainty of the results, particularly with respect to the efficacy of daptomycin in the smallest final diagnosis subgroup involving patients with infective endocarditis. (3) The study population was not fully characterized in terms of prognostic factors that could affect outcome at the primary and secondary endpoints in the all-comers population and in the IEAC final diagnosis subgroups, including portal(s) of entry, presence of eradicable foci of infection, presence of metastatic foci, and community or nosocomial acquisition. In the absence of that information, it is not possible to determine to what extent the study population is representative of all patients with *S. aureus* bacteremia and endocarditis, which limits generalizability of the results. (4) There were multiple study design and conduct issues that tended to reduce observable differences between the two treatment groups, thereby sustaining the conclusion of non-inferiority. (5) Post-randomization data (central echocardiography) was used by the IEAC in assessing outcome at the primary efficacy endpoint and in classifying subjects into final diagnosis subgroups.

In addition to the statistical and study design issues described above, there were observed differences between the treatment groups that were clinically meaningful in terms of the mortality associated with microbiological failures due to persisting and relapsing *S. aureus* (PRSA) infections. In subjects whose baseline *S. aureus* blood culture isolates developed reduced susceptibility to daptomycin during or immediately following the completion of daptomycin treatment, there was a significant association with clinical failures, PRSA infections, and deaths (in a few cases), which gave rise to significant safety concerns. A similar pattern was not observed among comparator treated subjects who developed increasing MICs from baseline to vancomycin during or immediately following vancomycin therapy.

7. INTEGRATED REVIEW OF SAFETY

Please refer to the report of Dr. Charles Cooper for full details and discussion of the integrated safety review for this submission.

7.1 Methods and Findings

7.1.1 Deaths

7.1.2 Other Serious Adverse Events

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

7.1.3.2 Adverse events associated with dropouts

7.1.3.3 Other significant adverse events

7.1.4 Other Search Strategies

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

7.1.5.3 Incidence of common adverse events

7.1.5.4 Common adverse event tables

7.1.5.5 Identifying common and drug-related adverse events

7.1.5.6 Additional analyses and explorations

7.1.6 Less Common Adverse Events

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

7.1.7.4 Additional analyses and explorations

7.1.7.5 Special assessments

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

7.1.8.4 Additional analyses and explorations

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

7.1.9.4 Additional analyses and explorations

7.1.10 Immunogenicity

7.1.11 Human Carcinogenicity

7.1.12 Special Safety Studies

7.1.13 Withdrawal Phenomena and/or Abuse Potential

7.1.14 Human Reproduction and Pregnancy Data

7.1.15 Assessment of Effect on Growth

7.1.16 Overdose Experience

7.1.17 Postmarketing Experience

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

7.2.1.2 Demographics

7.2.1.3 Extent of exposure (dose/duration)

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

7.2.2.2 Postmarketing experience

7.2.2.3 Literature

7.2.3 Adequacy of Overall Clinical Experience

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

7.2.5 Adequacy of Routine Clinical Testing

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

7.2.8 Assessment of Quality and Completeness of Data

7.2.9 Additional Submissions, Including Safety Update

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

7.4.1.2 Combining data

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

7.4.2.2 Explorations for time dependency for adverse findings

7.4.2.3 Explorations for drug-demographic interactions

7.4.2.4 Explorations for drug-disease interactions

7.4.2.5 Explorations for drug-drug interactions

7.4.3 Causality Determination

8. ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dosage of daptomycin investigated in pivotal study DAP-IE-01-02 was 6 mg/kg q24h, which is a higher dosage compared to the current package labeling of 4 mg/kg q24h for the indication of complicated skin and skin structure infections.

8.2 Drug-Drug Interactions

Please refer to the integrated safety review by Dr. Charles Cooper.

8.3 Special Populations

A dramatic decline in the efficacy of daptomycin was observed in the all-comers population and in subjects with IE who were older than age 65 and who had mild to moderate renal insufficiency. The trends were in sharp contrast to the efficacy rates of the comparator in the all-comers population and in subjects with IE who were elderly and who had corresponding degrees of renal insufficiency. The reasons for the disparate efficacy trends are uncertain due to insufficient data in terms of characterizing the underlying heterogeneity of the study population, lack of death certificate data to explain mortality rates, and identification of other potential confounders.

8.4 Pediatrics

The efficacy of daptomcyin in pediatric patients with *S.aureus* bacteremia and endocarditis was not assessed in the pivotal study.

8.5 Advisory Committee Meeting

A meeting of the Anti-Infective Drug Advisory Committee to discuss this application was conducted on March 6, 2006. The Committee voted 9 to 0 that the pivotal study provided substantial evidence of safety and efficacy of daptomycin in the treatment of *S. aureus* bacteremia. The Committee voted 5 to 4 that the pivotal study provided substantial evidence of safety and efficacy of daptomycin in the treatment of *S. aureus* endocarditis. Please refer to the complete transcripts of the Advisory Committee Meeting for full details.

8.6 Literature Review

A review of selected articles from the published English-language medical literature was conducted. In addition, the code of federal regulations and pertinent FDA/Center for Drug Evaluation and Research guidances for industry were consulted.

8.7 Postmarketing Risk Management Plan

A prospective registry should be established for patients who are treated with daptomycin for the indications cited above who experience persistent or relapsing bacteremias and have *S. aureus* blood isolates that exhibit rising MICs to daptomycin during or immediately following the course of daptomycin therapy. In addition, post-marketing reports should be scrutinized for off-label use of the drug for suspected or proven infective endocarditis, with particular attention to cases in which the *S. aureus* isolate exhibited increasing MICs during or immediately following therapy compared to baseline

and for cases in which doses higher than the labeled 6 mg/kg q24h dosage for this indication were used by the prescriber.

8.8 Other Relevant Materials

There were no additional materials referenced for the review.

9. OVERALL ASSESSMENT

9.1 Conclusions

Based on the FDA assessment of the results of study DAP-IE-01-02, daptomycin was non-inferior to standard of care (SSP or vancomycin) in the treatment of *S. aureus* bacteremia in adults due to methicillin-susceptible and methicillin-resistant strains. However, the data was insufficient to demonstrate the efficacy of daptomycin in the treatment of *S. aureus* infective endocarditis. The efficacy of daptomycin in patients with osteomyelitis, prosthetic valve endocarditis, meningitis, and deep organ infections due to *S. aureus* was not assessed. The study involved a pathogen-driven, all-comers target population having at least one positive blood culture for *S. aureus* irrespective of the underlying clinical setting, but the relevance of the findings in the all-comers target population to the reference population of all subjects with *S. aureus* bacteremia and infective endocarditis was limited. As a consequence of limitations related to study design, conduct, and generalizability, and the lack of substantial evidence for efficacy in IE, labeling of the drug with the indication restricted to *S. aureus* bacteremia without concomitant infective endocarditis is warranted.

Multiple factors in the design and conduct of DAP-IE-01-02 limited assessment of the efficacy (treatment effect) of daptomycin in subjects with *S. aureus* bacteremia and diminished the ability to generalize the results from the all-comers population to the IEAC final diagnosis subgroups and infective endocarditis experience. The principal limiting factors were the following:

(1) As DAP-IE-01-02 was an open-label study, there was the potential for bias in terms of patient selection, attribution of adverse events (such as renal insufficiency and CPK elevations) to study drug, and duration of study medication prior for treatment or with respect to premature discontinuation due to clinical or microbiological failure from the Investigators' perspectives. The study lacked a double-blind design to minimize bias and sufficient assay sensitivity, which are characteristics of well-controlled, randomized clinical trials (5,6). The ability of the study to distinguish between active and inactive treatments in subjects with left IE was compromised due to the very low efficacy rate in the comparator group. In the absence of a placebo control group, we cannot be assured that the efficacy rate of 22% in the comparator group for subjects with left IE provided a valid comparison for the 11% efficacy rate among daptomycin-treated subjects.

Similarly, the ability of the study to distinguish between active and inactive treatments in subjects with right IE was compromised due to the low efficacy rate of the comparator (43.8%) compared to the published cure rates of 90-100% in right IE as cited by Petti and Fowler (7). In the absence of a placebo control group, we cannot be assured that the efficacy rate of 43.8% in the comparator group for subjects with right IE provided a valid comparison for the 42% efficacy rate among daptomycin-treated subjects.

(2) The study was powered in relation to the all-comers population and not in relation to the infective endocarditis experience. Thus, the study lacked appropriate size and power to make statistically meaningful inferences about the performance of the study drugs in each of the infective endocarditis subgroups (complicated and uncomplicated right IE and left IE). In addition, there was inconsistency of study drug efficacy across the infective endocarditis subgroups, as the comparator had better efficacy among subjects with complicated right IE, whereas daptomycin had better efficacy among subjects with uncomplicated right IE. In both of those subgroups, the number of subjects was small and there were six or fewer successes. The lack of consistency for daptomycin across all of the endocarditis strata is problematic in terms of drawing conclusions about the drug's efficacy from a single study of given use (8). A similar pattern of inconsistency was observed in the performance of daptomycin in the efficacy analysis of patients with SIRS. Although the efficacy rates of the two treatment groups were comparable in the all-comers population with SIRS, daptomycin had slightly better performance in subjects with uncomplicated right IE with SIRS but much worse performance than comparator in subjects with complicated right IE with SIRS. The small size and insufficient power did not enable statistically meaningful conclusions to be made. As a consequence, there was statistical uncertainty of the results, particularly with respect to the efficacy of daptomycin in the subgroups of patients with infective endocarditis.

(3) The study population was not fully characterized in terms of prognostic factors that could affect outcome assessments at the primary (TOC) and secondary (EOT) endpoints in the all-comers population and in the IEAC final diagnosis subgroups. The generalizability of the study results was limited, as the all-comers study population was not characterized in terms of portal(s) of entry, presence of eradicable foci of infection, presence of metastatic foci, and community or nosocomial acquisition. The portals of entry that precede the onset of *S. aureus* bacteremia reflect upon different disease entities that have varying pathophysiologies (such as cellulitis compared to pneumonia) and different inherent prognoses. *S. aureus* bacteremia ssociated with eradicable foci have a better outcome and less mortality compared to non-eradicable foci (9, 10). This finding is most relevant to catheter-related *S. aureus* bacteremias, which have lower complication rates and better outcomes following catheter removal (11). As surgical procedures are employed frequently to drain foci of infection, the impact of surgical interventions as confounders of the assessment of drug efficacy in this study is unknown. Community-acquired *S. aureus* bacteremia has a higher risk of non-eradicable foci, as the portal of entry is usually not related to a removable device (such as an intravenous catheter) and the duration of the bacteremia is frequently unknown (12). Metastatic foci are more common complications of *S. aureus* bacteremia than IE with a prevalence of 23% in the study of Libman and Arbeit (13). However, there was no systematic requirement for all

subjects in study DAP-IE-01-02 to undergo diagnostic imaging to assess for the presence of metastatic foci of infection. Thus, the extent of metastatic complications was unknown in the majority of the study population, and the overall magnitude of metastatic foci among the study participants was underestimated by relying on Investigator discretion alone to conduct diagnostic evaluations on an individual basis. Thus, in the absence of information about the presence or absence of the prognostic factors above, it is not possible to determine to what extent the study population is representative of all patients with *S. aureus* bacteremia and endocarditis.

(4) There were multiple study design and conduct issues that tended to reduce observable differences between the two treatment groups, thereby sustaining the conclusion of non-inferiority. They include the following: (a) The shifting of patients with uncomplicated bacteremia as identified and treated by the Investigators into the complicated bacteremia subgroup by the IEAC enabled data from subjects with less severe infections and better inherent prognoses to be used to buttress the efficacy rates of study drug among patients with more severe and complicated bacteremias. This reclassification of study subjects was based on application of protocol-specified definitions involving positive blood cultures on two or more calendar days that were not generally accepted in medical practice, and which tended to make the efficacy rates appear more uniform. (b) The use of PENS antibiotics was problematic in the study. There were no protocol-specified definitions or parameters to assess the use and impact of non-study antibiotics on therapeutic outcome with study drug. In addition, the IEAC did not have a pre-specified algorithm to assess PENS use; many of their assessments were made on a case-by-case basis involving subjective perspectives of the IEAC members. (c) The procedure used by the IEAC to make outcome assessments was not uniformly consistent with the protocol-specified criteria for success and failure, which required the study subjects to have received at least the minimum amount of study medication and not to have missing blood cultures at the EOT and TOC endpoints. The crucial role of the IEAC in reviewing endpoint data to determine whether it meets protocol-specified criteria has been described previously (14). The IEAC did not use the protocol-specified minimum treatment regimen guidelines to assess duration of study medication, as many subjects with complicated bacteremias who were assessed as successes did not have a 28-42 day treatment course as specified in the protocol guidelines. The IEAC did not consider all persons with missing blood cultures to be failures as specified in the protocol; instead, the IEAC used their clinical perspective to assess the cases individually and impute missing microbiological data for subjects who appeared clinically well without intercurrent use of PENS. In some of those instances, the IEAC overrode the Investigators assessment of failure at TOC due to an adverse event and imputed success, because the subjects were followed sufficiently post-EOT that their TOC blood culture was negative and there was no exposure to PENS antibiotics. (d) Permitting reassignment of subjects who would have been excluded from the PP population if they violated inclusion/exclusion criteria to be included in the PP population if it was felt that the violation(s) did not have had an impact on the assessment of efficacy could make it easier to show non-inferiority of the treatment groups and mask any true treatment efficacy differences. All of the above deviations from protocol tended to make the efficacy of the study drugs appear similar.

(5) Post-randomization data (central echocardiography) was used by the IEAC in assessing outcome at the primary efficacy endpoint and in classifying subjects into final diagnosis subgroups. The results of central echocardiography were not provided to the Investigators managing the subjects' care prospectively, yet may have had an impact on the subjects' clinical course and ultimate outcome.

In addition to the factors described above that limited efficacy assessment, the following observed differences between the two treatment groups were clinically meaningful: (1) The frequency of PRSA bacteremias were almost 2-fold higher in the daptomycin group compared to the comparator group. (2) The frequency of failures at the primary efficacy endpoint among daptomcyin-treated patients with *S. aureus* blood culture isolates that developed reduced susceptibility to daptomycin during or immediately following daptomycin therapy was higher than the frequency of failures among vancomycin-treated patients with *S. aureus* blood culture isolates that developed reduced susceptibility to vancomycin during or immediately following vancomycin therapy. (3) There were more deaths among patients with *S. aureus* blood culture isolates that developed reduced susceptibility to daptomycin during or immediately following daptomycin treatment who also developed PRSA bacteremias compared to the patients with *S. aureus* blood culture isolates that developed reduced susceptibility to vancomycin during or immediately following vancomycin therapy who also developed PRSA bacteremias. In a study by Fowler and others (15), persistent positive blood cultures at 48-96 hours is a strong predictor for complicated bacteremia. A study by Lesens and colleagues demonstrated that sustained bacteremia (>24 hours after beginning effective antibiotic therapy) is associated with a higher frequency of metastatic infections (16). Specific labeling recommendations relevant to PRSA bacteremias and *S. aureus* strains that exhibit reduced susceptibility are provided in Section 9.4

9.2 Recommendation on Regulatory Action

Based on the data contained in efficacy supplement SE1-008 to NDA 21572, there was sufficient evidence to support an approvable designation for daptomycin for the indication of *S. aureus* bacteremia without concomitant infective endocarditis from a clinical perspective pending agreement on the product label. Specific labeling recommendations are provided in Section 9.4 of this report that are relevant to the Indications and Usage section and to the Warning Section.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

A prospective registry should be established for patients who are treated with daptomycin for the indications cited above who experience persistent or relapsing bacteremias and have *S. aureus* blood isolates that exhibit rising MICs to daptomycin during or immediately following the course of daptomycin therapy. In addition, post-marketing reports should be scrutinized for off-label use of the drug for suspected or proven infective endocarditis, with particular attention to cases in which the *S. aureus* isolate

exhibited increasing MICs during or immediately following therapy compared to baseline and for cases in which doses higher than the labeled 6 mg/kg q24h dosage for this indication were used by the prescriber.

9.3.2 Required Phase 4 Commitments

Please refer to Section 9.3.3 below.

9.3.3 Other Phase 4 Requests

If the Sponsor desires to pursue a labeled indication for infective endocarditis due to *S. aureus*, the following phase 4 studies should be pursued:

(1) Extensive studies of the rabbit model of *S. aureus* endocarditis, in which concentrations of daptomycin are measured in cardiac vegetation tissues and a subset of treated animals are observed for several months after therapy (but prior to sacrifice) for evidence of relapse or metastatic complications. Studies of the effects of daptomycin in tissue biofilms should also be pursued.

(2) A comparative randomized clinical study of subjects with definite endocarditis by modified Duke criteria having sufficient size and power to permit meaningful statistical inferences about drug performance. All enrolled study subjects should have cardiac echocardiography and a protocol-specified diagnostic imaging assessment for metatstatic complications as part of the pre-randomization evaluation. A substantial proportion of the study subjects should have echocardiographically-demonstrable evidence of endocardial involvement that is suggestive of infective endocarditis.

9.4 Labeling Review

Based on the review of the results of pivotal study DAP-IE-01-02, the following labeling recommendations are provided:

(1) INDICATIONS AND USAGE Section: *Staphylococcus aureus* bacteremia (SAB) without concomitant infective endocarditis caused by methicillin-susceptible and methicillin-resistant strains. The efficacy of CUBICIN in patients with infective endocarditis due to *S. aureus* has not been demonstrated. CUBICIN has not been studied in patients with osteomyelitis, prosthetic valve endocarditis, meningitis, and deep organ infections due to *S. aureus*.

(2) WARNINGS: Persistent and relapsing *S. aureus* (PRSA) bacteremias were observed more frequently among daptomycin-treated patients compared to patients receiving standard of care. (See CLINICAL STUDIES). Six daptomycin-treated patients, including three patients with infective endocarditis, had *S. aureus* blood culture isolates that were susceptible to daptomycin at baseline and exhibited rising MICs $\geq$2 μg/ml to daptomycin during or immediately following therapy. All six patients were failures at the primary efficacy endpoint, and two patients with infective endocarditis died

subsequently. In order to monitor daptomycin-treated patients with *S. aureus* bacteremia for the development of PRSA infections and reduced susceptibility to the drug, blood cultures and daptomycin susceptibility testing by MIC using a standardized procedure should be repeated on a regular basis. Antibiotic treatment should be adjusted based on test results.

The labeling recommendations above are underpinned by the following evidence: (1) the lack of substantial evidence to demonstrate the efficacy of daptomycin in the treatment of infective endocarditis due to *S. aureus,* and (2) the clinical concerns underscored by the frequency of clinical failures and deaths among daptomycin-treated patients with PRSA infections and *S. aureus* blood culture isolates that exhibit reduced susceptibility to daptomycin during or immediately following treatment with the drug. The recommendations for the Indications and Usage Section and the Warnings Section are in accordance with the labeling requirements for prescription drugs as described in 21 CFR 201.57. In addition, the regulations specified in 21 CFR 314.126(b) regarding substantial evidence of effectiveness and 21 CFR 201.57(e) regarding warnings to describe serious adverse reactions, potential safety hazards, and special problems that may lead to death or serious injury for which a causal relationship need not have been proved are particularly pertinent to the above recommendations. It is recommended that the text described above for the Warning Section should be in bold type.

9.5 Comments to Applicant

There are no additional comments to the Applicant Sponsor.

10. APPENDICES

10.1 Review of Individual Study Reports

There are no additional comments for this section.

10.2 Line-by-Line Labeling Review

Please refer to Section 9.4.

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Alfred Sorbello
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MEDICAL OFFICER

Sumathi Nambiar
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MEDICAL OFFICER

Medical Team Leader's Review

Reviewer	Sumathi Nambiar MD MPH
Application Type	NDA 21-572/SE-1-008
Priority Designation	P
CDER Stamp Date	26 September 2006
PDUFA Goal Date	24 March 2006
Established Name	Daptomycin
Trade Name	Cubicin®
Applicant	Cubist Pharmaceuticals Inc.
Formulation	Injection
Dosing Regimen	6 mg/kg intravenously daily
Proposed Indication	*S. aureus* bacteremia including those with suspected or definite infective endocarditis caused by methicillin-susceptible and methicillin-resistant strains
Intended Population	Adults

Summary

Based on evidence from the open-label, randomized, active-controlled clinical trial submitted by the Sponsor, there is adequate efficacy and safety data to recommend approval of daptomycin in patients > 18 years of age, for the indication of *Staphylococcus aureus* bacteremia, provided that the Indications and Usage section clearly delineate that patients with certain clinical conditions such as osteomyelitis, meningitis, and prosthetic valve endocarditis were not studied. This is important because *S. aureus* bacteremia is often associated with a variety of clinical conditions such as skin and soft tissue infections, bone and joint infections, pneumonia or other deep seated infections.

Although data submitted in this application suggest that daptomycin may have activity in the treatment of infective endocarditis (IE), several issues preclude the ability to determine a true treatment effect. These issues include the small numbers of patients studied, lack of specificity of diagnosis, and low observed success rates. Infective endocarditis is a disease with high mortality and morbidity. The subgroup of patients with endocarditis in this study represented ~ 22 % of the total population, with the remainder of the patients having *S. aureus* bacteremia associated with different clinical conditions. The pathophysiology and prognosis in patients with *S. aureus* bacteremia is substantially different from that in patients with IE, thus limiting the ability to extrapolate efficacy data from the all-comers population to the IE subgroup.

S. aureus bacteremia and IE represent different aspects of the spectrum of illness caused by *S. aureus*. It is thus prudent that a statement be included in the Indications and Usage section, that the efficacy of daptomycin in the treatment of infective endocarditis has not been demonstrated.

In this study, increasing Minimum Inhibitory Concentration (MICs) to daptomycin relative to the baseline isolate was seen in seven patients. Six of these patients had persistent or relapsing *S. aureus* bacteremia and all were clinical failures. As increasing MICs were associated with clinical failure and some of these patients died, this information should be reflected in the Warnings section of the label.

Background

Daptomycin is a cyclic lipopeptide that acts by disrupting the plasma membrane resulting in loss of membrane potential and cell death. Daptomycin was approved in September 2003 for the treatment of complicated skin and skin structure infections (cSSSI).

Daptomycin is not effective in the treatment of pneumonia. Cubist had conducted two controlled clinical trials of similar design to evaluate daptomycin in the treatment of moderate to severe community-acquired pneumonia due to *Streptococcus pneumoniae*, including penicillin-resistant strains. In both trials, non-inferiority of daptomycin to comparator was not demonstrated. Daptomycin has been shown to interact *in vitro* with pulmonary surfactant.

In a Phase 2 study conducted by Lilly, the clinical efficacy of daptomycin 3 mg/kg q12 hours as treatment of *S. aureus* infective endocarditis was lower than that of comparator (usually nafcillin/gentamicin). It was postulated that the lower efficacy rate in the treatment of *S. aureus* endocarditis was due to low daptomycin levels with q 12 hour dosing.

Cubist had conducted a randomized, open-label, multicenter, Phase 2 study comparing three doses of intravenous daptomycin (4 mg/kg every 24 hour, 6 mg/kg every 24 hours, 3 mg/kg every 12 hours following a single 6 mg/kg loading dose) with a comparator agent (either i.v. vancomycin, or i.v. nafcillin/oxacillin) in patients with bacteremia caused by gram-positive pathogens. This Phase 2 study was terminated early due to slow enrollment. The efficacy of daptomycin 4 mg/kg q24h was similar to comparator for patients with bacteremia due to gram-positive pathogens. The daptomycin 3 mg/kg q12h regimen appeared to be less effective than either of those regimens. The Sponsor's assessment was that these observations were consistent with the pharmacodynamic characteristics of daptomcyin and support the utility of once daily dosing for the treatment of serious infections due to gram-positive pathogens. Success rates in patients in the daptomycin 6 mg/kg q24h treatment group were also lower than that of the comparator. The Sponsor postulated that other confounding clinical factors, including delayed adjunctive treatments (e.g., surgical drainage and removal of foreign bodies) affected outcomes among these patients.

Proposed Indication
S. aureus bacteremia including those with suspected or definite infective endocarditis caused by methicillin-susceptible and methicillin-resistant strains

Study DAP-IE-01-02
This was a multicenter, randomized (1:1), open-label study in patients with *S. aureus* bacteremia, including those with known or suspected IE. The study was conducted from 8/28/2002 to 02/16/05. According to the original protocol, patients with a high likelihood of left-sided IE were to be excluded. Following a protocol amendment in April 2004, patients with LIE were allowed in the study and were separately randomized to the two treatment groups.

Intravenous daptomycin was compared with semi-synthetic penicillins (nafcillin, oxacillin, cloxacillin, or flucloxacillin) or vancomycin. An independent external adjudication committee (IEAC), consisting of five infectious disease physicians (four members and one chair person) was convened to conduct a blinded clinical review of the data and to make assessments of diagnosis and outcomes at pre-specified time points in the study. The primary efficacy endpoint, clinical success at the test of cure visit was based on the IEAC assessment. The Test of Cure (TOC) visit was to occur 38 to 46 days after completion of study medication for all patients who completed the minimum duration of study treatment and who were considered to have a successful outcome at the EOT evaluation.

All patients were to have a transesophageal echocardiography (TEE) performed by the end of Day 5. The site results of the TEE were to be used by the investigator to determine

the presence or absence of IE. The IEAC determination of Entry and Final diagnoses was based on the echocardiogram results from the Duke CORE Echo laboratory. These results were not used by the Investigator.

Patients were classified into one of five diagnostic subgroups, namely left IE, complicated right IE, uncomplicated right IE, complicated bacteremia, or uncomplicated bacteremia. These subgroups were used by the investigator at EOT and by the IEAC at EOT and TOC. There was no requirement that echocardiographic evidence be present for a diagnosis of right-sided IE to be made.

Key issues identified during the review of Study DAP-IE-01-02

1. **Study Design:** The study was designed as non-inferiority trial in an all-comer patient population with one or more blood cultures positive for *S. aureus*. The study was not powered based on the IE population. Originally, the study was powered to detect a difference in right-sided IE patients. After several amendments, the study was modified and powered to detect a difference in the all-comers analysis. The size of the overall study population was small thus limiting the number of patients in each of the diagnostic subgroups.

2. **IEAC Assessments:** Although an IEAC was convened to assess data in a blinded manner, certain other biases inherent with an open-label study could not be overcome. As the assessments made by the IEAC were post-hoc, discrepancies between the assessments of the investigator and those of the IEAC were noted. The final diagnostic category as defined by the IEAC, took into consideration data such as the Central Echocardiogram results leading to discrepancies between the IEAC final diagnosis and investigator diagnosis. The length of treatment chosen by the investigator was based on data available to the investigator in real time, while the IEAC final diagnosis was based on all available data. Hence, the length of therapy chosen by the investigator did not always correspond to the final diagnostic subgroup determined by the IEAC and did not correspond to the minimum stipulated length of therapy as outlined in the protocol. For certain parameters such as potentially effective non-study drugs, the IEAC assessment was done on a case by case basis and was not based on a pre-specified algorithm. This raises the possibility of introducing bias and limits the ability to reproduce the IEAC assessments.

3. **Heterogeneity of Patient Population:** Though an all-comers population is fairly reflective of the spectrum of illnesses seen with *S. aureus* bacteremia, patient heterogeneity posed a number of challenges in the context of this clinical trial. The all-comers population included a very heterogenous mix of patients including cases of bacteremia with and without a known focus of infection, with and without an eradicable focus of infection, and patients with left or right-sided infective endocarditis. The presence or absence of an eradicable focus of infection can impact outcome significantly as outcomes (both morbidity and mortality) vary depending on the focus of infection and need for adjunctive surgical procedures.[1,

[2, 3] Data on foci of infection, development of metastatic foci of infection or need for adjunctive surgical procedures were not collected in a systematic manner, hence limiting the ability to assess the contribution of these to the overall outcome.

4. **Primary Endpoint:** Although non-inferiority was demonstrated for the primary efficacy endpoint of IEAC success at Test of Cure visit in the overall population, the only common factor in all these patients was the presence of one or more positive blood cultures for *S. aureus*. Presence of *S. aureus* in a blood culture is a laboratory finding and does not reflect the entire spectrum of illnesses associated with *S. aureus* bacteremia. Patients with osteomyelitis, prosthetic valve endocarditis, or meningitis were excluded. The pathophysiology, clinical course, and outcomes in patients with *S. aureus* bacteremia are highly variable. This raises an important question as to whether treatment benefit in the overall population can be extrapolated to the various subgroups that constitute the overall population especially the IE subgroup and to clinical entities such as osteomyelitis that were not studied.

5. **Data in patients with IE:**

    - The number of patients with either left or right-sided infective endocarditis was very small.
    - Though majority of patients had definite or possible IE at study entry based on modified Duke criteria, only a small number of patients had a final diagnosis of definite IE.
    - Success rates in patients with both right-sided and left-sided IE were low in both treatment groups.
    - The specificity of diagnosis of IE is important given that this disease has high morbidity and mortality. It also has unique characteristics such as the presence of vegetations, where both antibacterial activity and drug penetration are important. In this study specificity of IE diagnosis was limited for the following reasons:
        i. In patients with right-sided IE, the protocol did not require that they have echocardiographic criteria for IE. In patients with negative echocardiogram it is possible to have definite IE provided minor diagnostic criteria as outlined in the Duke criteria for definite IE are met.[4] In the absence of evidence for definite IE, it is difficult to assess the performance characteristics of a study drug. Treating a patient with possible IE as a definite IE in a clinical setting is acceptable, however in a clinical trial better specificity of the diagnosis is important in making any conclusions about drug efficacy.
        ii. Discrepancies in echocardiogram results between local and central laboratory readings raise additional concerns about the specificity of the diagnosis of IE. The numbers of patients with IE varied

depending on whether local or central echocardiographic findings were considered definitive.

6. **Microbiology:**
    - Decreased susceptibility of *S. aureus* to daptomycin on or after therapy was noted relative to baseline MICs. Reduced susceptibility was associated with clinical and microbiologic failures.
    - Persistent and relapsing bacteremias were seen more frequently in the daptomycin group.

Synopsis of Efficacy Data in study DAP-IE-01-02

All-Comers

A total of 246 patients were enrolled in the study, 206 from sites in the United States and 40 from all European sites combined. Of 246 patients enrolled, 236 were randomized and treated including 120 who received daptomycin and 116 who received a comparator regimen. One patient in the comparator group was enrolled with a suspicion of LIE prior to Amendment 4A and was excluded from the Intent-To-Treat (ITT) population. The Per Protocol (PP) population consisted of 139 patients, which included 79 in the daptomycin group and 60 in the comparator group.

Distribution of patients in the two treatment arms, based on the IEAC determined Entry Diagnosis and Final Diagnosis subgroups for the ITT population are outlined in the following table:

Table 1: Entry and Final Diagnostic Subgroups (ITT)

	Daptomycin (N=120)	**Comparator (N=115)**	**Total (N=235)**
IEAC Entry Diagnostic Subgroup [N (%)]			
Possible IE	73 (60.8%)	71 (61.7%)	144 (61.3%)
Definite IE	17 (14.2%)	20 (17.4%)	37 (15.7%)
Not IE	30 (25.0%)	24 (20.9%)	54 (23.0%)
IEAC Final Diagnostic Subgroup [N (%)]			
Complicated bacteremia	60 (50.0%)	61 (53.0%)	121 (51.5%)
Uncomplicated bacteremia	32 (26.7%)	29 (25.2%)	61 (26.0%)
Complicated RIE	13 (10.8%)	12 (10.4%)	25 (10.6%)
Uncomplicated RIE	6 (5.0%)	4 (3.5%)	10 (4.3%)
LIE	9 (7.5%)	9 (7.8%)	18 (7.7%)

Source: Sponsor Table 11-4, final study report

Although, the majority of patients (~75%) had an entry diagnosis of definite or possible IE, only 28 patients in the daptomycin arm and 25 in the comparator arm had a final diagnosis of IE. Using the modified Duke criteria to classify patients at study entry seems to suggest that a substantial number of patients have IE, the actual number of definite IE cases was however small. In the daptomycin arm, 63/73 (86.3%) patients with

"Possible IE" at entry had a final diagnosis of bacteremia. In the comparator arm, 66/71 (92.9%) patients with "Possible IE" at entry had a final diagnosis of bacteremia.

The following table summarizes the Sponsor's results for the primary efficacy endpoint of IEAC outcome at TOC in the overall ITT and PP population:

Table 2: Sponsor Primary Efficacy Analysis

	Daptomycin N (%)	Comparator N (%)	Difference in success rates (95 % CI)
ITT			
Total	120	115	
Success	53 (44.2%)	48 (41.7%)	2.4 % (-10.2, 15.1)
Failure	58 (48.3%)	53 (46.1%)	
Non-evaluable	9 (7.5%)	14 (12.2%)	
PP			
Total	79	60	
Success	43 (54.4%)	32 (53.3%)	1.1 % (-15.6, 17.8)
Failure	36 (45.6%)	28 (46.7%)	

Source: Sponsor Table 11-10, final study report

In the overall population, including cases with bacteremia and endocarditis, the study met its pre-defined endpoint of IEAC success in the ITT and PP population using a non-inferiority margin of -20, as evidenced by the lower bound of the 95% confidence limits not exceeding -20 and the confidence intervals including the value zero.

The following table summarizes the Sponsor's efficacy data based on IEAC outcome at TOC in the ITT population for the IEAC Final Diagnostic Subgroups:

Table 3: Success Rates by IEAC Final Diagnostic Subgroup (ITT)

IEAC Final Diagnostic Subgroup	Daptomycin n/N (%)	Comparator n/N (%)
Right sided IE	8/19 (42.1%)	7/16 (43.8%)
Complicated RIE	5/13 (38.5%)	6/12 (50.0%)
Uncomplicated RIE	3/6 (50.0%)	1/4 (25.0%)
Left sided IE	1/9 (11.1%)	2/9 (22.2%)
Bacteremia	44/92 (47.8%)	39/90 (43.3%)
Complicated bacteremia	26/60 (43.3%)	23/61 (37.7%)
Uncomplicated bacteremia	18/32 (56.3%)	16/29 (55.2%)

Source: Sponsor Table 11-12, final study report

Infective Endocarditis

As the total number of patients with IE was small and the study was not powered to detect statistical differences between the two treatment arms in patients with endocarditis, no formal statistical analyses in this subgroup were performed.

A total of 53 patients had an IEAC Final Diagnosis of IE in the ITT population, 28 in the daptomycin arm and 25 in the comparator arm. In the daptomycin arm there were 19 patients with right IE and 9 with left IE. In the comparator arm, 16 patients had right IE and 9 patients had left IE.
The median age of patients with IE was 45 years in the daptomycin group and 41 years in the comparator arm. History of IV drug use was present in 61% of patients in the daptomycin arm and 56 % in the comparator arm. About 55% of patients had MSSA and 45% had MRSA infections.

Among the 53 patients with IE, 34 had positive central echocardiogram reading, 18 patients (17 RIE, 1 LIE) had negative central echocardiogram readings and 1 patient did not have an echocardiogram. Discrepancies between the local echocardiography and the Duke Core Echo laboratory assessments were noted in 18 patients (35%), 10 patients with positive central echocardiogram findings had negative local echocardiogram findings while 8 patients with negative central echocardiogram findings had positive local echocardiogram findings. The actual number of patients who had echocardiographically demonstrable valvular vegetations and/or perforations varied from 32-42 depending on whether the local or central echocardiogram readings were considered definitive. These discrepancies in echocardiographic results limit the ability to accurately define a well-characterized group of patients with IE. Though it is possible to have endocarditis in the absence of demonstrable vegetations, the performance of the drug in the presence of vegetations provides evidence of penetration of the drug into the vegetations, which is an important characteristic of a drug being used to treat this disease.

Success rates reported in the literature in patients with right-sided endocarditis especially in those with intravenous drug use due to *S. aureus* are > 85%.[5] Success rates for patients with IE, based on the Sponsor's analysis are depicted in the following table for the ITT and PP populations:

Table 4: Clinical Success Rates in Patients with Infective Endocarditis

	ITT (N=53)		PP (N=33)	
IEAC Final Diagnosis	**Daptomycin n/N (%)**	**Comparator n/N (%)**	**Daptomycin n/N (%)**	**Comparator n/N (%)**
Uncomplicated RIE	3/6 (50)	1 /4 (25)	1 /2 (50)	0/2 (0)
Complicated RIE	5/13 (38.5)	6/12 (50)	5/10 (50)	4/6 (66.7)
Left IE	1/9 (11)	2/9 (22)	1/7 (14.2)	2/6 (33.3)

One comparator-treated and two daptomycin- treated patients had valve replacement surgery for LIE. The comparator-treated patient was a failure at TOC. One daptomycin- treated patient was a failure at TOC and the other was non-evaluable at TOC.

Microbiologic Failures

According to analyses performed by the Sponsor, of the 28 microbiologic failures in the daptomycin arm and 23 in the comparator arm, 18 patients in the daptomycin arm and 10 in the comparator arm had persisting or relapsing bacteremia. An additional one patient in each arm had positive culture from a non-blood source. During the FDA review two additional patients with persisting or relapsing bacteremia were identified in the

daptomycin arm. Persistent or relapsing *S. aureus* bacteremia was more common in the daptomycin arm, both in patients with bacteremia and IE.

Table 5: Persistent or relapsing *S. aureus* infections (ITT)

IEAC Final Diagnosis Category	Daptomycin N=21	Comparator N=11
Total IE	**8**	**5**
Complicated RIE	1	3
Uncomplicated RIE	3	0
Left IE	**4**	2
Total bacteremia	**12**	**5**
Complicated bacteremia	12	5
Uncomplicated Bacteremia	0	0
Persistent Infections	**1**	**1**

*includes 1 post-study relapse at Day 85P; ** persistent knee infection; persistent urinary tract infection

Increasing MIC to daptomycin (≥ 2 mcg/ml) relative to the baseline isolate was noted in seven patients treated with daptomycin. All except one of these patients had persisting/relapsing bacteremia and were clinical failures. In the one patient who was a clinical success, *S. aureus* with increasing MICs was identified from a wound specimen; this patient had an infected lumbar wound and osteomyelitis and was treated for 74 days.

The following table summarizes information on patients with increasing daptomycin MICs:

Table 6: Increasing Daptomycin MIC (ITT)

Study Group	Baseline Pathogen	Site	IEAC Final Diagnosis	IEAC Outcome at TOC	Study Day at which Daptomycin MIC ≥ 2 reported
Comparator	MRSA	Blood	Complicated RIE	Success	Day 11
Daptomycin	MRSA	Blood	Complicated bacteremia	Failure	Day 09P
Daptomycin	MSSA	Blood	Complicated RIE	Failure	Day 18
Daptomycin	MRSA	Blood	Complicated bacteremia	Failure	Day 20P
Daptomycin	MRSA	Blood	LIE	Failure	Day 4
Daptomycin	MRSA	Blood	LIE	Failure	Day 7
Daptomycin	MSSA	Wound	Complicated bacteremia	Success	Day 13
Daptomycin	MRSA	Blood	Complicated bacteremia	Failure	Day 7

In the comparator group, three patients had *S. aureus* isolates with MIC of 2 mcg/ml and one of these patients had persisting or relapsing *S. aureus* bacteremia.

Thus, the development of increasing MICs has significant clinical implications as it is associated with persisting or relapsing bacteremia and clinical failure. Though resistance to most antimicrobial agents develop with time following more widespread use it is unusual for the phenomenon of increasing MICs and its association with clinical failure to be noted in the context of a clinical trial that was fairly limited in size. This was not

noted in the complicated skin and skin structure infections (cSSSI) trials. The reason for this observation is unclear. Possible hypotheses include that this may be a reflection of the higher bacterial load in a disease like *S. aureus* bacteremia or IE, or maybe that in cSSSI adjunctive surgical procedures play an important part in eradicating the infection, while with bacteremia or IE ability for adjunctive surgical procedures may be limited in some situations.

Synopsis of Safety Data in Study DAP-IE-01-02

Overall, the median duration of exposure was 14 days in the daptomycin arm and 15 days in the comparator arm. Only limited safety data is available on patients treated for greater than 28 days as only 14 patients received daptomycin for more than 28 days.

There were 18 deaths (15%) in the daptomycin arm and 19 deaths (16.4%) in the comparator arm. The overall incidence of Adverse Event (AE) was similar in the two treatment arms. Infection-related Serious Adverse Events (SAEs) were more common in the daptomycin arm, and renal SAEs were more common in the comparator arm. Gram-negative SAE's were more common in the daptomycin arm. The reason for this observation is unclear. It is possible that concomitant gentamicin in the comparator group may have played a role in this finding.

Three patients in the daptomycin arm had CPK elevation of >500 U/L with associated musculoskeletal symptoms. None of the patients in the comparator group had an elevation in CPK >500 U/L with associated musculoskeletal symptoms. Eleven daptomycin-treated patients (9.2%) had treatment-emergent elevations in CPK to >500 U/L, including four patients with elevations >10X ULN. In 10 of these patients CPK levels returned to the normal range either during treatment, or during follow-up. One patient did not have follow-up values reported. Three patients discontinued daptomycin due to CPK elevation.

REGULATORY CONCLUSIONS

1. Based on the data submitted, the Sponsor has provided substantial evidence to support the indication of *S. aureus* bacteremia. The patient population studied excluded patients with certain clinical conditions such as osteomyelitis, meningitis, and prosthetic valve endocarditis. This information should be clearly outlined in the product label to inform practitioners of the limitations of the data.

2. Data submitted in this application do not provide substantial evidence of safety and efficacy in patients with infective endocarditis as outlined in 21 CFR §314.126 for the following reasons:

    - Only a small number of patients with either left or right-sided infective endocarditis were studied.
    - The specificity of the diagnosis was unclear in several patients. In a disease such as infective endocarditis, it is important that patients be well characterized to adequately understand the performance of the drug.
    - Success rates in both left and right-sided infective endocarditis were low in both daptomycin and comparator arms. In this trial, success rates seen in patients with right-sided infective endocarditis in both treatment arms were much lower than that reported in the literature, thus raising the issue of assay sensitivity.[5] In left-sided infective endocarditis with only one success in the daptomycin arm, and two successes in the comparator arm, no efficacy conclusions can be drawn.
    - As the pathophysiology and outcomes in patients with infective endocarditis is different from that in the all-comers population with *S. aureus* bacteremia, efficacy data from the all-comers population cannot be extrapolated to that in patients with infective endocarditis.

3. The Warnings section of the label should include a statement regarding the observation made in the clinical trial of increasing MICs to daptomycin and its association with clinical failure, even though a causal relationship has not been demonstrated. The recommendation to include this information in the Warnings section is consistent with 21CFR §201.57 (e), which states that under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. In a severe illness such as *S. aureus* bacteremia, lack of efficacy is associated with increased morbidity and mortality and it is important that the practitioner be made aware of this observation.

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Sumathi Nambiar
3/24/2006 05:18:03 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021572Orig1s008

PRODUCT QUALITY REVIEW(S)

DIVISION OF ANTI-INFECTIVES DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-572 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 30-Sep-05

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SE1-008	22-Sep-05	22-Sep-05	-----

NAME & ADDRESS OF APPLICANT:
Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
Lexington, MA 02421
Contact: Mary Kathryn Kottke **(**Manager, Regulatory Affairs)
Tel: 781-860-8357
Fax: 781-861-0566

DRUG PRODUCT NAME

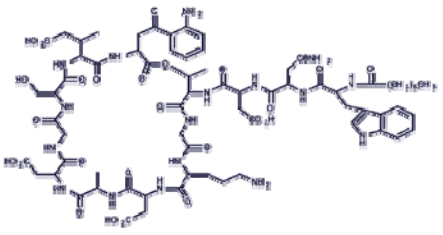
Proprietary:	CUBICIN®
Nonproprietary/USAN:	Daptomycin for Injection
Code Names/#'s:	N/A
Chemical Type:	1s
Therapeutic Classes:	Antibiotic

PHARMACOLOGICAL INDICATION: complicated skin and skin structure infections

DOSAGE FORM: Intravenous infusion
STRENGTHS: 250 mg/vial, 500 mg/vial
ROUTE OF ADMINISTRATION: Intravenous
DISPENSED: __X__ **Rx** __ **OTC**
SPECIAL PRODUCTS: ____ **Yes** __X__ **No**
(If yes, fill out the form for special products and deliver to TIA through team leader for data entry.)

CHEMICAL NAME, STRUCTURAL FORMULA, MOL. FORMULA, MOL.WT:

Chemical Name: *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 ε1-lactone
Molecular Formula: $C_{72}H_{101}N_{17}O_{26}$
Molecular Weight: 1620.67



REMARKS/COMMENTS:

NDA 21-572/SE1-008 is an sNDA supplement that provides for the use of the FDA-approved drug, CUBICIN®, in the treatment of patients with *Staphylococcus aureus* bacteremia, including those with known or suspected endocarditis caused by methicillin susceptible and methicillin-resistant strains. The proposed dose is 6 mg/kg administered as a 30-minute intravenous (i.v.) infusion once per day (q24h)

The submission contains no new chemistry information other than a request for a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR §25.31(b).

REVIEW

The company states the estimated Expected Introduction Concentration (EIC) will be below 1 part per billion for the production of daptomycin with the approval of this sNDA. This meets the 21 CFR §25.31(b) requirements for categorical exclusion from an environmental assessment.

No changes are made to the CMC approved in the original NDA 21-338 and subsequent supplements, except that the 250 mg/vial will not be used in this application. No changes are made to the CMC aspects of the labels except for the elimination of references to the 250 mg/vial. No changes are made to the approved facilities.

The supplement SE1-008 is recommended for approval as the CMC remains unchanged from the approved NDA 21-572.

CONCLUSIONS & RECOMMENDATIONS:

NDA 21-572/SE1-008 is recommended for approval.

Rapti D. Madurawe, Ph.D.
Review Chemist

cc: Orig. NDA# 21-572
HFD-520/Division File
HFD-520/ProjMan/Davi
HFD-520/Chem/Madurawe
HFD-520/TeamLdr/Vidra

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/s/

Rapti Madurawe
3/13/2006 02:24:45 PM
CHEMIST

Jim Vidra
3/13/2006 02:50:59 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021572Orig1s008

STATISTICAL REVIEW(S)

AMENDMENT

NDA/Serial Number:	21572 / SE1-008
Drug Name:	Cubicin® (daptomycin for injection)
Indication(s):	Treatment of *Staphylococcus aureus* bacteremia, including known or suspected endocarditis caused by methicillin-susceptible and methicillin-resistant strains.
Applicant:	Cubist Pharmaceuticals, Inc. 65 Hayden Ave. Lexington, MA 02421
Date(s):	Submitted: 24 September 2005 PDUFA: 24 March 2006

Table 5 in my original review was taken from the Sponsor's CSR Table 11-12. The inclusion of 95% confidence intervals for the diagnostic subgroups did not control for multiplicity. Because this could increase type I error, inferences should be based on confidence intervals adjusted for multiplicity. I have revised the table and included the 99% confidence intervals.

Table 5: IEAC Outcome at TOC by IEAC Final Diagnostic Subgroup

Population IEAC Final Diagnostic Subgroup	Daptomycin n/N (%)	Comparator n/N (%)	Differences in Success Rates (95% CI)	Differences in Success Rates (99% CI) (adj. for multiplicity)
ITT Population				
Overall	53/120 (44.2%)	48/115 (41.7%)	2.4% (-10.2, 15.1)	—
cRIE	5/13 (38.5%)	6/12 (50.0%)	-11.5% (-50.3, 27.2)	-11.5, (-62.4, 39.4)‡
uRIE	3/6 (50.0%)	1/4 (25.0%)	25.0% (-33.3, 83.3)	25.0, (-51.6, 1.0)
cBAC	26/60 (43.3%)	23/61 (37.7%)	5.6% (-11.8, 23.1)	5.6 (-17.3, 28.6)
uBAC	18/32 (56.3%)	16/29 (55.2%)	1.1% (-23.9, 26.0)	1.1 (-31.7, 33.9)
LIE	1/9 (11.1%)	2/9 (22.2%)	-11.1% (-45.2, 22.9)	-11.1 (-55.9, 33.6)
PP Population				
Overall	43/79 (54.4%)	32/60 (53.3%)	1.1% (-15.6, 17.8)	—
cRIE	5/10 (50.0%)	4/6 (66.7%)	-16.7% (-65.5, 32.2)	-16.7 (-80.8, 47.5)
uRIE	1/2 (50.0%)	0/2 (0.0%)	50.0% (-19.3, 100.0)	50.0 (-41.1, 100.0)
cBAC	19/39 (48.7%)	14/29 (48.3%)	0.4% (-23.6, 24.5)	0.4 (-31.1, 32.0)
uBAC	17/21 (81.0%)	12/17 (70.6%)	10.4% (-17.0, 37.8)	10.4 (-25.7, 46.4)
LIE	1/7 (14.3%)	2/6 (33.3%)	-19.0% (-64.8, 26.7)	-19.0 (-79.2, 41.1)

Sponsor CSR Table 11-12, revised to include 99% CI's.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Scott Komo, Dr.P.H.
Date:

Concurring Reviewer(s): Thamban Valappil, Ph.D.

cc:
Chris Davi
Fred Sorbello
Sumathi Nambiar
Janice Soreth
Scott Komo
Thamban Valappil
Daphne Lin
Mohammed Huque
Lillian Patrician
Robert O'Neil

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/s/

Scott Komo
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Thamban Valappil
5/25/2006 06:39:46 PM
BIOMETRICS

MEMO TO FILE

Date	**:**	**May 25, 2006**
NDA	**:**	**21-572/SE1-008**
Drug Name	**:**	**Cubicin® (daptomycin for injection)**
Date of Submission	**:**	**March 27, 2006**
**Medical Division ` **	**:**	**Division of Anti-Infective and phthalmology Products (HFD-520)**

Subject: Secondary Statistical Review and Evaluation

Conclusions and Recommendations:

The efficacy supplement SE1-008 for NDA 21-572 was submitted by the applicant on September 26, 2005 for the proposed labeled indication of daptomycin in the treatment of *Staphylococcus aureus* bacteremia (SAB) including those with known or suspected endocarditis caused by methicillin-susceptible and methicillin-resistant strains. Subsequently, on March 27, 2006, the sponsor revised the proposed indication to *Staphylococcus aureus* bloodstream infections (bacteremia), including those with right-sided infective endocarditis, caused by methicillin-susceptible and methicillin-resistant strains.

There were several issues with DAP-IE-01-02 study of NDA 21-572, including but not limited to study design, lack of specificity in the diagnosis of infective endocarditis (IE), lack of assay sensitivity, inadequate characterization of patients at baseline, lack of replicative evidence and lack of corroborative data from earlier phase 2 and 3 studies. Details regarding these issues can be found in the statistical review of Dr. Scott Komo and the clinical review of Dr. Alfred Sorbello, and the memorandum of regulatory briefing minutes held on 4/20/06.

Summarizing few important findings, the co-primary efficacy endpoints in the study were the Independent External Adjudication Committee (IEAC) success rates at the Test-of-Cure (TOC) visit in the all-comers ITT and Per Protocol (PP) populations and was evaluated using a non-inferiority margin of 20%. The overall IEAC success rates in the all-comers ITT population were 44.2% (53/120) in patients treated with CUBICIN and 41.7% (48/115) in patients treated with comparator (difference = 2.4%, 95% CI -10.2, 15.1). The success rates in the PP population were 54.4% (43/79) in patients treated with CUBICIN and 53.3% (32/60) in patients treated with comparator (difference = 1.1%, 95% CI -15.6, 17.8). Eighteen patients (18/120) in the CUBICIN arm and 19/116 patients in the comparator arm died during the study. This includes 3/28 CUBICIN and 8/26 comparator-treated patients with endocarditis and 8/19 CUBICIN- and 7/11 comparator-treated patients with persisting and relapsing *S. aureus* infections.

There were 182 patients with bacteremia and 53 patients with infective endocarditis (right and left sided) as assessed by the Adjudication Committee in the ITT population, including 35 with right-sided and 18 with left-sided endocarditis. The 182 patients with bacteremia included 121 with complicated and 61 with uncomplicated *S. aureus* bacteremia. Although non-inferiority was established in the all-comers population, efficacy of daptomycin was difficult to assess due to the heterogeneity in the vastly pooled, small patient subgroups.

In my assessment, the statistical evaluation of the data, do not provide adequate scientific evidence that daptomycin is effective in the treatment of *S. aureus* right-sided infective endocarditis (IE). Therefore, I do not recommend labeling daptomycin for use in right-sided endocarditis.

Thamban Valappil, Ph.D.
Statistical Team Leader,
DBIV/OB/OTS/CDER

Concur:

Mohammad Huque, Ph.D.
Division Director, DB IV/OB/OTS/CDER

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/s/

Thamban Valappil
5/25/2006 06:02:39 PM
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Secondary Statistical Review of Evaluation

Mohammad Huque
5/25/2006 06:12:46 PM
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	21572 / SE1-008
Drug Name:	Cubicin® (daptomycin for injection)
Indication(s):	Treatment of *Staphylococcus aureus* bacteremia, including known or suspected endocarditis caused by methicillin-susceptible and methicillin-resistant strains.
Applicant:	Cubist Pharmaceuticals, Inc. 65 Hayden Ave. Lexington, MA 02421
Date(s):	Submitted: 27 March 2006 PDUFA: 27 May 2006
Review Priority:	Priority
Biometrics Division:	Biometric Division IV
Statistical Reviewer:	Scott Komo, Dr.P.H.
Concurring Reviewers:	Thamban Valappil, Ph.D.
Medical Division:	Division of Anti-Infective and Ophthalmology Products (HFD-520)
Clinical Team:	Fred Sorbello, M.D. Chuck Cooper, M.D. Sumathi Nambiar, M.D.
Project Manager:	Chris Davi, M.S.

Keywords: active control/non-inferiority, NDA review, class cyclic lipopeptide,

Pop adult

Table of Contents

LIST OF TABLES

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The resubmission dated March 27, 2006 did not contain any new data but provides a rationale for their revised proposed labeling.

Overall the data in this submission provide substantial evidence that daptomycin is effective in the treatment of *Staphylococcus aureus* bacteremia. However, I do not feel that they provide substantial evidence that daptomycin is effective in the treatment of *S. aureus* infective endocarditis (IE). The reasons are given below. In addition, it should be noted that there are two possible issues: (1) rising minimum inhibitory concentration associated with persisting or relapsing bacteremia and (2) a trend of decreasing efficacy with increasing renal impairment

The single Phase III trial has weaknesses in both study design and conduct as summarized in §1.3 (for further details, see §5.1 in my review of the 9/24/05 submission, N21572/SE1-008). While it is true that these types of trials are difficult to conduct, the weaknesses in this trial make it difficult to interpret some of the findings. Because of the small sample and heterogeneity of the population, it is difficult to differentiate a true signal of drug effect from random variation. The Sponsor did demonstrate noninferiority in the all-comers analysis to comparator. In the study, the majority (77%) of the patients had bacteremia. The largest experience was in bacteremia patients. The results for both of the bacteremia subgroups (uncomplicated and complicated) were consistent with the results for the all-comers population. In addition, identification of bacteremia patients was not an issue as it was for the infective endocarditis subgroups. For the reasons just stated, I feel the study provided substantial evidence that daptomycin was effective in the treatment of *S. aureus* bacteremia. However, it should be noted that there are two possible issues: (1) rising minimum inhibitory concentration associated with persisting or relapsing bacteremia and (2) a trend of decreasing efficacy with increasing renal impairment.

The performance of daptomycin would need to be examined in the endocarditis subpopulation itself because differences in the pathophysiology of the diagnostic subgroups in the study (i.e. bacteremia, right- and left-sided endocarditis) make it difficult to extrapolate the findings from the all-comers population to the subgroups. I did not feel that the study provided substantial evidence of efficacy because there was both a small number of daptomycin treated endocarditis patients treated (28), divided into three subgroups (6 uncomplicated right-sided infective endocarditis (RIE), 13 complicated RIE, and 9 left-sided infective endocarditis (LIE)) and the response rate was lower than expected from the medical literature especially in left-sided patients where the response was poor (1/9). In addition, the results between the IE subgroups were not consistent. Furthermore, the assay sensitivity of this study to detect a treatment effect in IE patients is an issue. Finally, the issues of poor performance of the drug in the Phase II trials, the concern that the size of the compound makes it difficult to penetrate into the vegetation, and the concern that the drug is calcium dependent and highly protein bound should be taken into consideration in the determination of efficacy.

1.2 Brief Overview of Clinical Study

The single Phase III trial (Study DAP-01-02) was a multicenter, randomized (1:1), open-label study comparing daptomycin i.v. (6 mg/kg q24h) with conventional intravenous (i.v.) therapy [semi-synthetic penicillin (SSP) 2 g q4h (nafcillin, oxacillin, cloxacillin, or flucloxacillin) or vancomycin 1 g q12h, both with initial synergistic gentamicin] in the treatment of patients with infective endocarditis or bacteremia due to *Staphylococcus aureus.*

In the prior clinical studies, daptomycin performed poorly in two Phase II bacteremia and endocarditis studies, one conducted by Eli Lilly & Company using a 3 mg/kg q12 hr dose and the other a dose ranging study conducted by Cubist that included the proposed dose. In addition, daptomycin was found to be inferior to ceftriaxone in two Phase III trials for the treatment of community acquired pneumonia. It was hypothesized that an interaction with surfactant impeded the antimicrobial activity of the daptomycin. The following sentence is in the current label:

CUBICIN is not indicated for the treatment of pneumonia.

1.3 Statistical Issues and Findings

The study demonstrated the noninferiority of daptomycin to Comparator for the primary endpoint of IEAC outcome at TOC based on a noninferiority margin of 20%. In the all-comers ITT population, noninferiority was demonstrated with the treatment difference in Success rates (Daptomycin – Comparator) of 2.4% and a corresponding 95% CI of (-10.2, 15.1). Similarly, noninferiority was also demonstrated in the all-comers analysis PP population for the treatment difference in Success rates (Daptomycin – Comparator) of 1.1% and a corresponding 95% CI of (-15.6, 17.8).

Only in the daptomycin-treated subjects whose *staphylococcal* blood culture isolates exhibit increasing minimum inhibitory concentration (MIC) to daptomycin, vancomycin, or both drugs are persisting or relapsing bacteremia (PRSA) infections and deaths observed. Of the 6 daptomycin-treated subjects whose blood culture isolates exhibited increasing MICs to daptomycin or both drugs, all of them developed PRSA and 2 died. In contrast, none of the comparator-treated subjects whose blood culture isolated exhibited increasing MICs to daptomycin, vancomycin, or both drugs developed PRSA and there were no deaths among those patients (see Table 7 in the review for the 9/24/05 submission, N21572/SE1-008).

There is a trend where the IEAC response rate at TOC decreases as baseline renal function decreases for the daptomycin group (see Table 9 in the review for the 9/24/05 submission, N21572/SE1-008). One might hypothesize that poorer baseline renal function could be a surrogate for a sicker population and this would explain the decrease in outcome rates. However, this trend is not seen for the comparator group as would be expected if baseline renal function were a surrogate for a sicker patient population. Note that this trend was also seen in the initial NDA application for the complicated skin and skin structure indication.

The following were issues identified during the review:

Small study that was not powered to detect differences in diagnostic subgroups

In the original protocol, the study was originally powered to detect a difference in the RIE patients. After several amendments, the study was changed and the study was powered to detect a difference in the all-comers analysis. The Sponsor was told that the breadth of the indication would depend not only on the all-comers analysis but also on the performance as well as numbers in the diagnostic subgroups. The small sample size and the heterogeneity of patients between the diagnostic subgroups made it very difficult to determine the effectiveness of daptomycin. Because the sample size in the subgroups were so small it was difficult to differentiate between a signal of drug effect or random variation.

Potential biases introduced with the open-label design

The Sponsor attempted to address some of the potential issues with their use of an open-label design by using a blinded IEAC assess both outcome and diagnosis. However, the use of the IEAC still did not address the following issues:

- Duration of treatment

The duration length was to be determined by the Investigator's diagnosis and susceptibility of the *S. aureus* isolate. During the conduct of the study, actual treatment duration was based on Investigator discretion. The open-label nature of the study could affect treatment duration because duration was based on Investigator discretion. They might be either more or less willing to continue patients on the new treatment relative to the comparator.

- Determination of severe adverse events and adverse events

Investigators, who know what treatment patients receive, determined when either a SAE or an AE occurred without a strict definition of SAE or AE. This increased the potential for bias. An example of how knowledge of treatment received could affect the call of an AE would be if the patient was in the Comparator arm and it was known that the patient received gentamicin, which is known to have renal toxicity issues. Because patients who discontinued due to an AE would be considered treatment failures, this has the potential to bias the efficacy results even with the blinded adjudication committee.

- Potentially Effective Non-Study Drugs (PENS)

Investigators determined when PENS should be given and could thereby affect outcome even if a blinded adjudication committee since the administration of PENS would be considered Failures.

- Metastatic foci

The definition of the diagnostic subgroups complicated and uncomplicated *S. aureus* RIE involve evidence of extrapulmonary sites of infection, and the definitions of complicated and uncomplicated bacteremia refer to evidence of metastatic foci of infection. It is noteworthy that there is no requirement for all study subjects to have a standardized radiologic imaging evaluation for metastatic extrapulmonary infections. The decision as to the intensity and scope of such a diagnostic evaluation was left solely to the discretion of the individual Investigators. Thus, the magnitude of subjects with evidence of extrapulmonary metastatic sites of infection is likely an underestimate due to the lack of a systematic requirement for such diagnostic imaging for all study participants.

Identification of endocarditis patients

- Cannot determine who is an endocarditis patient at baseline.

A major issue is that one cannot determine who is an endocarditis patient at baseline. This is a problem because of the way that the diagnostic subgroups are determined using post-baseline information. The transesophageal echocardiography (TEE) could occur up to five days from the enrollment in the study.

- Difficulty in determining endocarditis patients
  - Discordance of echocardiographs (central vs. local)

There was substantial discrepancy between the readings of the local and central echocardiographs. Based on Cohen's kappa [κ=0.25; 2-sided 95% CI=(-0.01, 0.52)], there

was relatively poor agreement between the central and local echocardiography results. A fuller description of the discrepancies is given below in Table 10 in the review for the 9/24/05 submission, N21572/SE1-008.

Issues with the endocarditis patients

- Small number of IE patients

As shown in Table 5 in the review for the 9/24/05 submission, N21572/SE1-008, there are only 53 IE patients in the study. Of those 53, only 28 were treated with daptomycin. Of those 28 patients, only 19 were included in the PP population. The 28 subjects were spread across the three IE subgroups (6 uncomplicated RIE, 13 complicated RIE, and 9 LIE patients).

- Response rates

The response rates in the diagnostic subgroups were lower than the anticipated efficacy rates as described in the medical literature and the performance in the LIE group was especially poor (1/9).

Discordance of Investigator and IEAC Diagnosis

There was discordance in the diagnostic subgroup classification between the IEAC Final Diagnosis and the Investigator Diagnosis for the Complicated and Uncomplicated bacteremia patients. The majority of the discrepancies occurred in the bacteremia patients. For the daptomycin arm, in bacteremia patients, the IEAC classified 23 patients (23 out of 50) as having a more severe diagnosis (Uncomplicated to Complicated Bacteremia) than diagnosed by the Investigator. In contrast the IEAC classified 4 patients (4 out of 41) as having a less severe diagnosis than diagnosed by the Investigator.

For the Comparator arm, in bacteremia patients, the IEAC classified 24 patients (24 out of 44) as having more severe diagnosis (Uncomplicated to Complicated Bacteremia) than diagnosed by the Investigator. In contrast the IEAC classified 8 patients as having a less severe diagnosis than diagnosed by the Investigator.

The IEAC shifted a substantial number of patients in both treatment arms with uncomplicated bacteremia as assessed and managed clinically by the Investigators into a category of more severe disease (complicated bacteremia for which they were not treated). The overall effect of such shifting of patients is to erroneously enhance the success rates in the IEAC final diagnosis subgroups of complicated bacteremia by inclusion of subjects with uncomplicated disease, who had less severe disease, better prognoses, were managed clinically for uncomplicated bacteremia, and responded to treatment regimens appropriate for uncomplicated disease.

Duration of treatment

The median treatment duration for the diagnostic subgroups as defined by the IEAC Final Diagnosis is much shorter than specified in the protocol. This is because the IEAC upgraded the diagnosis group to the more severe category but the treatment duration was based on the Investigator EOT diagnosis.

IEAC outcomes and evaluability

The IEAC did not follow the protocol with respect to the handling of missing EOT or TOC blood cultures. The IEAC used blood culture data outside of the protocol-specified windows in order to determine IEAC outcome. The protocol stated that if either the EOT or TOC blood cultures were missing that the patient should be considered a failure.

The IEAC also changed outcomes from Failure to non-evaluable because they felt that patients were not properly managed. This was based on their "clinical judgment."

Heterogeneity of population

Patients were included in the study based on at least 1 positive blood. However, this included a broad range of severity of illness from uncomplicated bacteremia to LIE. These diagnostic subgroups require varying dosing durations as well as differing prognoses.

Noninferiority margin

The Sponsor used a noninferiority margin of 20%. The Division initially agreed to this margin in a study where the Sponsor assumed 80% response rates for both arms. Later, because of increasing MRSA rates, the Sponsor estimated the response rates to be 65% in both arms. Because it was felt that the placebo rate was low for this population of patients, it was felt that the size of the margin would not be determined by the smallest effect size that the active drug would be expected to have compared to placebo. Rather the determination of the noninferiority margin was based on the size of an acceptable possible loss in efficacy for which the Division felt that 20% was acceptable. However, in this study the response rates were lower than expected. In the ITT group, the daptomycin success rate was 44.2% vs. 41.7% for the Comparator. In addition, the response rates in the PP population were 54.4% vs. 53.3 for daptomycin vs. Comparator. What was really concerning was the performance in the endocarditis subgroup especially in the LIE group where the rates were 1/9 (11%) for daptomycin vs. 2/9 (22%) for the comparator. Given this low rate, the validity of a 20% noninferiority is questionable and impacts the assay sensitivity of the submission.

Primary focus of infection

The Sponsor did not prospectively collect information on the primary focus of infection. So no standardized procedures were in place to look for or document a primary focus of infection. This has bearing mostly on the bacteremia patients as the existence of a primary focus of infection would have bearing on their dosing duration and also what diagnostic category one would be placed.

2. DISCUSSION

This resubmission did not contain any new data but contained the rationale for the proposed labeling that the Sponsor is seeking. The following are issues that were identified in addition to those already addressed in §1.3.

Persistent or relapsing bacteremia

The following paragraph is from the Precautions as well as the Clinical Studies section of the Sponsor's proposed label:

(b) (4)

(b) (4) Table 1 contains the results from both the Sponsor's analysis and the FDA reanalysis.

Table 1: Persisting and Relapsing Bacteremia and Persisting Infections

		Daptomycin N=120	Vancomycin only N=53	SSP +/- vancomycin N=62
Sponsor	Total PRSA	N=19	N=9	N=2
	MSSA	7/74 (9.5%)	0/10 (0%)	2/60 (3.3%)
	MRSA	12/45 (26.7%)	9/43 (20.9%)	0/1 (0%)
	No baseline pathogen	1	0	1
FDA	Total PRSA	N=21	N=9	N=2
	MSSA	9/74 (12.2%)	0/10 (0%)	2/60 (3.3%)
	MRSA	12/45 (26.7%)	9/43 (20.9%)	0/1 (0%)
	No baseline pathogen	1	0	1

Duration of Treatment

The following is from the Sponsor's proposed Dosage and Administration section:

(b) (4)

(b) (4)

The Agency analysis does not agree with the results in the label. The Agency analysis of duration is given in Table 2.

Table 2: Duration of Daptomycin Therapy in Patients who Completed Treatment (ITT)

IEAC Final Diagnosis	N	Median	Minimum	Maximum
Left IE	4	14.0	12	42
Complicated RIE	8	28.0	14	42
Uncomplicated RIE	4	14.0	14	28
Complicated bacteremia	37	23.0	11	74
Uncomplicated bacteremia	27	14.0	11	28

(b) (4)

Lack of Confidence Intervals in Clinical Studies Section

In Table 12 of the Clinical Studies section of the proposed label, there are no confidence intervals; rather only response rates by treatment arm are presented. If it is decided to retain Table 12, I recommend that both the treatment difference and the confidence intervals be included as per the Guidance for Industry: Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format.

Entry Diagnosis

In Table 12 of the Clinical Studies section of the proposed label, response rates are presented by treatment arm for Definite or Possible Infective Endocarditis and Not Infective Endocarditis. The pooling of the rates for definite and possible infective endocarditis is not recommended because the diagnosis of possible infective endocarditis has low specificity for endocarditis as was seen in the Phase III trial where only 10/73 (13.7%) patients in the daptomycin arm with a baseline diagnosis of Possible endocarditis had a IEAC Final diagnosis of endocarditis. Similarly, only 5/71 (7.0%) patients in the comparator with a baseline diagnosis of Possible endocarditis had a IEAC Final diagnosis of endocarditis.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Scott Komo, Dr.P.H.
Date:

Concurring Reviewer(s): Thamban Valappil, Ph.D.

cc:
Chris Davi
Fred Sorbello
Charles Cooper
Sumathi Nambiar
Janice Soreth
Scott Komo
Thamban Valappil
Daphne Lin
Mohammed Huque
Lilian Patrician
Robert O'Neil

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Scott Komo
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Thamban Valappil
5/5/2006 02:44:24 PM
BIOMETRICS

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	21572 / SE1-008
Drug Name:	Cubicin® (daptomycin for injection)
Indication(s):	Treatment of *Staphylococcus aureus* bacteremia, including known or suspected endocarditis caused by methicillin-susceptible and methicillin-resistant strains.
Applicant:	Cubist Pharmaceuticals, Inc. 65 Hayden Ave. Lexington, MA 02421
Date(s):	Submitted: 24 September 2005 PDUFA: 24 March 2006
Review Priority:	Priority
Biometrics Division:	Biometric Division IV
Statistical Reviewer:	Scott Komo, Dr.P.H.
Concurring Reviewers:	Daphne Lin, Ph.D.
Medical Division:	Division of Anti-Infective and Ophthalmology Products (HFD-520)
Clinical Team:	Fred Sorbello, M.D. Chuck Cooper, M.D. Sumathi Nambiar, M.D.
Project Manager:	Chris Davi, M.S.

Keywords: active control/non-inferiority, NDA review, class cyclic lipopeptide,

Pop adult

Table of Contents

LIST OF TABLES

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Overall the data in this submission provide substantial evidence that daptomycin is effective in the treatment of *S. aureus* bacteremia. However, I do not feel that they provide substantial evidence that daptomycin is effective in the treatment of *S. aureus* infective endocarditis. The reasons are given below. In addition, it should be noted that there are two possible issues: (1) rising minimum inhibitory concentration associated with persisting or relapsing bacteremia and (2) a trend of decreasing efficacy with increasing renal impairment

The single Phase III trial has weaknesses in both study design and conduct as laid out in §5.1. While it is true that these types of trials are difficult to conduct, the weaknesses in this trial make it difficult to interpret some of the findings. Because of the small sample and heterogeneity of the population, it is difficult to differentiate a true signal of drug effect from random variation. The Sponsor did demonstrate noninferiority in the all-comers analysis to comparator. In the study, the majority (77%) of the patients had bacteremia. The largest experience was in bacteremia patients. The results for both of the bacteremia subgroups (uncomplicated and complicated) were consistent with the results for the all-comers population. In addition, identification of bacteremia patients was not an issue as it was for the infective endocarditis subgroups. For the reasons just stated, I feel the study provided substantial evidence that daptomycin was effective in the treatment of *S. aureus* bacteremia. However, it should be noted that there are two possible issues: (1) rising minimum inhibitory concentration associated with persisting or relapsing bacteremia and (2) a trend of decreasing efficacy with increasing renal impairment.

The performance of daptomycin would need to be examined in the endocarditis subpopulation itself because differences in the pathophysiology of the diagnostic subgroups in the study (i.e. bacteremia, right- and left-sided endocarditis) make it difficult to extrapolate the findings from the all-comers population to the subgroups. I did not feel that the study provided substantial evidence of efficacy because there was both a small number of daptomycin treated endocarditis patients treated (28), divided into three subgroups (uncomplicated RIE, complicated RIE, and LIE) and the response rate was lower than expected from the medical literature especially in left-sided patients where the response was poor (1/9). In addition, the results between the IE subgroups were not consistent. Finally, the assay sensitivity of this study to detect a treatment effect in IE patients is an issue.

1.2 Brief Overview of Clinical Study

The single Phase III trial (Study DAP-01-02) was a multicenter, randomized (1:1), open-label study comparing daptomycin i.v. (6 mg/kg q24h) with conventional intravenous (i.v.) therapy [semi-synthetic penicillin (SSP) 2 g q4h (nafcillin, oxacillin, cloxacillin, or flucloxacillin) or vancomycin 1 g q12h, both with initial synergistic gentamicin] in the treatment of patients with infective endocarditis (IE) or bacteremia due to *Staphylococcus aureus.*

1.3 Statistical Issues and Findings

The study demonstrated the noninferiority of daptomycin to Comparator for the primary endpoint of IEAC outcome at TOC based on a noninferiority margin of 20%. In the all-comers ITT population, noninferiority was demonstrated with the treatment difference in Success rates (Daptomycin – Comparator) of 2.4% and a corresponding 95% CI of (-10.2, 15.1). Similarly, noninferiority was also

demonstrated in the all-comers analysis PP population for the treatment difference in Success rates (Daptomycin – Comparator) of 1.1% and a corresponding 95% CI of (-15.6, 17.8).

Only in the daptomycin-treated subjects whose *staphylococcal* blood culture isolates exhibit increasing minimum inhibitory concentration (MIC) to daptomycin, vancomycin, or both drugs are persisting or relapsing bacteremia (PRSA) infections and deaths observed. Of the 6 daptomycin-treated subjects whose blood culture isolates exhibited increasing MICs to daptomycin or both drugs, all of them developed PRSA and 2 died. In contrast, none of the comparator-treated subjects whose blood culture isolated exhibited increasing MICs to daptomycin, vancomycin, or both drugs developed PRSA and there were no deaths among those patients (see Table 7).

There is a trend where the IEAC response rate at TOC decreases as baseline renal function decreases for the daptomycin group (see Table 9). One might hypothesize that poorer baseline renal function could be a surrogate for a sicker population and this would explain the decrease in outcome rates. However, this trend is not seen for the comparator group as would be expected if baseline renal function were a surrogate for a sicker patient population. Note that this trend was also seen in the initial NDA application for the complicated skin and skin structure indication.

The following were issues identified during the review:

Small study that was not powered to detect differences in diagnostic subgroups

In the original protocol, the study was originally powered to detect a difference in the RIE patients. After several amendments, the study was changed and the study was powered to detect a difference in the all-comers analysis. The Sponsor was told that the breadth of the indication would depend not only on the all-comers analysis but also on the performance as well as numbers in the diagnostic subgroups. The small sample size and the heterogeneity of patients between the diagnostic subgroups made it very difficult to determine the effectiveness of daptomycin. Because the sample size in the subgroups were so small it was difficult to differentiate between a signal of drug effect or random variation.

Potential biases introduced with the open-label design

The Sponsor attempted to address some of the potential issues with their use of an open-label design by using a blinded IEAC assess both outcome and diagnosis. However, the use of the IEAC still did not address the following issues:

- Duration of treatment

  The duration length was to be determined by the Investigator's diagnosis and susceptibility of the *S. aureus* isolate. During the conduct of the study, actual treatment duration was based on Investigator discretion. The open-label nature of the study could affect treatment duration because duration was based on Investigator discretion. They might be either more or less willing to continue patients on the new treatment relative to the comparator.

- Determination of severe adverse events and adverse events

  Investigators, who know what treatment patients receive, determined when either a SAE or an AE occurred without a strict definition of SAE or AE. This increased the potential for bias. An example of how knowledge of treatment received could affect the call of an AE would be if the patient was in the Comparator arm and it was known that the patient received gentamicin, which is known to have renal toxicity issues. Because patients who discontinued due to an AE would

be considered treatment failures, this has the potential to bias the efficacy results even with the blinded adjudication committee.

- Potentially Effective Non-Study Drugs (PENS)

Investigators determined when PENS should be given and could thereby affect outcome even if a blinded adjudication committee since the administration of PENS would be considered Failures.

- Metastatic foci

The definition of the diagnostic subgroups complicated and uncomplicated *S. aureus* RIE involve evidence of extrapulmonary sites of infection, and the definitions of complicated and uncomplicated bacteremia refer to evidence of metastatic foci of infection. It is noteworthy that there is no requirement for all study subjects to have a standardized radiologic imaging evaluation for metastatic extrapulmonary infections. The decision as to the intensity and scope of such a diagnostic evaluation was left solely to the discretion of the individual Investigators. Thus, the magnitude of subjects with evidence of extrapulmonary metastatic sites of infection is likely an underestimate due to the lack of a systematic requirement for such diagnostic imaging for all study participants.

Identification of endocarditis patients

- Cannot determine who is an endocarditis patient at baseline.

A major issue is that one cannot determine who is an endocarditis patient at baseline. This is a problem because of the way that the diagnostic subgroups are determined using post-baseline information. The transesophageal echocardiography (TEE) could occur up to five days from the enrollment in the study.

- Difficulty in determining endocarditis patients
  - Discordance of echocardiographs (central vs. local)

    There was substantial discrepancy between the readings of the local and central echocardiographs. Based on Cohen's kappa [κ=0.25; 2-sided 95% CI=(-0.01, 0.52)], there was relatively poor agreement between the central and local echocardiography results. A fuller description of the discrepancies is given below in Table 10.

Issues with the endocarditis patients

- Small number of IE patients

As shown in Table 5, there are only 53 IE patients in the study. Of those 53, only 28 were treated with daptomycin. Of those 28 patients, only 19 were included in the PP population. The 28 subjects were spread across the three IE subgroups (6 uncomplicated RIE, 13 complicated RIE, and 9 LIE patients).

- Response rates

The response rates in the diagnostic subgroups were lower than the anticipated efficacy rates as described in the medical literature and the performance in the LIE group was especially poor (1/9).

Discordance of Investigator and IEAC Diagnosis

There was discordance in the diagnostic subgroup classification between the IEAC Final Diagnosis and the Investigator Diagnosis for the Complicated and Uncomplicated bacteremia patients. The majority of the discrepancies occurred in the bacteremia patients. For the daptomycin arm, in bacteremia patients, the IEAC classified 23 patients (23 out of 50) as having a more severe diagnosis (Uncomplicated to Complicated Bacteremia) than diagnosed by the Investigator. In contrast the IEAC classified 4 patients (4 out of 41) as having a less severe diagnosis than diagnosed by the Investigator.

For the Comparator arm, in bacteremia patients, the IEAC classified 24 patients (24 out of 44) as having more severe diagnosis (Uncomplicated to Complicated Bacteremia) than diagnosed by the Investigator. In contrast the IEAC classified 8 patients as having a less severe diagnosis than diagnosed by the Investigator.

The IEAC shifted a substantial number of patients in both treatment arms with uncomplicated bacteremia as assessed and managed clinically by the Investigators into a category of more severe disease (complicated bacteremia for which they were not treated). The overall effect of such shifting of patients is to erroneously enhance the success rates in the IEAC final diagnosis subgroups of complicated bacteremia by inclusion of subjects with uncomplicated disease, who had less severe disease, better prognoses, were managed clinically for uncomplicated bacteremia, and responded to treatment regimens appropriate for uncomplicated disease.

Duration of treatment

The median treatment duration for the diagnostic subgroups as defined by the IEAC Final Diagnosis is much shorter than specified in the protocol. This is because the IEAC upgraded the diagnosis group to the more severe category but the treatment duration was based on the Investigator EOT diagnosis.

IEAC outcomes and evaluability

The IEAC did not follow the protocol with respect to the handling of missing EOT or TOC blood cultures. The IEAC used blood culture data outside of the protocol-specified windows in order to determine IEAC outcome. The protocol stated that if either the EOT or TOC blood cultures were missing that the patient should be considered a failure.

The IEAC also changed outcomes from Failure to non-evaluable because they felt that patients were not properly managed. This was based on their "clinical judgment."

Heterogeneity of population

Patients were included in the study based on at least 1 positive blood. However, this included a broad range of severity of illness from uncomplicated bacteremia to LIE. These diagnostic subgroups require varying dosing durations as well as differing prognoses.

Noninferiority margin

The Sponsor used a noninferiority margin of 20%. The Division initially agreed to this margin in a study where the Sponsor assumed 80% response rates for both arms. Later, because of increasing MRSA rates, the Sponsor estimated the response rates to be 65% in both arms. Because it was felt

that the placebo rate was low for this population of patients, it was felt that the size of the margin would not be determined by the smallest effect size that the active drug would be expected to have compared to placebo. Rather the determination of the noninferiority margin was based on the size of an acceptable possible loss in efficacy for which the Division felt that 20% was acceptable. However, in this study the response rates were lower than expected. In the ITT group, the daptomycin success rate was 44.2% vs. 41.7% for the Comparator. In addition, the response rates in the PP population were 54.4% vs. 53.3 for daptomycin vs. Comparator. What was really concerning was the performance in the endocarditis subgroup especially in the LIE group where the rates were 1/9 (11%) for daptomycin vs. 2/9 (22%) for the comparator. Given this low rate, the validity of a 20% noninferiority is questionable and impacts the assay sensitivity of the submission.

Primary focus of infection

The Sponsor did not prospectively collect information on the primary focus of infection. So no standardized procedures were in place to look for or document a primary focus of infection. This has bearing mostly on the bacteremia patients as the existence of a primary focus of infection would have bearing on their dosing duration and also what diagnostic category one would be placed.

2. INTRODUCTION

2.1 Overview

This supplemental NDA contains the review of a single phase III trial (DAP-01-02) submitted to demonstrate the efficacy and safety of Cubicin® (daptomycin) in the treatment of patients with *Staphylococcus aureus* bacteremia, including those with known or suspected endocarditis caused by methicillin-susceptible and methicillin-resistant strains. Daptomycin is currently approved for the treatment of complicated skin and skin structure infections (cSSSI) caused by susceptible strains of the following Gram-positive organisms: *Staphylococcus aureus* (including methicillin-resistant strains [MRSA]), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subsp. *equisimilis* and *Enterococcus faecalis* (vancomycin-susceptible strains only).

Cubicin contains daptomycin, a cyclic lipopeptide antibacterial agent derived from the fermentation of *Streptomyces roseosporus*.

The proposed dose is 6 mg/kg administered as a 30-minute intravenous (i.v.) infusion once per day for a minimum duration of 2 to 6 weeks, depending on the clinical condition.

The single Phase III trial (Study DAP-01-02) was a multicenter, randomized (1:1), open-label study comparing daptomycin i.v. (6 mg/kg q24h) with conventional i.v. therapy [semi-synthetic penicillin (SSP) 2 g q4h (nafcillin, oxacillin, cloxacillin, or flucloxacillin) or vancomycin 1 g q12h, both with initial synergistic gentamicin] in the treatment of patients with infective endocarditis (IE) or bacteremia due to *S. aureus.*

2.2 Data Sources

The submitted data was stored in folder \\CDSESUB1\N21572\S_008\2005-09-22\crt\datasets and \\CDSESUB1\N21572\S_008\2005-10-24\crt\datasets.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Description

The single Phase III trial (Study DAP-01-02) was a multicenter, randomized (1:1), open-label study comparing daptomycin i.v. (6 mg/kg q24h) with conventional i.v. therapy [semi-synthetic penicillin (SSP) 2 g q4h (nafcillin, oxacillin, cloxacillin, or flucloxacillin) or vancomycin 1 g q12h, both with initial synergistic gentamicin] in the treatment of patients with infective endocarditis (IE) or bacteremia due to *S. aureus*

3.1.2 Study Objectives

Primary Objective:

To demonstrate that daptomycin is not inferior to comparator in the treatment of *S. aureus* bacteremia and infective endocarditis (IE) as assessed by the Independent External Adjudication Committee (IEAC) outcome at Test of Cure (TOC) in the Intent-to-Treat (ITT) population.

Reviewer's Comment:
The Sponsor was repeatedly told that the Division considers the analysis of both the ITT and Per Protocol (PP) populations to be co-primary because both analyses have the potential for bias in noninferiority trials. The Sponsor agreed and included the following statement: "The primary endpoint associated with the primary objective was to be evaluated in both the ITT and PP populations to determine the success of the trial."

Secondary Objectives

1. To compare clinical success rates between daptomycin and comparator in the treatment of *S. aureus* bacteremia and IE as assessed by the IEAC outcome at End of Treatment (EOT) in the ITT population.
2. To compare clinical success rates between daptomycin and comparator in the treatment of S. aureus bacteremia and IE as assessed by the IEAC outcome at EOT and TOC in the Per Protocol (PP) population.
3. To compare clinical success rates between daptomycin and comparator in the treatment of S. aureus bacteremia and IE as assessed by the IEAC outcome at EOT for each of the diagnoses defined by the IEAC in the ITT population.
4. To compare clinical success rates between daptomycin and comparator in the treatment of S. aureus bacteremia and IE as assessed by the IEAC outcome at EOT for each of the diagnoses defined by the Investigator in the ITT population.
5. To compare microbiologic eradication rates between daptomycin and comparator.
6. To demonstrate that survival rates are similar between daptomycin and comparator in the ITT population.
7. To evaluate the safety of daptomycin as compared to comparator in the safety population.
8. To assess the pharmacokinetics of daptomycin.

3.1.3 Study Design

Study DAP-01-02 was a multicenter, randomized (1:1), open-label study comparing daptomycin i.v. (6 mg/kg q24h) with conventional i.v. therapy [semi-synthetic penicillin (SSP) 2 g q4h (nafcillin, oxacillin, cloxacillin, or flucloxacillin) or vancomycin 1 g q12h, both with initial synergistic gentamicin] in the treatment of patients with infective endocarditis (IE) or bacteremia due to *S. aureus*. In patients with normal renal function, vancomycin was to be administered 1 g q12h; vancomycin dosing was to be adjusted based on renal function and plasma levels according to the Investigator's standard practice and manufacturer's guidelines. Initial synergistic gentamicin was to be administered to patients randomized to comparator and to LIE patients randomized to daptomycin; dosing of gentamicin also was to be adjusted based on renal function.

Patients may have been randomized and study medication initiated on the basis of a single positive peripheral blood culture for S. aureus. Prior to Amendment 4A, patients whom the Investigator believed to have a high-likelihood of left infective endocarditis (LIE) were excluded. Subsequent to this amendment, patients with LIE were permitted enrollment and were separately randomized to ensure an equal distribution of these patients in the 2 treatment groups. If susceptibility results were unknown at the time of randomization, patients assigned to conventional therapy were to receive vancomycin. If the organism proved to be MSSA, therapy was to be changed to SSP, unless contraindicated by a documented prior history of penicillin or β-lactam drug allergy. Baseline evaluations were to be performed within 2 calendar days prior to first dose and included medical, antibiotic and medication history,

physical examination, blood cultures, chest x-ray, electrocardiogram (ECG), and clinical laboratory tests. All patients were to undergo transesophageal echocardiography (TEE) for the diagnosis of IE by the end of Day 5. During study treatment, daily and weekly assessments were to be performed including blood cultures, physical examinations, vital signs, ECGs, and clinical laboratory tests, as well as appropriate tests to rule-out metastatic foci of infection. An EOT evaluation was to be performed on the day of, or within 3 days after, study treatment completion or early termination.

Patients completing the minimum duration of study treatment who had a successful clinical outcome as assessed by the Investigator (Cured, Improved) at EOT were to have a follow-up evaluation performed 42 days (TOC) after completion of study medication; similarly, patients who completed the minimum duration of study treatment and who had a successful clinical outcome (Cured, Improved) at TOC were to have a follow-up evaluation performed 84 days (Post Study [PS]) after completion of study medication to assess for late relapse. Most patients who completed therapy and had an unsuccessful outcome at EOT (i.e., failure) and all patients who prematurely terminated treatment had a follow-up safety visit conducted 42 days after completion of study medication. Patients prematurely terminating treatment who were continued on alternate therapy were to be followed weekly through completion of their alternate therapy or to a maximum of 12 weeks from discontinuation.

The study treatment regimen was to be based on the patient's diagnosis and the susceptibility of the *S. aureus* isolate. The specific treatment regimens are detailed in Section 9.4.

Baseline diagnosis was based on the Modified Duke Criteria and included the following categories:

- Definite IE.
- Possible IE.
- Not IE.

Diagnosis at EOT was defined as follows and reflected the Investigator's chosen duration of therapy:

- S. aureus LIE
    - Definite or possible IE according to the Modified Duke Criteria[1]; and
    - echocardiographic evidence of involvement or predisposing pathology of the mitral or aortic valve.
- Complicated S. aureus RIE
    - Definite or possible IE according to the Modified Duke Criteria; and
    - echocardiographic evidence indicating no predisposing pathology or active involvement of either the mitral valve or the aortic valve; and
    - any of the following additional criteria:
        - patient was not an IV drug abuser
        - evidence of extrapulmonary sites of infection,
        - serum creatinine ≥2.5 mg/dL,
        - blood cultures yielded MRSA.
- Uncomplicated S. aureus RIE
    - Definite or possible IE according to the Modified Duke Criteria[1]; and
    - echocardiographic evidence indicating no predisposing pathology or active involvement of either the mitral valve or the aortic valve; and

  - history of intravenous drug use; and
  - no evidence of extrapulmonary sites of infection; and
  - serum creatinine <2.5 mg/dL; and
  - blood cultures yielded only MSSA.
- Complicated S. aureus bacteremia
  - Patient did not have IE according to the Modified Duke Criteria; and
  - *S. aureus* was isolated from blood cultures obtained on at least two different calendar days up through Day 5 (one blood culture must have been obtained from a fresh venipuncture site and one blood culture must have been obtained on the calendar day of or the day immediately preceding the first dose of study medication (Day –1 or Day 1); and/or
  - metastatic foci of infection (deep tissue involvement) was present including, for example, septic arthritis, deep tissue abscess, or infection involving prosthetic material including intravascular foreign material not removed by Day 4.
- Uncomplicated S. aureus bacteremia
  - Patient did not have IE according to the Modified Duke Criteria}; and
  - *S. aureus* was isolated from blood culture(s) obtained on a single calendar day within 2 calendar days preceding the first dose of study medication (Day –2 or Day –1); and
  - no metastatic foci of infection was present; and
  - no infection of prosthetic material was present (not including intravascular foreign material removed by Day 4).

The IEAC also determined Entry, EOT and Final Diagnoses using these same definitions. Specifically, they used Modified Duke criteria for Entry Diagnosis and Definitions above for EOT and Final Diagnoses.

Patients with LIE or complicated RIE were to receive inpatient parenteral antibiotic therapy (IPAT) for at least 28 days. If conditions required outpatient parenteral antibiotic therapy (OPAT), these patients were to have had at least 5 days of documented clearance of bacteremia, had a stable ECG, and been free of systemic symptoms prior to switch to OPAT.

Patients with uncomplicated RIE, or complicated or uncomplicated bacteremia without IE were to receive at least 5 days of IPAT. Prior to OPAT, these patients were to have had at least 3 days of documented clearance of bacteremia, had a stable ECG, and been free of systemic symptoms.

3.1.4 Study Endpoints

3.1.4.1 Primary Efficacy Point

IEAC Outcome at the TOC visit in the ITT and PP populations

3.1.4.2 Secondary Efficacy Points

1. IEAC Outcome at End of Treatment (EOT) visit in the ITT population.
2. IEAC Outcome at EOT visit in the Per Protocol (PP) population.
3. IEAC Outcome at EOT visit for each of the diagnoses defined by the IEAC in the ITT population.

4. IEAC Outcome at EOT visit for each of the diagnoses defined by the Investigator in the ITT population.
5. Microbiologic eradication rates
6. Survival rates in the ITT population.

3.1.5 Analysis Populations

3.1.5.1 Intent to Treat Population

The ITT population included all patients who were randomized and received at least one dose of study medication. Patients enrolled prior to Amendment 4A who were considered by the Investigator to have a high likelihood of LIE were to be excluded from the ITT population and all efficacy analyses.

3.1.5.2 Per Protocol Population

The PP population includes those patients in the ITT population with documented adherence to the protocol. Patients in the PP population were to be analyzed according to their randomized treatment group. The following considerations were to be made in a hierarchical manner when determining the composition of the PP population:

1). Patients were to be excluded from the PP population if they violated inclusion/exclusion criteria that could have had an impact on the assessment of efficacy. The following criteria were to be evaluated on a per-patient basis. If it was felt that the extent of the violation would impact the assessment of efficacy, then the patient was to be excluded from the PP population. This evaluation was to be performed by a manual review of by the Sponsor of the clinical relevance of these violations prior to unblinding of the data:

Inclusion Criteria
- ≥18 years of age.
- adequate birth control for females.

Exclusion Criteria
- weight >150 kg or <50 kg.
- investigational drug within 30 days.
- CLcr <30 mL/min.
- ALT >5×ULN.
- AST >5×ULN.
- total bilirubin ≥3.0 mg/dL.
- CD4 lymphocytes <0.200×103/μL.
- absolute neutrophil count <0.500×103/μL.
- absolute neutrophil count <0.500×103/μL anticipated due to chemotherapy.
- considered unlikely to comply.
- pregnant, nursing, or lactating.

- Patients expected to receive HMG CoA Reductase Inhibitors were not to be excluded from the PP population.
- Patients with a polymicrobial bacteremia at Baseline, as determined by the IEAC, were to be excluded from the PP population.
- The inclusion criterion for the blood culture window was to be determined programmatically. All patients assigned a Baseline Infecting Pathogen of S. aureus were to be considered to have met this inclusion criterion.

- Patients in violation of any of the inclusion/exclusion criteria not specifically mentioned above were to be excluded from the PP population.

2). Patients were to be excluded from the PP population if their duration of treatment with study drug was less than 4 days.
3). Patients not excluded from the PP population based on Items 1 and 2 above were to be included in the PP population if, according to the Investigator, they terminated early from study medication because of an adverse event, microbiologic failure, or clinical response of unsatisfactory.
4). With the exception of those patients identified in Item 3 (who are included in the PP population), the remaining patients were to be excluded from the PP population if they satisfied any of the following criteria:

- Did not receive the correct study drug per randomization.
- Received <80% of the minimum expected total daily doses for the duration of study drug treatment as determined by a manual Sponsor review of the data by a non-study physician who was not otherwise involved in the conduct of the study on a by-patient basis prior to unblinding.
- Did not have evaluations performed at major specified time points (Baseline, EOT, and TOC [if required]). At Baseline, these evaluations include the Investigator's Entry Diagnosis and a blood culture; at EOT and TOC these evaluations each included the Investigator's assessment of clinical response and a blood culture.
- Were determined to be "Non-evaluable" per the IEAC.

3.1.5.3 Safety Population

Patients who received at least one dose of i.v. study medication were included in the safety population. The safety population was to be analyzed according to the study drug actually received.

3.1.6 Statistical Methodologies

Efficacy was to be assessed using Outcome as determined by the IEAC. Patients were to be classified as a "Success", "Failure" or "Non-evaluable". Patients were classified as Nonevaluable at TOC if they were classified as "Non-evaluable" at EOT. Patients were determined to be "Failures" at TOC if they were determined to be "Failures" at EOT. The IEAC Outcome at TOC is the primary efficacy endpoint in this study. The efficacy analysis was to be conducted by evaluating the IEAC success rates at TOC by treatment group and calculating the 95% confidence interval (CI) for the difference in success rates (daptomycin minus comparator), with a correction for continuity. Patients designated Failure or Non-evaluable by the IEAC at EOT were given the same designation at TOC. The success rate was defined as the proportion of patients in a population with an IEAC Outcome of "Success" and was calculated from the IEAC Outcome as follows:

ITT Analysis: Success Rate = Success / (Success + Failure + Non-evaluable)
PP Analysis: Success Rate = Success / (Success + Failure)

The overall difference in success rates and 95% CI around the difference in rates between treatment groups (daptomycin minus comparator) based on a normal approximation to the binomial distribution

The non-inferiority test was based upon a comparison of the lower 95% confidence bound relative to a margin of 20%. The null hypothesis is that the lower bound of the CI around the difference in success rates is ≤ -20%; the alternative hypothesis (clinical non-inferiority of daptomycin relative to comparator) is that the difference in success rates is > -20% and the interval contains 0.

Reviewer's Comment:
The 20% noninferiority margin was agreed to by the Division. However, the study results especially in some of the endocarditis subgroups make one question the validity of the 20% margin. Further discussion on this topic can be found in §5.1.

3.1.7 Disposition of Patients

The Disposition of patients is shown in Table 1.

Table 1: Disposition of Patients

Disposition	Daptomycin n (%)	Comparator n (%)	Total n (%)
Randomized	124	122	246
Randomized but not treated	4	6	10
Safety population	120	116	236
Completed therapy	80 (66.7%)	78 (67.2%)	158 (66.9%)
Prematurely discontinued therapy	40 (33.3%)	38 (32.8%)	78 (33.1%)
Reason for discontinuation of study treatment[a]			
Adverse event	20 (16.7%)	21 (18.1%)	41 (17.4%)
Microbiologic failure	9 (7.5%)	3 (2.6%)	12 (5.1%)
Withdrew consent	1 (<1%)	2 (1.7%)	3 (1.3%)
Discontinued therapy against medical advice	1 (<1%)	2 (1.7%)	3 (1.3%)
Unsatisfactory clinical response	1 (<1%)	1 (<1%)	2 (<1%)
Care transferred to another physician	1 (<1%)	1 (<1%)	2 (<1%)
Other	7 (5.8%)	8 (6.9%)	15 (6.4%)
Completed therapy and study	54 (45.0%)	50 (43.1%)	104 (44.1%)
Completed therapy, prematurely discontinued study	26 (21.7%)	28 (24.1%)	54 (22.9%)
Reason for discontinuation of study[b]			
Lost to follow-up	7 (5.8%)	9 (7.8%)	16 (6.8%)
Adverse event	6 (5.0%)	5 (4.3%)	11 (4.7%)
Withdrew consent	1 (<1%)	0	1 (<1%)
Other	12 (10.0%)	14 (12.1%)	26 (11.0%)

Note: percents are based on the number of patients in the Safety population.
[a] Primary reason for discontinuation from treatment as reported by the Investigators; only one reason could be given.
[b] Primary reason for premature discontinuation for patients who completed therapy.
Source: Sponsor's CSR Table 10-1

3.1.8 Demographic and Other Baseline Characteristics

The demographics of the population are summarized in Table 2. The two treatment groups appeared similar with respect to demographic baseline characteristics. Other baseline characteristics and diagnostic subgroup information is provided in Table 3. It is noteworthy that the majority of the patients had *S. aureus* bacteremia , either complicated or uncomplicated).

Table 2: Summary of Demographic Characteristics (ITT)

Characteristic	Daptomycin (N=120)	Comparator (N=115)	Total (N=235)
Age			
N	120	115	235
Mean (SD)	52.6 (17.56)	56.4 (15.59)	54.5 (16.69)
Median	50.5	55.0	53.0
Minimum, Maximum	21, 87	25, 91	21, 91
p-value[a]			0.087
Age, years [N (%)]			
N	120	115	235
<65	90 (75.0%)	78 (67.8%)	168 (71.5%)
≥65	30 (25.0%)	37 (32.2%)	67 (28.5%)
≥75[b]	19 (15.8%)	5 (13.0%)	34 (14.5%)
p-value[c]			0.223
Gender [N (%)]			
N	120	115	235
Female	50 (41.7%)	44 (38.3%)	94 (40.0%)
Male	70 (58.3%)	71 (61.7%)	141 (60.0%)
p-value[c]			0.594
Race [N (%)]			
N	120	115	235
Caucasian	75 (62.5%)	81 (70.4%)	156 (66.4%)
Black	32 (26.7%)	23 (20.0%)	55 (23.4%)
Hispanic	8 (6.7%)	5 (4.3%)	13 (5.5%)
Asian	1 (<1%)	2 (1.7%)	3 (1.3%)
Other	4 (3.3%)	4 (3.5%)	8 (3.4%)
p-value[c]			0.623
BMI, kg/m^2			
N	119	115	234
Mean (SD)	28.20 (6.387)	27.08 (5.462)	27.65 (5.964)
Median	26.90	25.67	26.47
Minimum, Maximum	17.6, 49.7	17.0, 44.0	17.0, 49.7
p-value[a]			0.152
Creatinine clearance, mL/min[d]			
N	120	115	235
Mean (SD)	95.70 (44.815)	85.96 (40.820)	90.93 (43.093)
Median	86.44	83.61	84.56
Minimum, Maximum	28.0, 246.9	17.9, 277.0	17.9, 277.0
p-value[a]			0.083
Creatinine clearance, mL/min[d]			
N	120	115	235
< 30	2 (1.7%)	3 (2.6%)	5 (2.1%)
30 to <50	17 (14.2%)	19 (16.5%)	36 (15.3%)
50 to 80	34 (28.3%)	34 (29.6%)	68 (28.9%)
>80	67 (55.8%)	59 (51.3%)	126 (53.6%)
p-value[c]			0.870

Note: 1 Comparator treated subject was excluded from the ITT population because they were a LIE patient who was randomized prior to amendment 4A
[a] p-value based on 2-sample t-test.
[b] Age category >75 years is a subset of the category >65 years.
[c] p-value based on Chi square test; for age, test is based on the categories of <65 and >65 years.
[d] Calculated by the Sponsor using the Cockcroft-Gault equation.
Source: Sponsor's CSR Table 11-2

Table 3: Patient Characteristics (Safety)

		Daptomycin (N=120)	Combined Comparator (N=116)	Vancomycin (N=53)	SSP+/-Vanco (N=63)
Baseline Demographics	Diabetes Mellitus	44 (36.7)	42 (36.2)	21	21
	Prior Endocarditis	7 (5.8)	6 (5.2)	3	3
	Shock	1 (0.8)	0 (0)	0	0
	SIRS	89 (74)	87 (75.6)	39	48
	HIV (+)	8 (6.7)	1 (0.9)	0	1
	IVDA	25 (20.8)	25 (21.7)	11	14
Study Populations	ITT (n =235)	120 (100)	115 (99.1)	53 (100)	62 (98.4)
	PP (n =139)	79 (65.8)	60 (51.7)	22 (41.5)	38 (60.3)
	Safety Population*	120 (100)	116 (100)	53 (100)	63 (100)
	Non-evaluable by IEAC	9 (7.5)	14 (12)	8 (15)	6 (9.5)
Baseline Pathogen	MSSA	74 (61.7)	71 (61.2)	10	61
	MRSA	45 (37.5)	44 (37.9)	43	1
	No BLP	1 (0.8)	1 (0.9)	0	1
IEAC Entry Dx	Definite IE	17 (14)	20 (17)	7 (13)	13 (21)
	Possible IE	73 (61)	72 (62)	37 (70)	35 (55)
	Not IE	30 (25)	24 (21)	9 (17)	15 (24)
IEAC Final Dx (ITT)	Uncomp Bacteremia	32 (26.7)	29 (25)	15 (28.3)	14 (22.2)
	Uncomp RIE	6 (5.0)	4 (3.4)	0 (0)	4 (6.4)
	Left IE	9 (7.5)	10 (8.6)	4 (7.6)	6 (9.5)
	Comp Bacteremia	60 (50)	61 (52.6)	28 (52.8)	33 (52.4)
	Comp RIE	13 (10.8)	12 (10.3)	6 (11.3)	6 (9.5)
Patient Disposition	Deaths	18 (15)	19 (16)		
	D/C due to an Adverse Event	17 (14)	15 (13)		
	Lost to follow-up	9 (7.5)	10 (8.6)		
	Withdrew consent	2 (1.7)	3 (2.3)		
	Transferred Care	1	0		
	Other	13 (11)	17 (15)		

3.1.9 Efficacy Results

3.1.9.1 Primary Analysis

For the primary endpoint of IEAC outcome at TOC, noninferiority was demonstrated in the all-comers ITT population with a treatment difference in Success rates (Daptomycin – Comparator) of 2.4% with a corresponding 95% CI of (-10.2, 15.1). Similarly, noninferiority was also demonstrated in the all-comers analysis PP population with a treatment difference in Success rates (Daptomycin – Comparator) of 1.1% and a corresponding 95% CI of (-15.6, 17.8).

Table 4: IEAC Outcome at TOC

IEAC Outcome at TOC	ITT Population		PP Population	
	Daptomycin (N=120) n (%)	Comparator (N=115) n (%)	Daptomycin (N=79) n (%)	Comparator (N=60) n (%)
Success	53 (44.2%)	48 (41.7%)	43 (54.4%)	32 (53.3%)
Failure	58 (48.3%)	53 (46.1%)	36 (45.6%)	28 (46.7%)
Non-Evaluable[a]	9 (7.5%)	14 (12.2%)	--	--
Difference in Success Rates (95% CI)				
Overall	2.4% (-10.2, 15.1)		1.1% (-15.6, 17.8)	
Overall with continuity correction	2.4% (-9.4, 15.9)		1.1% (-14.2, 19.3)	

[a] Patients were classified as non-evaluable at TOC if they were classified as non-evaluable at EOT; they are considered Failures in the analysis based on the ITT population.
[b] Difference in success rates and the associated 95% CI around the difference (daptomycin minus comparator) with adjustment for IEAC diagnostic subgroups.

Sponsor CSR Table 11-10

Because of the differences in underlying pathophysiology between primary bacteremia, secondary bacteremia, and IE, it was felt that in addition to the all-comers analysis that the performance of the drug would have to be investigated in the diagnostic subgroups. The necessity of this approach was relayed to the Sponsor in the November 3, 2004 meeting where the following was stated:

> The Agency stated that it would be willing to consider an indication for primary bacteremia due to *S. aureus*, and RIE if there is sufficient data including an adequate experience in complicated *S. aureus* bacteremia. Adequate data would include both sufficient numbers of patients as well as an acceptable success rate. The breadth of the indication will depend upon the quality of the data,

The IEAC Success rates by IEAC Final Diagnosis are presented in Table 5.

The majority (~77%) of the patients had *S. aureus* bacteremia while patients with IE were in the minority (~23%). Despite comparability with respect to outcomes in the all-comers population, the point estimates in all IEAC Final Diagnosis subgroups of complicated and uncomplicated bacteremia and endocarditis were low compared to the anticipated efficacy rates as described in the medical literature. It is unclear why the rates are much lower than expected.

Table 5: IEAC Outcome at TOC by IEAC Final Diagnostic Subgroup

Population IEAC Final Diagnostic Subgroup	Daptomycin n/N (%)	Comparator n/N (%)	Differences in Success Rates (95% CI)
ITT Population			
Overall	53/120 (44.2%)	48/115 (41.7%)	2.4% (-10.2, 15.1)
cRIE + uRIE + cBAC	34/79 (43.0%)	30/77 (39.0%)	4.1% (-11.3, 19.5)
RIE (cRIE + uRIE)	8/19 (42.1%)	7/16 (43.8%)	-1.6% (-34.6, 31.3)
cRIE	5/13 (38.5%)	6/12 (50.0%)	-11.5% (-50.3, 27.2)
uRIE	3/6 (50.0%)	1/4 (25.0%)	25.0% (-33.3, 83.3)
cBAC	26/60 (43.3%)	23/61 (37.7%)	5.6% (-11.8, 23.1)
uBAC	18/32 (56.3%)	16/29 (55.2%)	1.1% (-23.9, 26.0)
LIE	1/9 (11.1%)	2/9 (22.2%)	-11.1% (-45.2, 22.9)
PP Population			
Overall	43/79 (54.4%)	32/60 (53.3%)	1.1% (-15.6, 17.8)
cRIE + uRIE + cBAC	25/51 (49.0%)	18/37 (48.6%)	0.4% (-20.8, 21.5)
RIE (cRIE + uRIE)	6/12 (50.0%)	4/8 (50.0%)	0.0% (-44.7, 44.7)
cRIE	5/10 (50.0%)	4/6 (66.7%)	-16.7% (-65.5, 32.2)
uRIE	1/2 (50.0%)	0/2 (0.0%)	50.0% (-19.3, 119.3)
cBAC	19/39 (48.7%)	14/29 (48.3%)	0.4% (-23.6, 24.5)
uBAC	17/21 (81.0%)	12/17 (70.6%)	10.4% (-17.0, 37.8)
LIE	1/7 (14.3%)	2/6 (33.3%)	-19.0% (-64.8, 26.7)

Sponsor CSR Table 11-12

FDA Readjudication

Fred Sorbello, the reviewing Medical Officer, readjudicated the both the outcomes at EOT and TOC as well as the evaluability. He used the following guidelines:

1. Use of a Potentially Effective Non-Study (PENS) agent for ≥4 days was assessed as a failure at TOC
2. Subjects with TOC blood cultures but missing EOT blood cultures could have the EOT assessment imputed based on the TOC culture results.
3. Subjects with missing TOC blood cultures were considered failures at TOC even if they had a Post-study blood culture. The TOC window was considered to extend up to Day 60P. Blood cultures obtained on Days 61P and later were considered Post-study Blood cultures.
4. Subjects treated with <3 days of study med were considered non-evaluable

The results of the FDA Reanalysis are given below. After the readjudication, success rates were slightly lower for both groups; however, the success rates were similar between groups (daptomycin: 38.3%; Comparator: 38.3%) with a treatment difference (daptomycin – comparator) of 0% and the corresponding 95% CI of (-12.4, 12.5). The lower bound of the 95% CI was similar to the Sponsor's result presented in Table 6.

Table 6: FDA Reanalysis (ITT Population)

ITT (all-comers)	Daptomycin		Comparator	
	Sponsor	FDA	Sponsor	FDA
Success	53/120 (44.2%)	46/120 (38.3)	48/115 (41.7%)	44/115 (38.3)
Failure	58/120 (48.3%)	68/120 (56.7%)	53/115 (46%)	57/115 (49.6%)
Non-evaluable	9/120 (7.5%)	6/120 (5%)	14/115 (12.2%)	14/115 (12.2%)

Note: Difference (D-C) and 2-sided 95% for FDA analysis: 0.1% (-12.4, 12.5)

Increasing MIC's while on study and persisting or relapsing bacteremia

In Table 7 it can be seen that

- Among 96 comparator-treated subjects for whom full MIC data was available, a total of 4 subjects had Staphylococcal isolates that exhibited increasing MICs to vancomycin or daptomycin: 3 subjects had a highest vancomycin MIC of 2 ug/ml and one subject had increasing MICs to both drugs. Of the 4 patients, there were 3 successes and 1 failure at TOC. Out of those 4 subjects, 2 had MSSA at baseline with both subjects being TOC successes. The other two subjects had MRSA at baseline with 1 subject a TOC Success and the other a TOC failure. There were not subjects with PRSA infections or who died.
- Among 113 daptomycin-treated subjects for whom full MIC data was available, a total of 9 subjects had *Staphylococcal* isolates that exhibited increasing MICs to vancomycin or daptomycin: Three (3) exhibited increasing MICs to vancomycin only, 4 had isolates with increasing MICs only to daptomycin, and 2 subjects had isolates with increasing MICs to both drugs. Of the 9 patients, there was only 1 success and 8 failures at TOC (including all subjects whose isolates exhibited increasing MICs to daptomycin while receiving daptomycin therapy). In these 9 patients, 6 had MRSA at baseline and 3 had MSSA at baseline. In the 6 MRSA subjects, all were failures at TOC, 5 had PRSA infections, and 1 subject died. In the 3 MSSA subjects, there were 2 successes and 1 failure at TOC; and 1 subject had a PRSA infection.
- Only among daptomycin-treated subjects whose *staphylococcal* blood culture isolates exhibit increasing MICs to daptomycin, vancomycin, or both drugs do we observe PRSA infections and deaths. Of the 6 daptomycin-treated subjects whose blood culture isolates exhibited increasing MICs to daptomycin or both drugs, all of them developed PRSA and 2 died. In contrast, none of the comparator-treated subjects whose blood culture isolated exhibited increasing MICs to daptomycin, vancomycin, or both drugs developed PRSA and there were no deaths among those patients.

Table 7: Increasing MIC's during the study of Daptomycin and Vancomycin associated with PRSA and Death

		n	IEAC TOC Success	PRSA	Deaths
Comparator N=96	Vancomycin MIC=2	3	2	0	0
	Daptomycin MIC ≥2	0	0	0	0
	Increased MICs to both drugs	1	1	0	0
	Total Subjects	4	3	0	0
Daptomycin N=113	Vancomycin MIC=2	3	1	0	1
	Daptomycin MIC ≥2	4	0	4	1
	Increased MICs to both drugs	2	0	2	1
	Total Subjects	9	1	6	3

For more efficacy results, please see the clinical review of Fred Sorbello.

3.2 Evaluation of Safety

Please refer to the clinical review of the reviewing Medical Officer, Dr. Charles Cooper.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The response rates by subgroups are presented in Table 8. There is a decrease in IEAC outcome rates as age increases. This occurs in both treatment arms in the ITT population but is much more pronounced in the daptomycin arm. In the PP population, this trend again occurs in the daptomycin arm but not in the comparator arm.

The IEAC outcome rates were relatively similar being ethnic subgroups except that there appeared to be a decrease in response rate with increasing age. However, this trend was similar in both treatment arms. In addition, the Black subgroup had much higher response rates than the other subgroups in the daptomycin arm.

Table 8: IEAC TOC Outcome by Subgroups

Demographic group	Success (ITT Population)			Success (PP Population)		
	Daptomycin (D) (N=120) n (%)	Comparator (C) (N=115) n/N (%)	Difference (D-C) (95% CI)	Daptomycin (D) (N=79) n/N (%)	Comparator (C) (N=60) n/N (%)	Difference (D-C) (95% CI)
All patients	53 (44.2%)	48 (41.7%)	2.4 (-10.2, 15.1)	43 (54.4%)	32 (53.3%)	1.1% (-15.6, 17.8)
Age						
< 65 years	47/90 (52.2%)	35/78 (44.9%)	7.4% (-7.8, 22.5)	38/61 (62.3%)	21/38 (55.3%)	7.0% (-12.9, 27.0)
≥ 65 years	6/30 (20.0%)	13/37 (35.1%)	-15.1% (-36.1, 5.9)	5/18 (27.8%)	11/22 (50.0%)	-22 2% (-51.6, 7 2)
≥ 75 years	2/19 (10 5%)	5/15 (33.3%)	-22.8% (-50.4, 4.8)	2/10 (20.0%)	4/7 (57.1%)	-37.1% (-81.4, 7.1)
Gender						
Male	35/70 (50.0%)	30/71 (42.3%)	7.7% (-8.7, 24.2)	27/46 (58.7%)	21/40 (52.5%)	6.2% (-14.8, 27.2)
Female	18/50 (36.0%)	18/44 (40.9%)	-4.9% (-24.6, 14.8)	16/33 (48.5%)	11/20 (55.0%)	-6.5% (-34.2, 21 2)
Race						
Caucasian	27/75 (36.0%)	35/81 (43.2%)	-7.2 (-22.5, 8.1)	21/48 (43.8%)	23/44 (52.3%)	-8.5% (-28.9, 11.8)
Black	21/32 (65.6%)	10/23 (43.5%)	22.1 (-4.0, 48.2)	17/21 (81.0%)	6/10 (60.0%)	21.0% (-13.7, 55.7)
Other	5/13 (38 5%)	3/11 (27.3%)	11.2 (-26.1, 48.5)	5/10 (50.0%)	3/6 (50.0%)	0.0% (-50.6, 50.6)

Source: Sponsor's CSR Tables 14.2.3.6.1, 14.2.3.6.3, 14.2.3.6.5, 14.2.3.6.2, 14.2.3.6.4, and 14.2.3.6.6

4.2 Other Special/Subgroup Populations

4.2.1 Renal Function

In Table 9, there appears to be a trend where the IEAC TOC response rate decreases with increasing renal impairment for the daptomycin group. One might hypothesize that poorer baseline renal function could be a surrogate for a sicker population and this would explain the decrease in response rates. However, this trend is not seen for the comparator group as would be expected if baseline renal function were a surrogate for a sicker patient population. Note that this trend was also seen in the initial NDA application for the complicated skin and skin structure indication.

Table 9: IEAC TOC Outcome by Renal Function (ITT Population)

Subgroup	Daptomycin (D) n/N (%)	Comparator (C) n/N (%)	Difference (D-C) (95% CI)
CLcr >80 mL/min	38/67 (56.7%)	25/59 (42.4%)	14.3 (-3.0, 31.7)
CLcr ≤80 mL/min	15/53 (28.3%)	23/56 (41.1%)	-12.8 (-30.5, 4.9)
50 to 80 mL/min	13/34 (38.2%)	14/34 (41.2%)	-2.9 (-26.2, 20.3)
30 to <50 mL/min	2/17 (11.8%)	9/19 (47.4%)	-35.6 (-62.8, -8.4)
<30 mL/min	0/2	0/3	--

Source: Sponsor's CSR Tables 14.2.1.4.1, 14.2.1.4.2

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The following were issues identified during the review:

Small study that was not powered to detect differences in diagnostic subgroups

In the original protocol, the study was originally powered to detect a difference in the RIE patients. After several amendments, the study was changed and the study was powered to detect a difference in the all-comers analysis. The Sponsor was told that the breadth of the indication would depend not only on the all-comers analysis but also on the performance as well as numbers in the diagnostic subgroups. The small sample size and the heterogeneity of patients between the diagnostic subgroups made it very difficult to determine the effectiveness of daptomycin. Because the sample size in the subgroups were so small it was difficult to differentiate between a signal of drug effect or random variation.

This can be seen in the history given below:

In the original protocol, the study was originally powered to detect a difference in the RIE using the sample size assumptions:

- 80% clinical success rate for subjects with IE given comparator therapy;
- 80% clinical success rate for subjects with IE given daptomycin;
- significance level of 0.025 to test the null hypothesis.

With 63 clinically evaluable patients in each treatment group, there is 80% power. Among ITT subjects, the frequency of IE is estimated to be 75% and the Clinical Evaluability rate is estimated to be 75%, giving a target ITT population of 224 patients.

In a subsequent amendment, the sample size was increased to 420 ITT patients because the Sponsor changed the expected frequency of RIE from 75% to 40%.

Finally in Amendment 4A (4/1/04), the sample size changed from being powered for RIE patients to the all-comers approach. The Sponsor proposed to use the following sample size calculation:

Recent reports indicate that with the increasing MRSA rates, clinical success rates are expected to be much lower, approximately 65% in both test and reference populations. Thus, based on the same assumptions for alpha (0.025, one-sided) and power (80%), and assuming 65% efficacy in test and reference groups, a sample size of 90 subjects (minimum) per treatment group would be required in the overall ITT population.

When asked by the Sponsor at 11/3/2004 meeting the Sponsor asked the following questions and received the following responses:

Does the Agency agree with Cubist's decision to stop clinical study DAP-IE-01-02 without accruing 20 left-sided IE patients?

The Agency informed the Sponsor that it is the Sponsor's choice as to when to discontinue a given study. If the Sponsor chooses to discontinue the study at the present time (allowing time for adequate follow-up of all currently enrolled patients, the acquired data may be able to support an indication for *S. aureus* bacteremia with appropriate labeling to indicate which forms of diseases (e.g. left and right sided endocarditis) had and had not been adequately studied. There was insufficient experience in patients with LIE to assess drug efficacy for the potential indication of LIE. The Agency encouraged the Sponsor to consider a future study for patients with left sided endocarditis. The Agency cautioned however, that discontinuing the study at this point carries with the risk that the study will be underpowered. The Sponsor acknowledged this, and informed the Agency that they have completed enrollment in the study, and will stop any future enrollment. The Sponsor will be announcing this in a press release.

Does the Agency agree that study DAP-IE-01-02 (if positive) would be sufficient to support an indication for CUBICIN for the treatment of S. aureus bacteremia and endocarditis (if supported by the data)?

The Agency stated that it would be preferable to see an adequate experience for left-sided as well as right-sided endocarditis within the same trial, but recognized the dissimilarities in patient demographics, and the related challenges of enrollment, particularly where LIE patients are concerned. The Agency stated that it would be willing to consider an indication for primary bacteremia due to *S. aureus*, and RIE if there is sufficient data including an adequate experience in complicated *S. aureus* bacteremia. Adequate data would include both sufficient numbers of patients as well as an acceptable success rate. The breadth of the indication will depend upon the quality of the data.

Both parties agreed that pursuit of a left sided indication would not be feasible with the current study design, but could be considered at a later time using a stepwise approach. In addition, it was agreed that labeling will have to reflect any limitations in the data (i.e., lack of study experience with complicated bacteremia, RIE and/or LIE) in the data.

Potential biases introduced with the open-label design

The Sponsor attempted to address some of the potential issues with their use of an open-label design by using a blinded IEAC assess both outcome and diagnosis. However, the use of the IEAC still did not address the following issues:

- Duration of treatment

The duration length was to be determined by the Investigator's diagnosis and susceptibility of the *S. aureus* isolate. During the conduct of the study, actual treatment duration was based on Investigator discretion. The open-label nature of the study could affect treatment duration because duration was based on Investigator discretion. They might be either more or less willing to continue patients on the new treatment relative to the comparator.

- Determination of severe adverse events and adverse events

Investigators, who know what treatment patients receive, determined when either a SAE or an AE occurred without a strict definition of SAE or AE. This increased the potential for bias. An example of how knowledge of treatment received could affect the call of an AE would be if the patient was in the Comparator arm and it was known that the patient received

gentamicin, which is known to have renal toxicity issues. Because patients who discontinued due to an AE would be considered treatment failures, this has the potential to bias the efficacy results even with the blinded adjudication committee.

- Potentially Effective Non-Study Drugs (PENS)

Investigators determined when PENS should be given and could thereby affect outcome even if a blinded adjudication committee since the administration of PENS would be considered Failures.

- Metastatic foci

The definition of the diagnostic subgroups complicated and uncomplicated *S. aureus* RIE involve evidence of extrapulmonary sites of infection, and the definitions of complicated and uncomplicated bacteremia refer to evidence of metastatic foci of infection. It is noteworthy that there is no requirement for all study subjects to have a standardized radiologic imaging evaluation for metastatic extrapulmonary infections. The decision as to the intensity and scope of such a diagnostic evaluation was left solely to the discretion of the individual Investigators. Thus, the magnitude of subjects with evidence of extrapulmonary metastatic sites of infection is likely an underestimate due to the lack of a systematic requirement for such diagnostic imaging for all study participants.

Identification of endocarditis patients

- Cannot determine who is an endocarditis patient at baseline.

A major issue is that one cannot determine who is an endocarditis patient at baseline. This is a problem because of the way that the diagnostic subgroups are determined using post-baseline information. The transesophageal echocardiography (TEE) could occur up to five days from the enrollment in the study.

- Difficulty in determining endocarditis patients
    - Discordance of echocardiographs (central vs. local)

    There was substantial discrepancy between the readings of the local and central echocardiographs. Based on Cohen's kappa [κ=0.25; 2-sided 95% CI=(-0.01, 0.52)], there was relatively poor agreement between the central and local echocardiography results. A fuller description of the discrepancies is given below in Table 10.

Table 10: Discordance of Local and Central echocardiographs in IE subjects (ITT)

Central echo	Local echo		Total
Frequency	**Positive**	**Negative**	
Positive	24	10	34
Negative	8	10	18
Total	32	20	52

Note: 1 subject did not have an echocardiograph

Issues with the endocarditis patients

- Small number of IE patients

As shown in Table 5, there are only 53 IE patients in the study. Of those 53, only 28 were treated with daptomycin. Of those 28 patients, only 19 were included in the PP population. The 28 subjects were spread across the three IE subgroups (6 uncomplicated RIE, 13 complicated RIE, and 9 LIE patients).

- Response rates

The response rates in the diagnostic subgroups were lower than the anticipated efficacy rates as described in the medical literature and the performance in the LIE group was especially poor (1/9).

Discordance of Investigator and IEAC Diagnosis

There was discordance in the diagnostic subgroup classification between the IEAC Final Diagnosis and the Investigator Diagnosis for the Complicated and Uncomplicated bacteremia patients. The majority of the discrepancies occurred in the bacteremia patients. For the daptomycin arm, in bacteremia patients, the IEAC classified 23 patients (23 out of 50) as having a more severe diagnosis (Uncomplicated to Complicated Bacteremia) than diagnosed by the Investigator. In contrast the IEAC classified 4 patients (4 out of 41) as having a less severe diagnosis than diagnosed by the Investigator.

For the Comparator arm, in bacteremia patients, the IEAC classified 24 patients (24 out of 44) as having more severe diagnosis (Uncomplicated to Complicated Bacteremia) than diagnosed by the Investigator. In contrast the IEAC classified 8 patients as having a less severe diagnosis than diagnosed by the Investigator.

The IEAC shifted a substantial number of patients in both treatment arms with uncomplicated bacteremia as assessed and managed clinically by the Investigators into a category of more severe disease (complicated bacteremia for which they were not treated). The overall effect of such shifting of patients is to erroneously enhance the success rates in the IEAC final diagnosis subgroups of complicated bacteremia by inclusion of subjects with uncomplicated disease, who had less severe disease, better prognoses, were managed clinically for uncomplicated bacteremia, and responded to treatment regimens appropriate for uncomplicated disease.

Duration of treatment

The median treatment duration for the diagnostic subgroups as defined by the IEAC Final Diagnosis is much shorter than specified in the protocol. This is because the IEAC upgraded the diagnosis group to the more severe category but the treatment duration was based on the Investigator EOT diagnosis.

IEAC outcomes and evaluability

The IEAC did not follow the protocol with respect to the handling of missing EOT or TOC blood cultures. The IEAC used blood culture data outside of the protocol-specified windows in order to determine IEAC outcome. The protocol stated that if either the EOT or TOC blood cultures were missing that the patient should be considered a failure.

The IEAC also changed outcomes from Failure to non-evaluable because they felt that patients were not properly managed. This was based on their "clinical judgment."

Heterogeneity of population

Patients were included in the study based on at least 1 positive blood. However, this included a broad range of severity of illness from uncomplicated bacteremia to LIE. These diagnostic subgroups require varying dosing durations as well as differing prognoses.

Noninferiority margin

The Sponsor used a noninferiority margin of 20%. The Division initially agreed to this margin in a study where the Sponsor assumed 80% response rates for both arms. Later, because of increasing MRSA rates, the Sponsor estimated the response rates to be 65% in both arms. Because it was felt that the placebo rate was low for this population of patients, it was felt that the size of the margin would not be determined by the smallest effect size that the active drug would be expected to have compared to placebo. Rather the determination of the noninferiority margin was based on the size of an acceptable possible loss in efficacy for which the Division felt that 20% was acceptable. However, in this study the response rates were lower than expected. In the ITT group, the daptomycin success rates was 44.2% vs. 41.7% for the Comparator. In addition, the response rates in the PP population were 54.4% vs. 53.3 for daptomycin vs. Comparator. What was really concerning was the performance in the endocarditis subgroup especially in the LIE group where the rates were 1/9 (11%) for daptomycin vs. 2/9 (22%) for the comparator. Given this low rate, the validity of a 20% noninferiority is questionable and impacts the assay sensitivity of the submission.

Primary focus of infection

The Sponsor did not prospectively collect information on the primary focus of infection. So no standardized procedures were in place to look for or document a primary focus of infection. This has bearing mostly on the bacteremia patients as the existence of a primary focus of infection would have bearing on their dosing duration and also what diagnostic category one would be placed.

5.2 Conclusions and Recommendations

Overall the data in this submission provide substantial evidence that daptomycin is effective in the treatment of *S. aureus* bacteremia. However, I do not feel that it provides substantial evidence that daptomycin is effective in the treatment of *S. aureus* infective endocarditis. The reasons are given below. However, it should be noted that there are two possible issues: (1) rising minimum inhibitory concentration associated with persisting or relapsing bacteremia and (2) a trend of decreasing efficacy with increasing renal impairment.

The single Phase III trial has weaknesses in both study design and conduct as laid out in §5.1. While it is true that these types of trials are difficult to conduct, the weaknesses in this trial make it difficult to interpret some of the findings. Because of the small sample and heterogeneity of the population, it is difficult to differentiate a true signal of drug effect from random variation. The Sponsor did demonstrate noninferiority in the all-comers analysis to comparator. In the study, the majority (77%) of the patients had bacteremia. The largest experience was in bacteremia patients. The results for both of the bacteremia subgroups

(uncomplicated and complicated) were consistent with the results for the all-comers population. In addition, identification of bacteremia patients was not an issue as it was for the infective endocarditis subgroups. For the reasons just stated, I feel the study provided substantial evidence that daptomycin was effective in the treatment of *S. aureus* bacteremia. However, it should be noted that there are two possible issues: (1) rising minimum inhibitory concentration associated with persisting or relapsing bacteremia and (2) a trend of decreasing efficacy with increasing renal impairment.

The performance of daptomycin would need to be examined in the endocarditis subpopulation itself because differences in the pathophysiology of the diagnostic subgroups in the study (i.e. bacteremia, right- and left-sided endocarditis) make it difficult to extrapolate the findings from the all-comers population to the subgroups. I did not feel that the study provided substantial evidence of efficacy because there was both a small number of daptomycin treated endocarditis patients treated (28), divided into three subgroups (uncomplicated RIE, complicated RIE, and LIE) and the response rate was lower than expected from the medical literature especially in left-sided patients where the response was poor (1/9). In addition, the results between the IE subgroups were not consistent. Finally, the assay sensitivity of this study to detect a treatment effect in IE patients is an issue.

Appendix

References

Fleiss JF, Levin B, Paik MC (2003). Statistical Methods for Rates and Proportions, 3rd edition. New Jersey: Wiley-Interscience, . 604.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Scott Komo, Dr.P.H.
Date:

Concurring Reviewer(s): Daphne Lin, Ph.D.

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Scott Komo
3/24/2006 03:19:44 PM
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Daphne Lin
3/24/2006 03:31:05 PM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021572Orig1s008

CLINICAL MICROBIOLOGY/VIROLOGY REVIEW(S)

Division of Anti-Infective and Ophthalmology Products
Clinical Microbiological Review # 3

NDA: 21-572 SN008 **Date Completed: March 14, 2006**

Applicant:
Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
Lexington, MA 02421
781-860-8660

Therapeutic Type: Daptomycin for injection

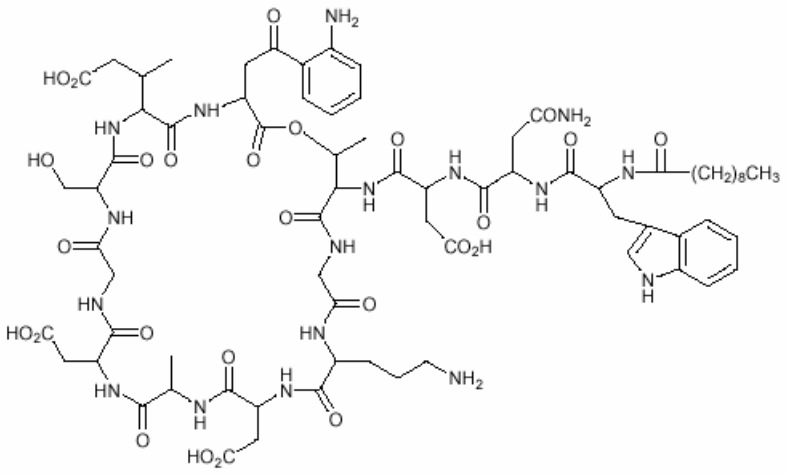
Submission Reviewed: Efficacy supplement NDA 21-572 SN008

Providing for: treatment of bacteremia and endocarditis caused by *Staphylococcus aureus*

Product Name:
Proprietary: Cubicin ®
Non-proprietary: Daptomycin

Chemical Name: *N*-decanoyl-L-tryptophyl-D-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.

Structural Formula:



Molecular Formula: $C_{72}H_{101}N_{17}O_{26}$; the molecular weight is 1620.67.

Dosage Form and Route of Administration: Six mg/kg administered over a 30-minute period by intravenous infusion in 0.9% sodium chloride injection, USP once every 24 hours for 7-14 days.

Pharmacological Category: Anti-Infective

Dispensed: Rx X OTC

Initial Submission Dates:
Received by CDER: September 22, 2005
Received by Reviewer: September 30, 2005
Review Completed: March 14, 2006

Related Documents: IND 57,693, NDA 21-572

Remarks:
The Applicant submits an efficacy supplement to NDA 21-572 (the "sNDA") in accordance with 21 CFR 314.70. The purpose of this sNDA is to expand the labeled indication for Cubicin® (daptomycin for injection) to include the treatment of *Staphylococcus aureus* bacteremia (SAB), including those with known or suspected endocarditis (SAIE) caused by methicillin-susceptible and methicillin-resistant (MRSA) strains. The clinical study at the core of the sNDA (DAP-IE-01-02) was the result of collaborations between the Applicant and the Agency that began in 2001 with protocol development. As discussed at the July 20, 2005, meeting with the Division, this study of CUBICIN at 6 mg/kg once daily met its primary end points of non-inferiority in the intent-to-treat (ITT) and per protocol (PP) populations.

The Applicant is requesting priority review of this supplemental NDA, based on the clinical outcomes described in the submission and the lack of therapeutic options for *Staphylococcus aureus* (*S. aureus*) bacteremia and endocarditis. The seriousness of the condition and the limitations of existing therapies were important findings of Study DAP- IE-01-02. Almost 40% of patients were infected with MRSA, and the overall mortality rate was approximately 15%. The study also demonstrated that CUBICIN 6 mg/kg as monotherapy (once daily IV) was as effective as standard of care (semisynthetic penicillin or vancomycin 2 to 6 times daily IV with initial synergistic gentamicin). Non- inferiority criteria were met in both the ITT and PP populations, and CUBICIN demonstrated efficacy irrespective of methicillin susceptibility. In MRSA infections, the response rates for C°ICW were higher than those observed in the comparator group. CUBICIN was well tolerated at 6 mg/kg administered IV once daily in patients with *S. aureus* bacteremia and endocarditis, and the safety profile was similar to that at the currently approved dose of 4 mg/kg once daily.

Prior Agreements. The Applicant and the Agency had many meetings prior to, during, and after Study DAP-IE-Ol- 02, and key agreements are noted here. The initial version of the DAF-IE-01-02 study protocol was submitted to FDA on November 9, 2001. Early discussions with the Agency focused on issues of study design and endpoints (meeting date January 16, 2002), resulting in the choice of an open-label design, a margin of non-inferiority of 20%, and the use of a Data Monitoring Committee (DMC) to ensure patient safety.

At a meeting on February 11, 2005, the statistical analysis plan for Study DAP-IE-01-02 was discussed, and it was agreed that outcome as determined by an Independent Expert Adjudication Committee (IEAC) at the test of cure (TOC) visit for the ITT and PP populations would be co-primary endpoints for the study. The composition of the ITT population was also agreed to at this meeting.

In conjunction with the Applicant's compilation of the sNDA, the Agency made several requests on June 22 and July 6, 2005, and in a face-to-face meeting on July 20, 2005. The

Applicant response to requests for analyses, datasets, and listings are included in the sNDA submission. At the July 20, 2005, meeting, the Agency requested the submission of case report forms (CRFs) for every patient in the study, and Cubist agreed to provide CRFs not included in the sNDA (as required) in a minor amendment to the sNDA to be submitted within 30 days of the sNDA.

At a meeting on September 8, 2005, Cubist agreed to provide additional information to ease the review of the sNDA and to clarify specific issues. It was agreed that the submission of supplementary data would be part of the minor amendment to the sNDA to be submitted within 30 days of the sNDA.

Recommendations/Conclusions:
Based on the lack of efficacy in endocarditis patients and inadequate number of endocarditis patients, ***this Reviewer recommends that daptomycin not be approved for the treatment of endocarditis.***

Based on the efficacy of daptomycin in bacteremia patients and adequate number of bacteremia patients, ***this Reviewer recommends that daptomycin be approved for the treatment of bacteremia contingent upon the following:***

1. Acceptance of the changes made by this Reviewer to the Microbiology Portion of the Package Insert shown below.
2. The Applicant agrees to a Phase 4 commitment to monitor daptomycin MICs from bacteremia/infective endocarditis patients infected with *S. aureus*. This surveillance study should be performed over the two years following approval of this Application. Results should be conveyed to the Agency on an annual basis.

MICROBIOLOGY PORTION OF THE PACKAGE INSERT

Note: This Reviewer indicates recommended changes to the Microbiology portion of the Package Insert as follows. Deletions are in ~~red and strikethrough font~~; additions are in blue and underlined font.

(b) (4)

4 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

EXECUTIVE SUMMARY

Daptomycin is an antibacterial agent of a new class of antibiotics, the cyclic lipopeptides. Daptomycin is a natural product which has clinical utility in the treatment of infections caused by aerobic Gram-positive bacteria. The *in vitro* spectrum of activity of daptomycin encompasses most clinically relevant Gram-positive pathogenic bacteria. Daptomycin retains potency against antibiotic resistant Gram-positive bacteria including isolates resistant to methicillin, vancomycin, and linezolid.

CUBICIN® (daptomycin for injection) is an antibacterial agent approved in the United States for the treatment of complicated skin and skin structure infections (cSSSI) caused by susceptible strains of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subs. *equisimilis*, and *Enterococcus faecalis* (vancomycin-susceptible strains only).

The Applicant provides this supplemental NDA to support an indication for the treatment of patients with *Staphylococcus aureus* bacteremia, including those with known or suspected endocarditis caused by methicillin-susceptible and methicillin-resistant strains. The proposed dose is 6 mg/kg administered as a 30-minute intravenous (IV) infusion once per day for a minimum duration of two to six weeks, depending on the clinical condition.

The mechanism of action of daptomycin is distinct from any other antibiotic. Daptomycin binds to bacterial membranes and causes a rapid depolarization of membrane potential. The loss of membrane potential leads to inhibition of protein, DNA, and RNA synthesis, which results in bacterial cell death.

Daptomycin exhibits rapid, concentration-dependent bactericidal activity against Gram-positive organisms *in vitro*. This has been demonstrated both by time-kill curves and by MBC/MIC ratios using broth dilution methodology.

In vitro studies have demonstrated additive or indifferent interactions of daptomycin with other antibiotics. Antagonism, as determined by kill curve studies, has not been observed. *In vitro* synergistic interactions occurred with aminoglycosides and β-lactam antibiotics against some isolates of staphylococci and enterococci, including some MRSA isolates.

Increasing daptomycin MICs have been documented both *in vitro* and *in vivo* and were also seen during the course of this clinical trial. Currently, *S. aureus* isolates with an MIC ≤ 1 μg/ml are considered susceptible to daptomycin; *S. aureus* isolates with an MIC > 1 μg/ml are considered non-susceptible to daptomycin. Breakpoints for intermediate and resistant isolates have yet to be established. For purposes of the discussion below, *S. aureus* isolates with a MIC >1 μg/ml are considered resistant.

The primary question that arises is whether the increasing MICs raise concern regarding the use of daptomycin for the treatment of bacteremia/infective endocarditis. The answer to this question may be addressed by examining results from the different microbiology components of this submission.

Does in vitro evidence suggest that there is potential for daptomycin resistance to occur?

The Applicant has noted that spontaneous mutations leading to daptomycin resistance is rare in Gram-positive bacteria and that there are no known transferable elements that confer daptomycin resistance. In a recently published study, no spontaneously resistant mutants were obtained from any clinical or laboratory isolates after a single passage in daptomycin. However, stable resistant organisms have been isolated after multiple (n=20) passages in liquid media containing progressively increasing concentrations of daptomycin (initiated from sub-inhibitory MIC levels) and following chemical mutagenesis [94]. Daptomycin MICs for *S. aureus* isolates were 16-fold higher than the parental isolates. In another published study, daptomycin resistant mutants were not found to be resistant to vancomycin or ampicillin as would be expected because of the differences in their mechanisms of action [95]. However, cross resistance to nisin, an antimicrobial similar in structure to daptomycin was found.

Do data from animal models suggest there is potential for daptomycin resistance to occur?

The Sponsor has presented data from a number of animal models (rabbits, rats, and mice) that include bacteremia, endocarditis, fibrin clot, hematogenous pneumonia, and experimental meningitis. Daptomycin efficacy was measured by either a $\log_{10}$ reduction in bacterial burden in the target tissue or by increased survival. The daptomycin dose used produced $AUC_{0\text{-}24}$ exposures achievable at the human clinical dosage of 6 mg/kg q24h.

In published studies, daptomycin was shown to be more efficacious than comparators in the rabbit model of endocarditis. In one study, daptomycin was dosed at 8 mg/kg q8h for 4 days and compared to vancomycin treated rabbits. Daptomycin was more efficacious than vancomycin or teicoplanin against two strains of MSSA and one strain of MRSA as measured by percent sterile vegetations and by CFU/g per vegetation. Two of 16 animals yielded organisms resistant to daptomycin; one organism had a four-fold rise in MIC and another, an eight-fold rise in MIC (175). *Thus, while daptomycin was more efficacious than either teicoplanin or vancomycin, diminished susceptibility developed during therapy.* The investigators theorized that resistant organisms were selected for by sub-inhibitory concentrations of daptomycin deep within the vegetations. The investigators warned that extensive clinical use will be required to establish whether resistance to daptomycin will be a major clinical problem, but their findings in the rabbit animal model raises concerns regarding this possibility.

The evidence for pathogenesis of biofilms in infective endocarditis is strong. I has been noted that 60% of daptomycin penetrates into cardiac vegetations, however, 90% of daptomycin is protein-bound, therefore, it would be expected that < 60%of daptomycin would penetrate into vegetations. Once developed, vegetations manifest biofilm-like antibiotic resistance that cannot be completely explained by poor penetration of antimicrobials. Studies show that the composition of the valve biofilm has direct bearing on clinical outcomes. Taken together, these data demonstrate an association between the biofilm composition and its clinical manifestations, and support the concept that infectious endocarditis can be manipulated by targeting biofilm development.

Is there evidence in surveillance data that daptomycin MIC increases occurs in recent clinical isolates?

The Applicant's data from surveillance studies in North America and Europe from 2000 to 2004 are shown in Table I.

Table I: Activity of Daptomycin against Staphylococci

Species	Study /Year	N	Daptomycin MIC Distribution, n (%)				
			≤ 0.12 µg/ml	0.25 µg/ml	0.5 µg/ml	1 µg/ml	2 µg/ml
MSSA	2000-1	1601	304 (18.9%)	1165 (72.7%)	131 (8.2%)	1 (0.1%)	0 (0%)
	2002	1547	83 (5.4%)	1140 (73.7%)	319 (20.6%)	3 (0.2%)	2 (0.1%)
	2003	2894	229 (7.9%)	2371 (81.9%)	285 (9.9%)	8 (0.3%)	1 (<0.1%)
	2003-4	3284	70 (2.1%)	1891 (57.6%	1297 (39.5%)	25 (0.8%)	1 (<0.1%)
MRSA	2000-1	639	51 (7.9%)	396 (61.9%)	187 (29.3%)	5 (0.8%)	0 (0%)
	2002	1076	20 (1.9%)	655 (60.9%)	388 (36.1%)	13 (1.2%)	0 (0%)
	2003	1468	40 (2.7%)	963 (65.6%)	452 (30.8%)	13 (0.9%)	0 (0%)
	2003-4	1976	10 (0.5%)	878 (44.4%)	1047 (52.9%)	40 (2.0%)	1 (<0.1%)

MIC_{90} is highlighted
Source: Table 2.7.2—24, NDA 21-572 SN008

When the percentages of isolates for each MIC dilution are calculated, the data show the percentage of isolates with MICs of ≤ 0.12 µg/ml and 0.25 µg/ml *decreasing* over time and the percentage of isolates with MICs of 0.5, 1, and 2 µg/ml *increasing* over time from studies performed in 2000-2001 to 2004. This trend is evident in both methicillin- susceptible and methicillin-resistant isolates of *S. aureus*.

Recent data from [redacted] (b) (4) supports this trend. Data for daptomycin MIC distributions of *S. aureus* isolates show that between 2004 and 2005, the percentage of isolates with a MIC ≤ 1 µg/ml ***decreased*** from 99.1% of isolates to 96.7% of isolates, respectively. Also during this time period, the percentage of *S. aureus* isolates with a MIC > 1 µg/ml ***increased*** from 0.9% of isolates in 2004 to 3.3% of isolates in 2005; this represents an increase of more than 3 fold.

Thus, daptomycin MICs of clinical isolates of *S. aureus*, regardless of methicillin susceptibility, have increased over time.

Eight publications from the recent literature report "resistance" to daptomycin in clinical isolates from patients on therapy. A synopsis of these reports is shown in Table II.

Table II. Recent Reports from the Literature on Daptomycin Resistance

Organism	Condition	Source	Dose (mg/kg)	Highest MIC (µg/ml)	Reference
Enterococcus faecium	bacteremia	blood	6	>32	(97)
MRSA	bacteremia	blood	4	2	(98)
Enterococcus faecalis (VRE)	bacteremia	blood	*	16	(99)
Enterococcus faecalis (VRE)	febrile neutropenia	blood	??	??	(100)
MRSA	osteomyelitis	blood	6	4	(101)
Enterococcus faecium	fever	blood	none	4	(102)
MRSA	bacteremia	blood	8	4	(103)
MRSA	bacteremia	blood	6	4	(104)

*400 mg q48h

As most of these patients were bacteremic, the data cause concern for patients on therapy for infective endocarditis or bacteremia. Consequently, this Reviewer posed the following question:

Do patients treated with daptomycin develop resistant organisms during therapy?

The Applicant had provided an overview of isolates with treatment associated decreases in daptomycin susceptibility following commercial availability.
These data are summarized in Table III.

Table III: Overview of Isolates with Treatment Associated Decreases in Daptomycin Susceptibility Following Commercial Availability

Isolate	Source	Daptomycin Base	MIC (µg/ml) Final
E. faecium	Blood	4	> 32
E. faecium	Urine/Blood	4	32
S. aureus	Blood	0.5	4
S. aureus	Blood	0.5	4
S. aureus	*	0.25	4
S. aureus	Blood	0.5	4
S. aureus	**	0.5	4
S. aureus	Blood	1	2--4
S. aureus	Blood	0.5	4
S. aureus	Blood	0.5	4
S. aureus		0.5	8
*VRE****			8
S. aureus	Blood	0.25	1
*VRE****	Blood		4
MRSA		0.25	1.5

Source: Table **2.7.2-29,** NDA 21-572 SN008
Note: one additional patient had a *S. aureus* isolate with baseline MIC= 0.5 µg/mL and non-susceptible isolate on treatment (MIC= 4.0 µg/mL) that were not related as determined by PFGE. Therefore emergence of resistance could not be confirmed.
*initial source was right tibial tubercle, final source was epidural fat tissue
**initial source was blood, final source was spine
*** not speciated

Table III shows that 15 patients developed MICs to daptomycin ≥ 1 µg/ml since daptomycin was approved by the Agency. (Isolates with a MIC ≤ 1 µg/ml are considered susceptible to daptomycin). Of these 15 patients, 9 patients had *S. aureus* isolated from blood. Of these 15 patients, 10 patients demonstrated a three step increase in daptomycin MIC.

Do patients treated with daptomycin for endocarditis or bacteremia due to* S. aureus *develop organisms with increased MICs during therapy?

The Applicant has provided patient report forms that contain MIC data for patients given daptomycin or comparators to treat endocarditis or bacteremia. Table IV was constructed to show the numbers and percentages of patients in both study arms showing number of

patients with increases in daptomycin and vancomycin MICs and those who developed daptomycin or vancomycin resistance.

Table IV: Frequency of Increased MICs and Resistance to Daptomycin and Vancomycin in Patients during Therapy

	N, % Increased daptomycin MIC from baseline***	N, % increased vancomycin MIC from baseline***	N, % developed daptomycin resistance	N, % developed vancomycin resistance
clinical successes				
daptomycin arm	***17/53 (32.1%)****	12/53 (22.6%)*	1/53 (1.9%)*	0/53 (0%)*
comparator arm	10/46 (21.7%)	11/46 (23.9%)	1/46 (2.2%)	0/46 (0%)
clinical failures				
daptomycin arm	***21/60 (35.0%)***	14/59 (23.7%)*	***6/60 (10.0%)***	0/59 (0.0%)*
comparator arm	11/50 (22.0%)*	14/51 (27.5%)*	0/50 (0.0%)**	0/50 (0.0%)**

*determination of MICs not done for one patient
**determination of MICs not done for two patients
*** one or more dilution increase

The data from Table IV show that patients in the daptomycin arm, whether they were clinical successes or clinical failures, were *more likely* to demonstrate *increased MICs* to daptomycin than patients in the comparator arm. Also, patients in the daptomycin arm that were clinical failures were more likely to develop resistance to daptomycin (6/60, 10%) than clinical successes or patients treated with the comparator. The data also showed that increases in daptomycin MICs and daptomycin resistance are not correlated with increases in vancomycin MICs or vancomycin resistance.

Table V was constructed from the patient report forms and shows more detailed data from the patients in whom isolates developed at least a two dilution step increase with in daptomycin MIC.

Table V: Clinical Failures in Daptomycin Arm with Increased Daptomycin MICs

Case #	Final Diagnosis	Organism	Baseline MIC	High MIC	MIC Step Increase
(b) (6)	complicated bacteremia	MRSA	0.25	2	3
	complicated RIE	MSSA	0.25	4	4
	complicated bacteremia	Both	0.25	2	3
	left IE	Both	0.25	2	3
	left IE	MRSA	0.5	2	2
	complicated bacteremia	MRSA	0.5	2	2
	left IE	MRSA	0.25	1	2
	left IE	MRSA	0.25	1	2

Note: Data is not limited to baseline MICs. At baseline, case# (b) (6) had only MRSA in the blood and MSSA was not isolated until Day 20P. The baseline pathogen was MRSA for case # (b) (6) and MSSA was not isolated from blood until Day 04.

All cases demonstrated a MIC step increase of at least two steps with the exception of two patients (b) (6) and (b) (6) All cases demonstrated a highest level of MIC of at least 1 µg/ml and 6/8 patients had MICs of 2 µg/ml or greater.

Data from patient report forms were used to construct the following table. Table VI presents the MIC distributions (by dilution) for patients with bacteremia or endocarditis in the ITT population.

Table VI: Distribution of MICs for Daptomycin Treated Patients (ITT)

Clinical success	MIC (µg/mL) 0.12	0.25	0.5	1	2	4
(N=53)	1/53 (1.9%)	36/53 (67.9%)	14/53 (26.4%)	2/53 (3.8%)	1/53 (1.9%)	0/53 (0%)
bacteremia						
uncomplicated	1/53 (1.9%)	11/53 (20.7%)	3/53 (5.7%)			
complicated		18/53 (33.9%)	9/53 (16.9%)	2/53 (3.8%)		
RIE						
uncomplicated		3/53 (5.7%)	1/53 (1.9%)			
complicated		3/53 (5.7%)	1/53 (1.9%)			
LIE		1/53 (1.9%)				
Clinical failure	**MIC (µg/mL) 0.12**	**0.25**	**0.5**	**1**	**2**	**4**
(N=59)	1/59 (1.7%)	34/59 (57.6%)	15/59 (25.4%)	3/59 (5.1%)	***5/59 (8.5%)***	***1/59 (1.7%)***
bacteremia						
uncomplicated		9/59 (15.3%)	4/59 (6.8%)			
complicated	1/59 (1.7%)	19/59 (32.2%)	6/59 (10.2%)	1/59 (1.7%)	3/59 (5.1%)	
RIE						
uncomplicated		1/59 (1.7%)	2/59 (3.4%)			
complicated		3/59 (5.1%)	2/59 (3.4%)			1/59 (1.7%)
LIE		2/59 (3.4%)	1/59 (1.7%)	2/59 (3.4%)	2/59 (3.4%)	
total	**2/112 (1.8%)**	**70/112 (62.5%)**	**29/112 (25.9%)**	**5/112 (4.4%)**	**5/112 (4.5%)**	**1/112 (0.9%)**

Data from Table VI indicate there were more patients with daptomycin MICs of ≥ 1 µg/ml among clinical failures than among clinical successes. Six patients with complicated bacteremia, one patient with complicated RIE, and four patients with LIE had pathogens demonstrating MICs ≥ 1 µg/ml. Six patients who were clinical failures developed resistance (MIC >1µg/ml) during treatment with daptomycin. These data indicate that greater than 10% of clinical failures had a MIC =2 µg/ml or greater.

Table VII shows data from patients with relapsing or persistent bacteremia. The table shows clinical failures associated with MSSA, MRSA, MICs equal to or greater than 1 µg/ml, and MICs that increased by ≥ 2-fold dilutions.

Table VII: Changes in MICs for Relapsing or Persistent Bacteremia Patients

	MIC ≥ 1	**≥ 2 steps**	**MRSA**	**MSSA**
daptomycin arm (N=20)	***9/20 (45.0%)***	***9/20 (45.0%)***	12/20 (60.0%)*	11/20 (55.0%)*
comparator arm (N=11)	1/11 (9.1%)	0/11 (0%)	8/11 (72.7%)	2/11 (18.2%)
Total (N=31)	10/31 (32.2%)	9/31 (29.0%)	20/31 (64.5%)	13/31 (41.9%)

*3 patients had both MSSA and MRSA

Data from Table VII indicate that patients with relapsing or persistent bacteremia in daptomycin arm were more likely to have pathogens with a MIC ≥ 1 µg/ml and demonstrate a two or more increase in MIC dilution steps than relapsing or persistent bacteremia patients treated with comparator.

To summarize, i*n vitro* studies have demonstrated that bacteria develop increased daptomycin MICs when subjected to sub-inhibitory concentrations of daptomycin, such as may be found in endocarditis vegetations. Daptomycin does not exhibit cross-resistance to vancomycin or ampicillin but does exhibit cross-resistance to nisin. In a rabbit model of *S. aureus* endocarditis, daptomycin was more efficacious than vancomycin but diminished daptomycin susceptibility developed during therapy. Bacteremia/infective endocarditis patients on daptomycin therapy who were clinical failures were more likely to demonstrate increased daptomycin MICs and develop non-susceptibility to daptomycin than those patients who were clinical successes. Many of these clinical failures had MIC values ≥ 1 µg/ml, the criterion for non-susceptibility. Patients with relapsing or persistent bacteremia were more likely to have increased MICs if treated with daptomycin rather than comparator. This was irrespective of whether *S. aureus* demonstrated oxacillin susceptibility or resistance.

These concerns were aired by this Reviewer at an Anti-Infective Drugs Advisory Committee meeting held 6 March 2006. In addition to the concerns regarding increasing MICs to daptomycin in patients on therapy, concerns regarding both efficacy and safety of daptomycin for use in endocarditis and bacteremia were aired. The committee voted for the approval of daptomycin for bacteremia by a vote of 9-0. However, the committee was divided over the approval of daptomycin for endocarditis and voted 5-4 for the approval of daptomycin for endocarditis.

Their logic is supported by the data in Table VIII.

Table VIII. Success Rates in ITT Population at TOC by IEAC Subgroups (Final Diagnosis)

	Daptomycin n/N (%)	Comparator n/N (%)
bacteremia (total)	44/92 (47.8%)	39/90 (43.3%)
uncomplicated	18/32 (56.3%)	16/29 (55.2%)
complicated	26/60 (43.3%)	23/61 (37.7%)
endocarditis	9/28 (32.1%)	9/25 (36.0%)
uRIE	3/6 (50.0%)	1/4 (25.0%)
cRIE	5/13 (38.5%)	6/12 (50.0%)
LIE	1/9 (11.1%)	2/9 (22.2%)

Source: Table 2.5—7

Table VIII was assembled using the data provided by the Applicant in Table 2.5—7 of this submission. This table shows that success rates for bacteremia patients in the daptomycin arm (47.8%) were ***higher*** than success rates for bacteremia patients in the comparator arm (43.3%); however, success rates for endocarditis patients in the daptomycin arm (32.1%) were ***lower*** than success rates for endocarditis patients in the comparator arm (36.0%).

Infective endocarditis is certainly a more serious disease than bacteremia. In addition, LIE is a more serious subgroup of endocarditis than RIE and more complicated to treat. Greater efficacy for of a drug for the treatment of LIE would be a tremendous asset for any

drug intended to treat endocarditis. Here, the success of patients in the daptomycin arm was lower (11.1%) than success of patients in the comparator arm (22.2%).

Overall, the efficacy of daptomycin is greater than comparator for bacteremia but the efficacy of daptomycin is lower than comparator for endocarditis.
This could be interpreted to mean that daptomycin would be preferable to vancomycin/SSP for the treatment of bacteremia and vancomycin/SSP would be preferable to daptomycin for the treatment of endocarditis.

The endocarditis results also bring to light the low number of patients treated for endocarditis in this clinical trial. While these low numbers may account for the lack of efficacy of either daptomycin or comparator for the treatment of endocarditis, the low number of endocarditis patients also suggests that the number of patients is too low to determine the statistical significance of efficacy of either drug. For a more detailed examination of the Statistical elements of this submission, the reader is referred to the Statistical Reviewer, Dr. Scott Komo.

Based on the efficacy of daptomycin in bacteremia patients and adequate number of bacteremia patients, this Reviewer recommends that daptomycin be approved for the treatment of bacteremia.

In addition, due to the occurrence of increasing MICs during therapy, this Reviewer recommends that a warning be placed in the Package Insert.

However, based on the lack of efficacy in endocarditis patients and inadequate number of endocarditis patients, this Reviewer recommends that daptomycin <u>not</u> be approved for the treatment of endocarditis.

Consequently, the question arises, should a new breakpoint for *S. aureus* be set that addresses the indication for infective endocarditis or bacteremia?

The following table may shed some light on the answer to this question.

Table IX. Clinical Outcome by Baseline MIC

	MIC (µg/ml)				
	0.12	0.25	0.5	1	ALL-Comers
Daptomycin					
clinical success (N=54)	7/12 (58.3%)	41/86 (47.7%)	6/15 (40.0%)	0 (0%)	54/113 (47.8%)
clinical failure (N=59)	5/12 (41.7%)	45/86 (52.3%)	9/15 (60.0%)	0 (0%)	59/113 (52.2%)
Comparator					
clinical success (N=54)	10/18 (55.6%)	31/63 (49.2%)	5/10 (50.0%)	0 (0%)	46/92 (50.0%)
clinical failure (N=59)	8/18 (44.4%)	32/63 (50.8%)	5/10 (50.0%)	1/1 (100%)	46/92 (50.0%)

Note: patients missing a recorded baseline MIC were excluded.

Table IX is a compilation of data from the Applicant's clinical trial sorted by clinical outcome for both daptomycin and comparator treated patients by <u>baseline</u> daptomycin MIC. When clinical outcome is examined in the patients from the daptomycin arm, clinical success occurred in 47.8% of patients and clinical failure occurred in 52.2% of patients regardless of baseline MIC.

However, when clinical success and clinical failure rates are examined for patients from the daptomycin arm at individual baseline MIC steps, the rates differ from the overall rates. Clinical success was greater in patients with a MIC = 0.12 μg/ml (58.3%) than patients overall (47.8%) in the daptomycin arm. Success rates were similar between the patients with a baseline MIC = 0.25 μg/ml (47.7%) and the patients overall (47.8%) in the daptomycin arm. However, patients with a MIC = 0.5 μg/ml had a noteably lower success rate (40.0%) than patients overall (47.8%) in the daptomycin arm. The corresponding changes in clinical failure rates ensued.

Interestingly, clinical success rates were similar among patients in the comparator arm regardless of baseline daptomycin MIC (0.12, 0.25, or 0.5 μg/ml). This would be expected as these patients were treated with an alternative antibiotic and not exposed to daptomycin.

It is worth noting that the current susceptibility breakpoint for *S. aureus* (MIC ≤ 1 μg/ml) was established based on data derived from two cSSSI clinical trials. This disease is not as severe and does not require the extensive adjunct therapy as that of the current disease (bacteremia/endocarditis) for which an indication is sought. Consequently, a modified susceptibility breakpoint may be necessary and beneficial to determine if daptomycin therapy should be initiated in patients diagnosed with bacteremia/endocarditis.

These data suggest that to increase the chance of clinical success, the attending physician may want to use the baseline daptomycin MIC as a factor in his decision for the choice of antibiotic for infective endocarditis/bacteremia. Thus, if the baseline daptomycin MIC is 0.12 μg/ml or less, there is greater chance of success in treating the patient. If the baseline daptomycin is 0.5 μg/ml or greater, the physician may want to discontinue daptomycin therapy and use an alternative antibiotic.

This Reviewer recommends that bacteremia/infective endocarditis patients be placed on alternative therapy if *S. aureus* isolated from blood cultures demonstrates a baseline MIC > 0.25 μg/ml.

APPEARS THIS WAY ON ORIGINAL

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INTRODUCTION

S. aureus bacteremia and endocarditis

S. aureus is part of the normal flora colonizing the anterior nares, skin, and gastrointestinal tract. Up to 30% of individuals in the population are persistent nasal carriers and another 30% are intermittent carriers of the organism. *S. aureus* is particularly successful at exploiting defects in host defense associated with surgical wounds, percutaneous catheters, and non-specific suppression of host phagocytes [5]. Consequently, staphylococcal infections have emerged as the paragon of diseases of medical progress and are among the most prominent causes of nosocomial infections, particularly bacteremia.

S. aureus is most commonly recognized as the cause of skin and soft tissue infections, but has the capacity to invade and cause bacteremia in both immunocompromised and normal hosts and is almost unique in its capacity to cause infective endocarditis (IE) of structurally normal heart valves. Infective endocarditis is the most serious manifestation of *S. aureus* infection and may occur after a clinically unapparent primary bacteremia. Moreover, in a recently published international study, the leading cause of IE in the developed world is now *S. aureus*, with an incidence of 31.4% [1]. The authors conclude that this is likely related to increasing use of medical procedures and devices in an older population. In the United States (US), the overall incidence of MRSA among all *S. aureus* IE was 37% [1].

Infections due to *S. aureus*, historically known to be of high virulence in the pre-antibiotic era and associated with very high mortality when associated with bacteremia [6], are proving ever more challenging for present-day physicians to treat for several reasons. Epidemiologic data demonstrate an increasing incidence of both nosocomially- acquired and community-associated (CA) MRSA infections [2-4]. Equally troubling are the recent finding of an 8% to 20% incidence of CA-MRSA isolates among all MRSA isolates associated with staphylococcal infections in three US communities [7] and the finding that 76% of *S. aureus* isolated from community-acquired infections in Houston children in 2004 were MRSA [8].

Moreover, these CA-MRSA strains appear to be of clonal origin and are of particularly high infectivity and virulence [9], demonstrating the convergence of resistance and virulence in *S. aureus* [10]. Compounding the problem is that morbidity and mortality are increased when available therapy is inappropriate, delayed, or both [11-16], which becomes more likely when ß-lactam antibiotics are used as the mainstay of empirical therapy for presumed Gram-positive infections at a time of increasing resistance to these agents. For these reasons, many clinicians are now using vancomycin as preferred therapy for suspected or diagnosed serious infections due to *S. aureus*. In this context, it is of particular concern that vancomycin therapy has been associated with suboptimal outcomes when used to treat *S. aureus* bacteremia or endocarditis [17-19]. Some have speculated that this suboptimal effect of vancomycin may be related to its weak bactericidal ability [20], which may be worsening (i.e., increasing vancomycin tolerance in strains of *S. aureus*) [see Section 2.7.2.4, this submission]. Some MRSA strains cannot be treated with vancomycin; there are now four reports of high-level vancomycin resistance among clinical MRSA isolates [see Section 2.7.2.4, this submission]. In a recent review of bloodstream infections

caused by enterococci, vancomycin resistance was found to be a significant independent predictor of increased mortality, even after controlling for all known co- morbidities [21].

Perhaps in part because of increasing antibiotic resistance, recent clinical evidence suggests that the morbidity of *S. aureus* infections is increasing. In recently published series, up to 50% of patients with *S. aureus* bacteremia were found to have IE [22-26]. While structurally abnormal valves (e.g., bicuspid aortic valve, rheumatic mitral valve) are at increased risk of being seeded by staphylococci, normal valves may also be affected. Among patients with *S. aureus* bacteremia, 43% are marked by a clinically significant complication, including metastatic deep tissue infection, such as visceral abscesses, vertebral osteomyelitis, and psoas abscess [27]. The risk of these morbidities is markedly increased in patients who have sustained or "high grade" *S. aureus* bacteremia documented to extend over two or more days [27, 28].

In the pre-antibiotic era, *S. aureus* bacteremia was associated with a mortality rate of 82% [3]. In the present time, *S. aureus* bacteremia and IE are associated with increasing mortality with reports of up to 64% mortality among patients with MRSA bacteremia, *S. aureus* infections with noneradicable foci, or both [11, 12, 15, 24, 27, 29, 30] and 20% to 50% among patients with IE [1, 31-33]. Without treatment, IE is uniformly fatal and treatment of inadequate intensity or duration is often followed by clinical and microbiological relapse.

In the most recent and comprehensive review, it was shown that, as compared with patients with IE due to organisms other than *S. aureus*, those with *S. aureus* IE are more likely to die (20% vs. 12%; $p < 0.001$), to experience an embolic event (60% vs. 31%; $p < 0.001$), or to have a central nervous system event (20% vs. 13%; $p < 0.001$) [33].

Treatment options for patients with *S. aureus* bacteremia or IE are currently limited and include semi-synthetic penicillin (SSP) (e.g., nafcillin) or cefazolin for methicillin-susceptible *S. aureus* (MSSA), and vancomycin for those with allergy to ß- lactam antibiotics or with infections due to MRSA. Gentamicin is often added to these regimens, particularly in the presence or suspicion of IE.

The course and standard treatment of IE vary depending on the valves involved [34]. Infective endocarditis involving only the tricuspid or pulmonic valve or both is referred to as right-sided IE (RIE). *S. aureus* RIE is most commonly seen in intravenous drug users (IVDU) and has also been described as a complication of *S. aureus* bacteremia in patients with prolonged use of central venous catheters. Potential complications include: large pulmonary abscesses, empyema, and metastatic visceral infection. Multiple, small, bilateral pulmonary nodules are a common manifestation of small septic emboli shed directly into the lungs and are not considered a clinically significant complication [35]. It has been suggested that *S. aureus* RIE in IVDU, if the course is uncomplicated (according to strict definitions) and the organism is methicillin-susceptible, can be successfully treated with two weeks of SSP and an aminoglycoside (e.g., gentamicin) [36]. Treatment with vancomycin (required when the organism is methicillin-resistant or the patient is penicillin-

allergic) for only two weeks is frequently associated with relapse and is not an acceptable regimen [36].

Infective endocarditis involving the mitral or aortic valve, or both, is referred to as left-sided IE (LIE). Successful medical treatment requires at least four weeks of a bactericidal parenteral antibiotic. The current standard of care for MSSA LIE is SSP, including nafcillin, oxacillin, cloxacillin, or flucloxacillin, administered at 2 g every four hours i.v. for 4 to 6 weeks (or cephalosporin at high doses). The standard for MRSA LIE (or for patients with penicillin-allergy) is vancomycin 1 g every 12 hours i.v. (with adjustment for renal function) for 4 to 6 weeks.

Because of the high mortality and morbidity rates in *S. aureus* IE, some experts have recommended the addition of a potentially synergistic aminoglycoside antibiotic to be given with penicillinase-resistant ß-lactam antibiotics (for MSSA) or with vancomycin (for MRSA) [1, 34]. The only multicenter prospective study to address this issue compared nafcillin alone with nafcillin plus gentamicin (for the initial 2 weeks of therapy) in the treatment of IE due to *S. aureus* [37]. Although bacteremia cleared faster in the gentamicin-treated group, there was a greater likelihood of azotemia and no difference in overall outcome in this group. Because of these results, some have recommended a shorter duration of gentamicin (i.e., 4-5 days, rather than 2 weeks) to optimize the speed of bacterial clearance while minimizing the risk of aminoglycoside- associated nephrotoxicity [1, 34]. These recommendations are part of the American Heart Association guidelines [38]. Despite appropriate therapy, the incidence of serious morbidity, including septic emboli, metastatic infection, and valve destruction requiring cardiac surgery, remains high.

Thus, treatment options are limited, especially for patients with MRSA infections and those with MSSA who are allergic to or intolerant of ß-lactam antibiotics. Not only do patients infected with MRSA tend to have worse outcomes than patients with MSSA [11], but vancomycin treatment itself has been associated with worse outcomes [17-19]. In a prospective, multi-center study of the impact of antibiotic treatment on *S. aureus* bacteremia and the risk of recurrence, Chang et al [19] found that 9.4% of patients with MSSA bacteremia experienced a recurrence but that bacteriologic failure occurred more frequently with vancomycin (19%) than with nafcillin (0%). In addition, Fowler et al [27] have demonstrated a high rate (43%) of complications (e.g., endocarditis, deep abscesses, septic arthritis, osteomyelitis) in individuals with *S. aureus* bacteremia with a five fold greater risk in patients whose bacteremia continued for 48 to 72 hours (as well as in those with continued fever).

These data emphasize the clinical need for new, potent agents for the treatment of bacteremia and IE, and have driven the use of daptomycin for this currently unapproved use. The latest information from Cubist Medical Affairs is that ~(b) (4)% of Cubicin use is for bacteremia with/without IE of which ~(b) (4)% is at the 4 mg/kg/day dose, rather than the dose used in the pivotal *S. aureus* bacteremia and IE trial of 6 mg/kg/day [39].

The Applicant asserts these data emphasize the clinical need for new, potent agents for the treatment of serious systemic infections caused by *S. aureus*.

Reviewer's comments: The Applicant introduces many pertinent data from the literature demonstrating the importance and significance of *S. aureus* in the etiology of infective endocarditis and bacteremia. However, the Applicant fails to address an important microbiological aspect of infective endocarditis, namely, the involvement of biofilms in the role of cardiac vegetations. What follows is pertinent data regarding the microbiology of biofilms and their role in the development of cardiac vegetations.

S. aureus may produce both chronic infections as well as acute invasive infections [40]. During chronic infection, *S. aureus* produces a biofilm. These biofilm bacteria can be up to 1000 times more resistant to antimicrobials than their free-swimming (planktonic) counterparts. Biofilms also make bacteria less conspicuous to the immune system as antigens may be hidden and key ligands repressed [41, 42].

Biofilms have a decreased invasiveness resulting from a combination of factors. Biofilm bacteria are adherent to a surface and confined within a matrix, and invasion and motility machinery are not expressed [42, 43]. This moderation of virulence may serve the interest of the bacteria by increasing the longevity of the host.

In many human infections, the bacteria are difficult to access and biofilm and planktonic growth may coexist. Biofilms are an organized mode of growth; consequently this phenotype is rapidly lost when bacteria are cultured *ex vivo*.

Infections caused by biofilms have several characteristics. First, the infecting bacteria are adherent to some substratum or are surface associated. Second, direct examination of infected tissue shows bacteria living in cell clusters, or microcolonies, encased in an extracellular matrix. Third, the infection is generally confined to a specific location. Finally, the infection is difficult or impossible to eradicate with antibiotics despite the fact that the responsible organisms are susceptible to killing in the planktonic state.

Evidence for the pathogenesis of biofilms in infective endocarditis is strong.

The primary infection lesion in infective endocarditis is known as a vegetation. It is a complex biofilm composed of both bacterial and host components located on a cardiac valve. Disease is caused by three mechanisms. First, the vegetation physically disrupts valve function, causing leakage when the valve is closed and turbulence and diminished flow when the valve is open. Second, the vegetation provides a source for near-continuous infection of the bloodstream that persists even during antibiotic treatment. Third, pieces of the infected vegetation can dislodge and be carried to a terminal point in the circulation (embolization) such as the brain, kidney, or the extremities. Successful treatment requires prolonged administration of intravenous antibiotics and, may require surgical removal and replacement of the infected valve.

Vegetations are composed primarily of bacteria and their exoproducts, platelets, and fibrin derived from the circulation, with the damaged endothelial surface serving as the substratum [44]. The rabbit serves as an excellent model and has yielded knowledge about how biofilms form *in vivo*.

There are five distinct stages of the pathogenesis of endocarditis [44]:

- Injury of the endothelial surface of the valve,
- Formation of a sterile clot-like lesion (thrombus) composed of platelets and fibrin at the site of injury,
- Adherence of bacteria to the thrombus,

- Micro colony formation by the bacteria, and
- Maturation of the vegetation biofilm and embolization of detached biofilm.

The endothelial lining of the rabbit heart is very resistant to infection; generally, direct instillation of bacteria into the circulation in the absence of valve injury will not produce endocarditis [45]. However, the degree of valve injury required experimentally to produce endocarditis is quite minor. In the rabbit, a five minute contact of a small-bore, flexible polyethylene tube suffices. In most human cases, injury results from turbulent blood flow caused by valve dysfunction. This injury promotes thrombus formation on the surface of the valve [46, 47].

Upon gaining access to the circulation, bacteria adhere to the thrombus via specific interactions. Bacterial exopolysaccharide act as adhesions that preferentially bind to injured valves [48, 49]. Additional bacterial adhesions such as fibronectin receptor have been implicated. Specific host components are also key to initial adherence; eliminating platelets from an *in vitro* fibrin matrix can significantly reduce bacterial attachment [49].

Once developed, vegetations manifest biofilm-like antibiotic resistance that cannot be completely explained by poor penetration of antimicrobials. This was demonstrated in a study in which radiolabeled penicillin, tobramycin, and teicoplanin were given to rabbits with endocarditis [50]. Astonishingly, the concentration of radioactivity was higher in the vegetations than in the blood. Other *in vivo* studies indicate that bacterial killing within vegetations require antibiotic levels 220-fold greater than the concentrations required to kill planktonic bacteria [51].

Studies show that the composition of the valve biofilm has direct bearing on clinical outcomes. In one study, valve-injured rabbits were treated with warfarin, which inhibits fibrin-platelet matrix formation [47]. Vegetation formation was altered even though the treatment did not affect the bacterial counts on the valve. The resulting illness was characterized by high fever, constant bacteremia, and increased mortality. However, antibiotic treatment was more effective in the warfarin-treated rabbits. Thus, interfering with biofilm formation on the valve both produced a more explosive disease and reduced the resistance of the bacteria. In another study, inhibiting platelet aggregation by aspirin treatment also significantly altered the disease course [52]. Taken together, these experiments demonstrate an association between the biofilm composition and its clinical manifestations, and support the concept that infectious endocarditis can be manipulated by targeting biofilm development.

PRECLINICAL EFFICACY— *IN VITRO*

MECHANISM OF ACTION

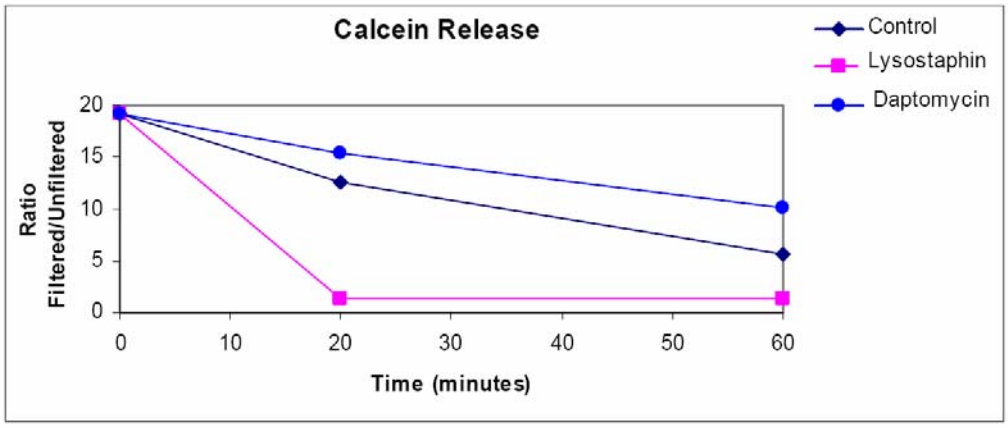
Extensive research on the daptomycin mechanism of action [53] has revealed the following theoretical 3- step model (see Figure 2.7.2- 6, p53, this submission).

• Step 1: In a calcium- dependent manner, daptomycin binds and inserts into the cytoplasmic membrane of Gram- positive bacteria.
• Step 2: A hypothetical ion- conduction structure, such as a channel, pore, or aggregate, is formed by the oligomerization of inserted drug.
• Step 3: The ion- conduction structure disrupts the functional integrity of the membrane, resulting in the release of intracellular potassium ions.

Daptomycin has been demonstrated to insert directly into the cytoplasmic membrane of Gram-positive cells in a calcium-dependent manner which results in the dissipation of the membrane potential. Depolarization of the membrane is followed by rapid arrest of bacterial DNA, RNA, and protein synthesis as well as cell death. The mechanism for the depolarization has been demonstrated through the release of potassium ions from bacterial cells exposed to daptomycin [53-57]. Recent studies have confirmed the proposed mechanism of action by investigating changes in the bacterial cell surface using both biochemical and morphological methods.

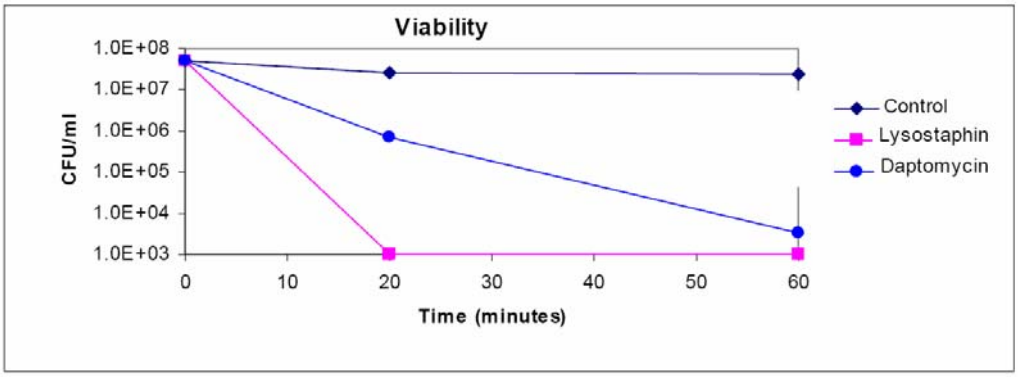
Calcein is a fluorescent molecule of MW 600 Daltons that is normally unable to cross intact membranes and is therefore used as a marker for membrane leakage and cell lysis. A modified form of Calcein can be introduced into cells but cannot exit intact cells. *S. aureus* was loaded with Calcein and treated for one hour with daptomycin and lysostaphin (an enzyme that degrades the *S. aureus* cell wall). Cells were monitored for viability and for leakage of Calcein over a 60-minute period (Figures 1 and 2) [Figure 2.7.2-7 and Figure 2.7.2-8, this submission]. Daptomycin produced nearly a 10,000- fold decrease in viability but no Calcein release relative to the untreated controls. Lysostaphin, in contrast, produced rapid bactericidal effect and complete release of intracellular calcein.

Figure 1: Calcein Leakage from *S. aureus* after Treatment with Either Daptomycin or Lysostaphin Calcein Release



Source: Figure 2.7.2- 7, this submission

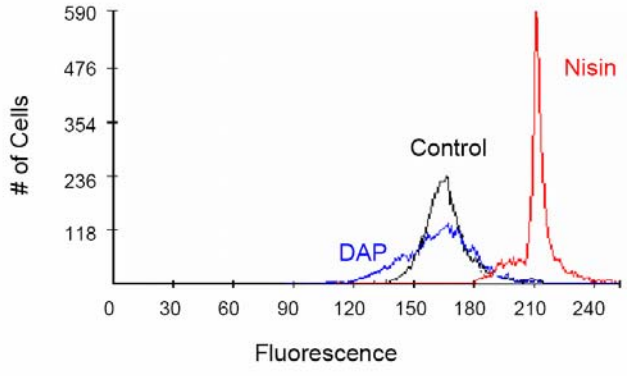
Figure 2: Viability of *S. aureus* Treated with Either Daptomycin or Lysostaphin During Calcein Leakage Viability



Source: Figure 2.7.2- 8, this submission

ToPro-3 is a fluorescent dye that, like Calcein, is unable to cross intact membranes. Fluorescence of ToPro-3 increases dramatically upon binding to DNA, which occurs only when the cell membrane is breached or with cell lysis. *S. aureus* was incubated with either daptomycin for up to 60 minutes or nisin, a pore forming antibiotic, for 10 minutes, prior to fluorescent- activated cell sorting (FACS). Fluorescence in nisin treated cells increased dramatically, indicating permeabilization of the membranes and/ or lysis, whereas fluorescence in the daptomycin- treated cells overlapped with the untreated controls (Figure 3) [Figure 2.7.2-9, this submission]. Both daptomycin and nisin produced > 1,000-fold reduction in viability during this assay.

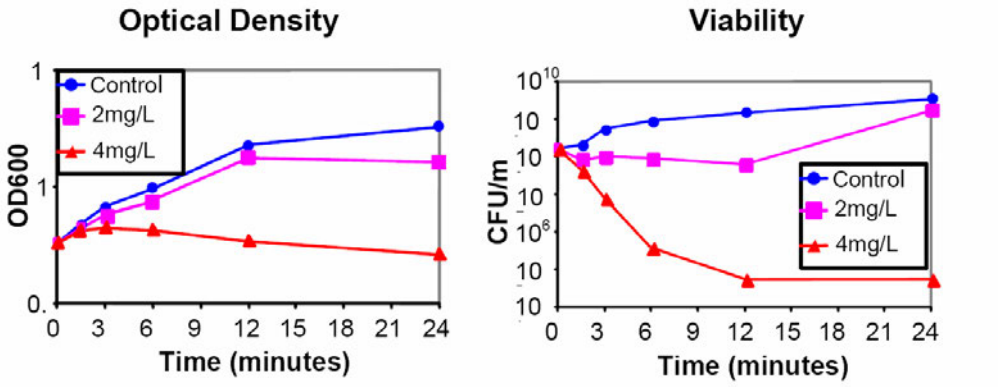
Figure 3: ToPro-3 Uptake in *S. aureus* Treated with Either Daptomycin or Nisin



Source: Figure 2.7.2- 9, this submission

Electron microscopy has been used to study the morphology of daptomycin- treated *S. aureus*. Thin section studies on glutaraldehyde-fixed, heavy metal- stained samples revealed significant alterations in the cell wall of daptomycin- treated *S. aureus*, but no significant lysis of cells. The single cell image shown in Figure 2.7.2-10 (p55, this submission) was taken after 60 minutes of daptomycin treatment at 4 mg/L, which resulted in > 1,000- fold reduction in population viability. In contrast, nisin treatment resulted in both rapid bactericidal effect and significant cellular lysis and leakage. It should also be noted that no decrease in OD_{600} was observed for this culture during the first two hours of daptomycin treatment, despite the decrease in viability (Figure 4) [Figure 2.7.2-11, this submission].

Figure 4: Optical Density (OD) and Viability of *S. aureus* Treated with 2 or 4 mg/L Daptomycin Optical Density



Source: Figure 2.7.2- 11, this submission

S. aureus treated with daptomycin at 4x the minimum inhibitory concentration (MIC) for 4 hours displayed limited morphological changes and no obvious lysis when observed by scanning electron microscopy, which was previously reported by Wale et al (Figure 2.7.2-12, this submission) [58]. Viability data were not available for these samples, but the dose used typically would produce > 1,000-fold loss of viability in the time period in question.

The only morphological changes visible are the appearance of surface protrusions or "blebs".

The Calcein, ToPro-3, and electron microscopy data all suggest that the bactericidal activity of daptomycin does not depend on cell lysis.

Reviewer's comments: The Applicant states [redacted] (b) (4) . However, this [redacted] (b) (4) (b) (4) is unsubstantiated.

SPECTRUM OF ACTIVITY

Overview

Daptomycin has *in vitro* activity against many clinically significant aerobic and anaerobic Gram-positive pathogens. Daptomycin has been approved for complicated skin and skin structure infections caused by *S. aureus*, ß-hemolytic streptococci, and vancomycin-susceptible *E. faecalis*. Daptomycin has *in vitro* activity against the most common Gram-positive pathogens, including staphylococci, streptococci, enterococci, and *Corynebacterium jeikeium*. The *in vitro* activity of daptomycin has continued to be evaluated against > 30,000 bacterial isolates between December 2002 and March 2005. These studies include both large-scale surveillance in North America and Europe using standard Clinical Laboratory Standards Institute (CLSI)/ NCCLS methodology [59] as well as smaller isolate sets from approximately 30 independent laboratories (Table 2.7.2-51 in Appendix 2.7.2.6). Table 1 summarizes the MIC results for *S. aureus* in the relevant microbiology studies sponsored by Cubist Pharmaceuticals from December 2002 through March 2005.

Daptomycin has demonstrated *in vitro* activity against the following Gram-positive etiological agents that can cause bacteremia and endocarditis: *S. aureus*, including methicillin-resistant and vancomycin-resistant strains, the majority of *S. aureus* with reduced susceptibility to vancomycin, linezolid- and synercid-resistant *S. aureus* as well as coagulase-negative staphylococci and the viridans group streptococci.

In vitro Susceptibility Profile of Daptomycin

The susceptibility profile of daptomycin was confirmed against contemporary Gram-positive clinical isolates in North America and Europe using NCCLS approved broth microdilution methods for daptomycin (NCCLS M7-A6, 2003) [59]. In these studies, each isolate was from a different patient and only one strain per patient was analyzed. Greater than 30,000 Gram-positive pathogens were tested in the following contracted multiregional profiling studies: [redacted] (b) (4)

Table 1: Summary of the Spectrum of Activity of Daptomycin

Organism	N	MIC Range	MIC50	MIC90	Reference
S. aureus	3202	≤ 0.12--2	0.25	0.5	62
	2499	≤ 0.12--2	0.25	0.5	171
	536	0.12--1	0.25--0.5	0.5	171
	3094	≤ 0.06--2	0.25	0.5	(b) (4)
	2166	≤ 0.06--2	0.25--0.5	0.5	
	107	0.5--1	1	1	63
	1041	≤ 0.12--1	0.25	0.5	176
	676	0.06--1	0.12--0.25	0.25	177
	100	0.25--2	0.5	1	64
	1666	≤ 0.12--1	0.25	0.25	Report Quale 2003
	1121	≤ 0.12--2	0.5	1	Report Quale 2003
	360	≤ 0.3--1	0.25	0.5	82
	92	0.25--1	0.5	1	65
	235	0.25--1	0.5	0.5--1	66
	20	≤ 0.5--1	≤ 0.5	≤ 0.5	Report Wilson 2005
	74	0.25--2	1	2	67
	557	0.12--1	0.5	0.5	178
	1018	0.03--0.5	0.25	0.25--0.5	60
	1222	≤ 0.015--1	0.25	0.5	61
	32	≤ 0.12--1	--	0.5	Report Piper 2005
	1863	≤ 0.016--1	0.25	0.25--0.5	Report (b) (4)
	105	≤ 0.12--1	0.5	0.5	Report (b) (4), Report 04-CUB-04
GISA	17	0.5--4	1	2	Report 04-CUB-04
GISA	8	0.25--2	--	--	68
GISA	8	1--2	--	--	69
GISA/hGISA	92	0.25--8	1	2	70
GISA/hGISA	39	≤ 0.12--2	0.5	1	71
hGISA	88	≤ 0.25--1	0.5	1	Report 04-CUB-04
hGISA	3	1--2	--	--	72
hGISA	10	0.5--2	1	2	Report (b) (4)
hGISA	55	0.5--4	1	2	73
VRSA	1	1	--	--	74
VRSA	1	0.5	--	--	79
VRSA	1	0.25	--	--	80
VRSA	1	≤ 0.5	--	--	81

Note: All units for MICs are µg/ml
Source: Table 2.7.2- 50, this submission

Additional *in vitro* daptomycin susceptibility data on > 30,000 Gram-positive isolates collected and tested since the daptomycin NDA filing (December 2002) are listed in Table 1 along with their corresponding publications.

Table 2: Summary of Daptomycin Global Surveillance Studies

Study	# of Gram + Isolates	# of Sites	Geographic Location	Reference
2001 (b) (4)	6973	50	US	[60]
2001 (b) (4)	5948	40	Europe	[61]
2002 (b) (4)	6737	75	North America, South America, Europe	[62]
2003 (b) (4)	5995	33	North America	(b) (4)
2003 (b) (4)	6035	25	Europe	
2004 (b) (4)	6252	29	North America	
2004 (b) (4)	5134	24	Europe	
Total	**43074**	**276**		

Source: Table 2.7.2- 22, this submission

***Reviewer's Comment*: :** The Applicant presents MIC data from December 2002 thorough March 2005 in Table 1 (Table 2.7.2—50, Appendix, pp 115-6) for *Staphylococcus aureus* isolates including Glycoprotein Intermediate *Staphylococcus aureus* (GISA), Heteroresistant Glycoprotein Intermediate *Staphylococcus aureus* (hGISA), and Vancomycin Resistant *Staphylococcus aureus* (VRSA). Most of the isolates present a MIC90 of 0.25—0.5 µg/ml. However, some isolates have MIC90s of 1—2 µg/ml. Isolates with a MIC of ≤ 1 µg/ml are considered susceptible and isolates with a MIC of 2 µg/ml are considered not susceptible by CLIS standards. Thus, those isolates considered to be on the brink of resistant (having a MIC90 of 1 or 2 µg/ml) are taken from Table 1 and used to construct Table A.

Table A. Summary of MICs of Borderline Daptomycin Susceptible Isolates

Organism	N	MIC Range	MIC50	MIC90	Reference
S. aureus	107	0.5--1	1	1	63
	100	0.25--2	0.5	1	64
	1121	≤ 0.12--2	0.5	1	Report Quale 2003
	92	0.25--1	0.5	1	65
	235	0.25--1	0.5	0.5--1	66
	74	0.25--2	1	2	67
GISA	17	0.5--4	1	2	Report 04-CUB-04
GISA	8	0.25--2	--	--	68
GISA	8	1--2	--	--	69
GISA/hGISA	92	0.25--8	1	2	70
GISA/hGISA	39	≤ 0.12--2	0.5	1	71
hGISA	88	≤ 0.25--1	0.5	1	Report 04-CUB-04
hGISA	3	1--2	--	--	72
hGISA	10	0.5--2	1	2	Report (b) (4)
hGISA	55	0.5--4	1	2	73
VRSA	1	1	--	--	74

Source: Table 2.7.2—50.

Among the *S. aureus* isolates that were neither GISA, hGISA nor VRSA, many of the isolates were of international origin, specifically European (references 64-67). *S. aureus* isolates cited in reference 63 were tested for susceptibility to daptomycin by Etest strips.

An additional observation regarding Table 1 (Table 2.7.2—50) is that while there are data for isolates from North America and Europe, there is a noticeable lack of isolates from other continents including Africa, Asia, Australia, and South America.

MIC50s and MIC90s from references 65, 67, 68, 69, 70, 71, 72, 73, Report Wilson 2005, Report Piper 2005, Report 04-CUB-04, and Report (b) (4), should not be considered true MIC50s or true MIC90s since these values were based on MICs from less than 100 isolates.

The following sections present the combined results of these studies for all isolates displayed in a summary table indicating the range of MICs, the MIC50 and MIC90 as well as tables outlining individual studies of important *S. aureus* isolate collections.

***Activity against* S. aureus**

Table 3 summarizes the *S. aureus* results from the 2002, 2003, and 2004 (b) (4) surveillance studies undertaken in North America and Europe [see Report (b) (4) Report (b) (4) Report (b) (4) this submission]. These data support previous surveillance studies that demonstrate daptomycin activity *in vitro* against oxacillin-susceptible and resistant *S. aureus*. Daptomycin was active against 99.9% of isolates with MIC values of ≤ 1 µg/mL. The activity of daptomycin against *S. aureus* was similar in both North America and Europe.

Table 3: Daptomycin Activity against *S. aureus* by Geographic Region from the (b) (4) (b) (4) Studies (2002-2004)

Resistance Phenotype	Geographic Region	N	MIC Range (µg/ml)	MIC50 (µg/ml)	MIC90 (µg/ml)
Oxacillin-Susceptible	North America	4000	≤ 0.06--2	0.25	0.25--0.5
	Europe	3550	≤ 0.06--2	0.25	0.5
Oxacillin-Resistant	North America	3069	≤ 0.12--1	0.25--0.5	0.5
	Europe	1292	≤ 0.12--2	0.25--0.5	0.5

Reference: Report (b) (4), Report (b) (4), Report (b) (4) and (b) (4)
Source: Table 2.7.2- 23, this submission

Reviewer's comments: The Applicant states that daptomycin was active against 99.9% of isolates with MIC values of ≤ 1 µg/mL; however, there is no reference cited to substantiate this claim. However, it can be stated from the data in Table 3 that daptomycin was active against more than 90% of the isolates with MIC values ≤ 0.5 µg/mL.

Table 4 presents the *in vitro* activity of daptomycin against almost 15,000 *S. aureus* isolates from the major surveillance studies, including the (b) (4) surveillance study from 2000-2001 [60, 61]. *According to the Applicant*, Table 4 illustrates that daptomycin susceptibility has remained consistent throughout the last four years. A total of 99.9% of wild-type isolates were susceptible to daptomycin with a MIC value range of = 0.015-1 µg/mL. A small percentage, 0.03%, of wild- type *S. aureus* isolates had a MIC = 2 µg/mL.

Based on these studies the MIC90 for all *S. aureus* is 0.5 µg/mL and daptomycin potency was not affected by resistance to methicillin.

Table 4: Activity of Daptomycin against Staphylococci (Number of Isolates)

Species	Study	N	Daptomycin MIC Distribution*				
			≤ 0.12	0.25	0.5	1	2
MSSA	(b) (4)	1601	304	1165	131	1	0
		1547	83	1140	319	3	2
		2894	229	2371	285	8	1
		3284	70	1891	1297	25	1
MRSA	(b) (4)	639	51	396	187	5	0
		1076	20	655	388	13	0
		1468	40	963	452	13	0
		1976	10	878	1047	40	1

MIC90 is highlighted
Source: Table 2.7.2- 24, this submission

Reviewer's comments: The Applicant presents data for daptomycin susceptibility in MSSA and MRSA from predominantly the US and Europe over a four year period. The MIC distribution, study names and organisms are presented in Table 4. According to the Applicant, Table 4 illustrates that daptomycin susceptibility has remained consistent throughout the last four years. However, careful examination of these data suggests otherwise.

In the table constructed below (Table B), the percentages of the number of organisms demonstrating a MIC dilution change relative to the total number of organisms are calculated using the data provided in Table 4. Note that the percentage of organisms demonstrating MICs of ≤ 0.12 and 0.25 µg/ml ***decreases*** over the four year time period. Conversely, the percentage of organisms demonstrating MICs of 0.5, 1, and 2 µg/ml ***increases*** over the time period. These trends occur for both MSSA and MRSA.

Recent data from (b) (4) supports this trend. Data for daptomycin MIC distributions of *S. aureus* isolates show that between 2004 and 2005, the percentage of isolates with a MIC ≤ 1 µg/ml ***decreased*** from 99.1% of isolates to 96.7% of isolates, respectively. Also during this time period, the percentage of *S. aureus* isolates with a MIC > 1 µg/ml ***increased*** from 0.9% of isolates in 2004 to 3.3% of isolates in 2005; this represents an increase of more than 3 fold.

Thus, the MIC data show there is a tendency for MICs to increase over time suggesting that an increase in non-susceptibility may follow.

Table B: Activity of Daptomycin against Staphylococci (# of Isolates and % of Isolates)

Species	Study	N	Daptomycin MIC Distribution*				
			≤ 0.12	0.25	0.5	1	2
MSSA	(b) (4)	1601	304 18.9%	1165 72.7%	131 8.2%	1 0.1%	0 0%
		1547	83 5.4%	1140 73.7%	319 20.6%	3 0.2%	2 0.1%
		2894	229 7.9%	2371 81.9%	285 9.9%	8 0.3%	1 <0.1%
		3284	70 2.1%	1891 57.6%	1297 39.5%	25 0.8%	1 <0.1%
MRSA	(b) (4)	639	51 7.9%	396 61.9%	187 29.3%	5 0.8%	0 0%
		1076	20 1.9%	655 60.9%	388 36.1%	13 1.2%	0 0%
		1468	40 2.7%	963 65.6%	452 30.8%	13 0.9%	0 0%
		1976	10 0.5%	878 44.4%	1047 52.9%	40 2.0%	1 <0.1%

Source: Table 2.7.2- 24, this submission

Activity against GISA

The incidence of *S. aureus* with reduced susceptibility to glycopeptides is increasing. These isolates tend to be multi- drug resistant and glycopeptide susceptibility can be difficult to detect in the clinical microbiology laboratory [75]. Daptomycin has demonstrated potent antimicrobial activity against GISA, the majority of heteroresistant-glycopeptide-intermediate *S. aureus* (hGISA) and VRSA. Several studies have evaluated the activity of daptomycin against hGISA and GISA isolates (Table 5). In general, the daptomycin MIC50 and MIC90 values for *S. aureus* strains with reduced susceptibility to vancomycin were 1 and 2 µg/mL respectively. This is a shift of 1 to 2 doubling dilutions higher than wild- type strains.

Table 5: Daptomycin Activity against hGISA and GISA Strains

		Daptomycin MIC Distribution [b]							
Study [a]	**N**	**< 0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**Reference**
CDC									
hGISA	3	0	0	0	1	2			[72, 76]
GISA	8	0	1	3	2	2			[68]
GISA	8	0	0	0	1	7			[69]
DSV [c]	16	0	0	0	6	5	2	3	[72, 76]
(b) (4)									
hGISA	88	0	2	***52***	34				[Report 04-CUB-04]
GISA	17	0	0	2	***7***	7	1		
AB Biodisk									
hGISA/GISA	92	0	3	36	***38***	9	4	2	[70]
(b) (4)									
hGISA	10	0	0	2	***4***	4			[Report (b) (4)
Rybak									(b) (4)
hGISA/GISA	39	2	9	***22***	5	1			[71]
Wootton									
hGISA	55	0	0	1	***41***	12	1		[73]

a GISA isolates from the different studies may be identical.
b MIC50s are in italics and bolded while MIC90s are highlighted.
c Decreased susceptibility to vancomycin (MIC = 4 µg/mL).
Source: Table 2.7.2- 25, this submission

Activity against VRSA

In 2002, VRSA strains were isolated from patients in both Michigan and Pennsylvania and were found to be susceptible *in vitro* to daptomycin. The Michigan VRSA was later confirmed to be *mecA*+ and *vanA*+. The activity of daptomycin against both of these isolates of VRSA is shown in Table 6. In 2004 a VRSA isolate was identified in New York and in 2005 a fourth VRSA was isolated in Michigan, these isolates were also found to be susceptible to daptomycin *in vitro* [74, 77, 78, 79].

Table 6: Daptomycin Activity against Four Vancomycin-Resistant *S. aureus* (VRSA)

Strain (Geographic Source)	**Daptomycin MIC (µg/ml)**	**Vancomycin MIC (µg/ml)**	**Reference**
S. aureus (Michigan)	1	> 128	[74]
S. aureus (Pennsylvania)	0.5	> 64	[79]
S. aureus (New York)	0.25	64	[80]
S. aureus (Michigan 2)	< 0.5	256	[81]

Source: Table 2.7.2- 26, this submission

Activity against multi- drug resistant* S. aureus *and community-acquired MRSA

The *in vitro* activity of daptomycin was characterized against multi-drug resistant *S. aureus* strains and against a panel of characterized community-associated *S. aureus* (CA-MRSA) (Table 7) [82]. The genetically characterized strains contained a variety of genes for well established virulence factors including: accessory gene regulator 1 to 4 (agr 1- 4), α, ß, γ hemolysins, Panton Valentine leukocidin (PVL), toxic shock syndrome toxin-1 (TSST-1) and several enterotoxins. Against the 42 genetically characterized strains, the MIC range

and MIC90 for daptomycin were 0.03-0.5 µg/mL and 0.5 µg/mL, respectively. Daptomycin was active against the 50 CA-MRSA as well, with a MIC90 of 0.25 µg/mL (Table 7) [82].

Table 7: Susceptibility of *S. aureus* and CA- MRSA with Known Virulence

Organism		MIC (µg/ml)		
Antimicrobial Agent	N	Range	MIC50	MIC90
S. aureus (genetically characterized)	42			
Clindamycin		0.12--> 4	0.25	0.25
Daptomycin		0.12--0.5	0.25	0.5
Erythromycin		1--> 16	1	> 16
Gentamicin		0.25--> 16	0.5	2
Linezolid		2--2	2	2
Oxacillin		< 0.06--> 8	0.25	4
Quinupristin-dalfopristin		0.12--1	0.12	0.25
Trimethoprim/sulfamethoxazole		< 0.25--> 4	< 0.25	< 0.25
Vancomycin		< 0.25--1	0.5	0.5
CA-MRSA*	50			
Clindamycin		0.5-- > 4	0.5	0.5
Daptomycin		0.03--0.5	0.25	0.25
Erythromycin		> 8--> 8	> 8	> 8
Gentamicin		0.5--0.5	0.5	0.5
Linezolid		< 0.5--4	2	4
Oxacillin		16--128	128	128
Quinupristin-dalfopristin		< 0.25--< 0.25	<0.25	< 0.25
Trimethoprim/sulfamethoxazole		< 2/38--< 2/38	< 2/38	< 2/38
Vancomycin		0.5--1	1	1

* Community-acquired MRSA
Source: Table 2.7.2- 27, this submission

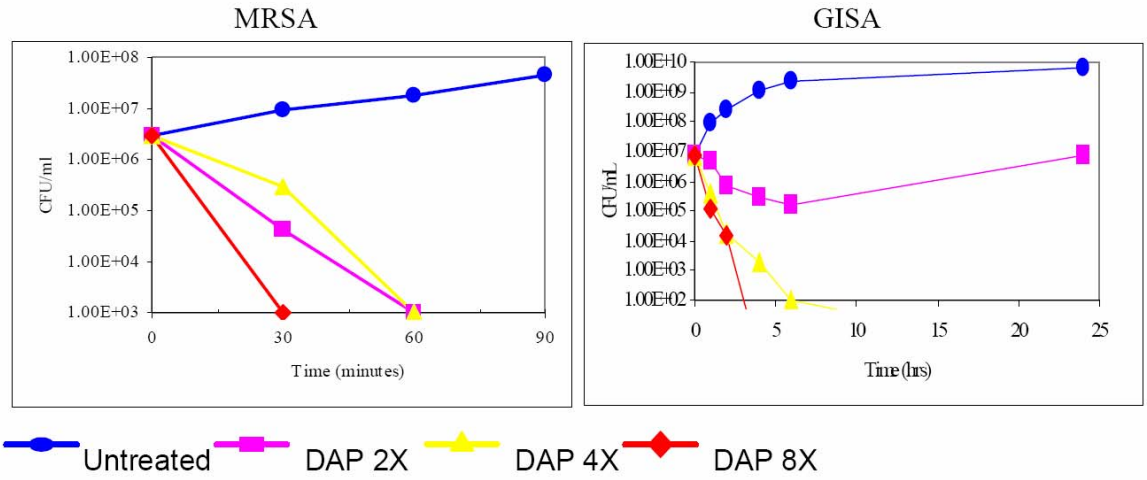
BACTERICIDAL ACTIVITY

Daptomycin is a concentration-dependent, rapidly bactericidal antibiotic against Gram-positive organisms as determined by both time-kill and minimum bactericidal concentration (MBC)/MIC ratio determinations [see Report 04-CUB-04] [83-92]. Representative time-kill curves illustrating the bactericidal activity of daptomycin against MRSA and GISA are shown in Figure 5. Against the MRSA strain, daptomycin achieves a 3-log10 reduction in viable organisms in 1 hour at each of the three concentrations used, 2X, 4X, and 8X the MIC. Figure 5 also illustrates the bactericidal effect of daptomycin against a GISA isolate [see Report DAP.025.MC].

Previous studies determined the bactericidal activity of daptomycin compared with that of vancomycin, quinupristin/dalfopristin and linezolid against over 100 isolates of staphylococci including GISA, MRSA, MRSE, MSSA, MSSE and *Staphylococcus haemolyticus* using both MBCs and time kill studies [92]. Daptomycin was bactericidal against all 108 (100%) staphylococcal isolates in this study, independent of species or resistance pattern to other antibiotics. Eighty-three percent of the isolates had an MBC/MIC ratio of 1. Time-kill studies of a random subset (n= 25, GISA 3; MRSA 5; MSSE 4;

MRSE 5; *S. haemolyticus* 5; population of the staphylococcal strains confirmed that at 2X the MIC, daptomycin was bactericidal for 92% (23/25) of the strains [92]. The two strains (*S. haemolyticus*) not killed by 2x MBC concentration had Daptomycin MBC= 0.25 µg/mL, but both were killed at 2 µg/mL.

Figure 5: Bactericidal Effects of Daptomycin against MRSA and GISA



Reference: Thorne, 2002 [44] and Report DAP. 025. MC
Source: Table 2.7.2- 13, this submission

Bactericidal activity against strains with decreased susceptibility to Vancomycin

The bactericidal activity of daptomycin against GISA, h-GISA and wild type MRSA strains was evaluated (Table 2.7.2-28) [see Report 04-CUB-04]. Daptomycin was highly bactericidal with 93.3% of isolates having a MBC of = 1 µg/mL. Eight of the 11 daptomycin MBC results of 2 µg/mL and all 3 MBC results of 4 µg/mL were observed among the GISA strains. Only 68.6% of the MRSA-WT isolates had vancomycin MBC results of = 4 µg/mL. Only 19.3% of the h-GISA and 0.0% of the GISA strains showed vancomycin MBC results at = 4 µg/mL. Table 8 shows the distribution of isolates according to the MBC/MIC ratio for daptomycin and vancomycin. All daptomycin MBC results were at the MIC or two-fold higher than the MIC, and the MBC/MIC ratio was not significantly affected by the susceptibility to vancomycin. All three groups showed very similar MBC/MIC ratio results for daptomycin. Conversely, 17.1% of MRSA-WT strains, 69.3% of h-GISA and all GISA strains showed a vancomycin MBC/MIC ratio of = 16. This study demonstrated that daptomycin was highly bactericidal against *S. aureus* strains and the bactericidal activity was not affected by decreased susceptibility to vancomycin.

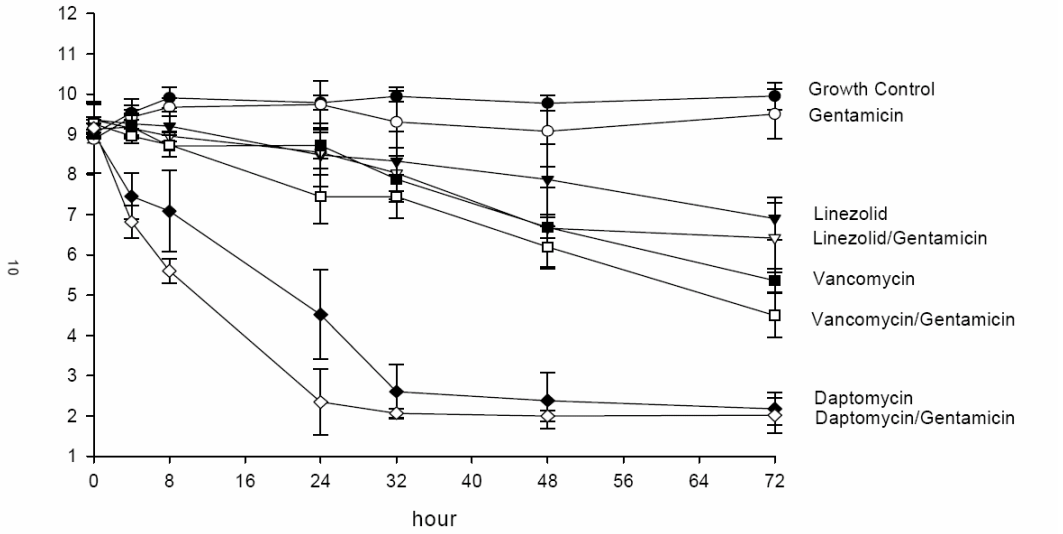
Table 8: Distribution of Isolates According to MBC/MIC Ratio for Daptomycin and Vancomycin

MBC/MIC Ratio	# of isolates (%)					
	Daptomycin			Vancomycin		
	MRSA-WT	hGISA	GISA	MRSA-WT	hGISA	GISA
1	81 (77.1%)	69 (78.4%)	12 (70.6%)	42 (40.0%)	11 (12.5%)	--
2	24 (22.9%)	19 (21.6%)	5 (29.4%)	19 (18.1%)	5 (5.7%)	--
4	--	--	--	12 (11.4%)	4 (4.5%)	--
8	--	--	--	14 (13.3%)	7 (8.0%)	--
≥ 16	--	--	--	18 (17.1%)	61 (69.3%)	17 (100%)

Reference: Report 04-CUB-04
Source: Table 2.7.2- 28, this submission

Daptomycin efficacy was studied in an *in vitro* pharmacodynamic model utilizing simulated endocardial vegetations (SEV) with a high density (10^{10} CFU/g) of both MRSA and MSSA clinical isolates [93]. The metabolism of the bacteria is altered at this cellular density and the cells enter stationary phase. In this high inoculum SEV model, daptomycin demonstrated bactericidal activity against stationary phase cultures with a > 3-log10 reduction (99.9% kill) in CFU/g vegetation in 24 hours (Figure 5) [Figure 2.7.2-14, this submission].

Figure 5: Bactericidal Activity of Daptomycin in a High Inoculum Infection versus MRSA



Reference: LaPlante, 2004 [71]
Note: Y axis on Figure 2.7.2-14 is log10 CFU/gm
Source: Figure 2.7.2- 14, this submission

***Reviewer's comments*:** The Applicant studied an *in vitro* pharmacodynamics model that simulated endocardial vegetations with a high density of both MRSA and MSSA isolates. In this model, daptomycin showed bactericidal activity against stationary phase cultures with a > 3 log10 reduction in CFU/g vegetation. The Applicant infers from this data that daptomycin can kill bacterial cells in similar metabolic state to biofilm and thus vegetative bacteria.

DAPTOMYCIN RESISTANCE

In vitro Selection

In vitro, the frequency of spontaneous daptomycin resistance mutation is rare and occurs at a frequency of 1 x 10^{-9} to 10^{-10} [84]. No known transferable daptomycin-resistance element has been described to date.

Reviewer's comments: In this application, the Sponsor has noted that spontaneous mutations leading to daptomycin resistance is rare in Gram-positive bacteria and that there are no known transferable elements that confer daptomycin resistance. In a recently published study, no spontaneously resistant mutants were obtained from any clinical or laboratory isolates after a single passage in daptomycin [94]. However, stable resistant organisms have been isolated after multiple (n=20) passages in liquid media containing progressively increasing concentrations of daptomycin (initiated from sub-inhibitory MIC levels) and following chemical mutagenesis. Daptomycin MICs for *S. aureus* isolates were 16-fold higher than the parental isolates. In another published study, daptomycin resistant mutants were not found to be resistant to vancomycin or ampicillin as would be expected because of the differences in their mechanisms of action [95]. However, cross resistance to nisin, an antimicrobial similar in structure to daptomycin was found.

Mechanism of Resistance

Genetic Characterization

In an amendment to this efficacy supplement (NDA 21-572 SN008 A011); the Applicant has supplied information on the genetic characterization of some genes associated with increasing daptomycin MIC values.

In 2002, the complete genome sequence of *S. aureus* MW2, a highly virulent community-acquired MRSA strain, was reported [96]. A series of clonally derived *S. aureus* strains with increasing daptomycin MIC values (1 to 16 µg/mL) were created in the laboratory by serial passage from the parental strain [Report DAP.026.MC]. Whole genome scanning techniques were employed to analyze this series of strains and to identify mutations associated with increased daptomycin MIC values. Four genes containing mutations were identified: *mprF*, *yycFG*, *rpoB*, and *rpoC* [see Report DAP.037.MC]. Hypothetical mechanisms for the impact of changes in these genes on daptomycin susceptibility are summarized in Table 9. The functional effects of these mutations have not been determined.

Table 9. Genes with Mutations Identified in *S. aureus* Strains with Daptomycin MIC Values of ≥ 2 µg/ml.

Gene/ Enzyme	Hypothesized Mechanism(s)
mprF (lysylphosphatidylglycerol synthetase)	Increased lysine on cell membrane leads to increase in positive charge, which may repel Ca2+ thereby reducing daptomycin binding
yycFG (histidine kinase; essential 2-component system)	No obvious hypothesis for how daptomycin susceptibility would be impacted.
rpoB, rpoC (RNA polymerase)	May reflect direct interaction of daptomycin with the polymerase, or may lead to changes in global gene expression that alter daptomycin susceptibility. Mutations outside the regions known to confer rifampin resistance; mutations do not overlap with those conferring resistance to other antibiotics (zwittermicin, streptolydigin, and microcin J25).

Table 10 summarizes the genetic mutations and the types of strains in which they have been identified (i.e., wild-type surveillance, laboratory-derived, and clinical) [Report DAP.037.MC].

Table 10. Summary of Genetic Changes and Strain Origin.

	Changes Present in:			
Gene	Wild-Type Strains	DAP-IE-01-02 Strains	Other Clinical Strains	Lab-Derived Strains
mprF	+	+	+	+
yycFG	-	-	+	+
rpoB	-	-	-	+
rpoC	-	-	-	+

Mutations in the *mprF* gene were observed in wild-type, lab-derived, and clinical (including Study DAP-IE strains with daptomycin MIC values of ≥ 2 µg/mL. A majority, but not all, of the laboratory-derived strains with daptomycin MIC values of ≥ 2 µg/mL had *mprF* mutations [Report DAP.037.MC.] A wide variety of *mprF* mutations have been observed, with 13 different amino acid alterations identified to date in wild-type, lab-derived, and clinical strains with daptomycin MIC values of 2 µg/mL. All of the Study DAP-IE-01-02 isolates from daptomycin-treated patients had *mprF* mutations.

In regional and global surveillance studies encompassing over 20,000 unique isolates of wild-type clinical *S. aureus* strains, no isolates were found with daptomycin MIC values of ≥ 4 µg/mL. Mutations in *yycFG* have been observed in both laboratory-derived and clinical *S. aureus* strains with daptomycin MIC values of ≥ 4 µg/mL. Multiple mutations may be required to acquire daptomycin MIC values of ≥ 4 µg/mL. For example, the three clinical strains with mutations in both the *yycFG* and *mprF* genes all had daptomycin MIC values of ≥ 4 µg/mL.

Mutations in *rpoB* and *rpoC* have been observed only in the laboratory-derived strains of *S. aureus* with MIC values ≥ 4 µg/mL.

Emergence of Resistance

In the 18 months since daptomycin was commercially available (November 2003-May 30, 2005), there have been nine cases identified with *S. aureus* infections resulting in treatment-emergent increases in daptomycin MICs (Table 11). The clonal relationship of baseline and on-therapy isolates was demonstrated by pulsed– field gel electrophoresis (PFGE) [see Report DAP.024.MC, this submission]. An additional isolate identified in Section 2.7.4.7 (this submission) from a 52-year old patient with bacteremia is not mentioned here since the baseline (MIC= 0.5 µg/mL) and non-susceptible isolate (MIC= 4.0 µg/mL) were not related as determined by PFGE. Therefore emergence of resistance could not be confirmed. The patients involved were being treated for serious conditions including osteomyelitis, endocarditis and bacteremia.

Table 11: Overview of Isolates with Treatment Associated Decreases in Daptomycin Susceptibility Following Commercial Availability

		LSI		Daptomycin		
Isolate	**Source**	**Number**	**Day**	**MIC (µg/ml)**	**AE Reported**	**AER Number** *
E. faecium	blood	(b) (6)	1	4	Yes	2004S10000131
E. faecium	blood		33	> 32		
E. faecium	blood		35	> 32		
E. faecium	Urine		1	4	Yes	2005S1000001
E. faecium	Blood		27	32		
S. aureus	Blood		1	0.5	No	No event
S. aureus	Blood		16	4		
S. aureus	Blood		1	0.5	Yes	2004S10000255
S. aureus	Blood		182	4		
S. aureus	Rt tibial tubercle		1	0.25	Yes	2004S10000228
S. aureus	Epidural Fat tissue		50	4		
S. aureus	Blood		1	0.5	Yes	2004S10000174
S. aureus	Blood		9	0.5		
S. aureus	Blood		14	4		
S. aureus	Blood		19	4		
S. aureus	Blood		1	0.5	Yes	2004S10000181
S. aureus	Blood		82	4		
S. aureus	Spine		83	2		
S. aureus	Spine		83	4		
S. aureus	Blood		1	1	Yes	2004S10000203
S. aureus	Blood		3	1		
S. aureus	Blood		15	2		
S. aureus	Blood		15	2--4		
S. aureus	Blood		1	0.5	No	No event
S. aureus	Blood		~90	4		
S. aureus	Blood		1	0.5	No	No event
S. aureus	Blood		19	4		

S. aureus		(b) (6)	~97	0.5	Yes	2005S1000105
S. aureus			1	0.5		
S. aureus			50	8		

Note: one additional patient had a *S. aureus* isolate with baseline MIC= 0.5 µg/mL and non-susceptible isolate on treatment (MIC= 4.0 µg/mL) that were not related as determined by PFGE. Therefore emergence of resistance could not be confirmed.
*See Section 2.7.4.7
Source: Table 2.7.2- 29, this submission

Reviewer's note: Table 11 is modified by this Reviewer to include the source of the sample. Reference: Report DAP.024.MC.

***Reviewer's comments*:** Table 11 was adapted from Report DAP.024.MC to compare isolates for MICs and PFGE profiles. Examination of PFGE profiles by this Reviewer confirms that all isolates from each patient were related. However, LSI numbers which demonstrated a profile differing by one band included LSI number: (b) (6) (b) (6) and (b) (6) No PFGE profiles were found for AER Number 2005S1000001 or AER Number 2005S10000105. No MIC data was found for AER Number 2005S10000105.

Table C: Overview of Isolates with Treatment Associated Decreases in Daptomycin Susceptibility Following Commercial Availability

		Daptomycin	MIC (µg/ml)
Isolate	**Source**	**Base**	**Final**
E. faecium	Blood	4	> 32
E. faecium	Urine/Blood	4	32
S. aureus	Blood	0.5	4
S. aureus	Blood	0.5	4
S. aureus	*	0.25	4
S. aureus	Blood	0.5	4
S. aureus	**	0.5	4
S. aureus	Blood	1	2--4
S. aureus	Blood	0.5	4
S. aureus	Blood	0.5	4
S. aureus		0.5	8
*VRE****			8
S. aureus	Blood	0.25	1
*VRE****	Blood		4
MRSA		0.25	1.5

Source: Table **2.7.2-29,** NDA 21-572 SN008
Note: one additional patient had a *S. aureus* isolate with baseline MIC= 0.5 µg/mL and non-susceptible isolate on treatment (MIC= 4.0 µg/mL) that were not related as determined by PFGE. Therefore emergence of resistance could not be confirmed.
*initial source was right tibial tubercle, final source was epidural fat tissue
**initial source was blood, final source was spine
*** not speciated

Table C shows that 15 patients developed MICs to daptomycin of ≥ 1 µg/ml since daptomycin was approved by the Agency for complicated skin and skin structure infections (cSSSI). Isolates with a MIC ≤ 1 µg/ml are considered susceptible to daptomycin.

Of these 15 patients, 9 patients had *S. aureus* isolated from blood. Of these 15 patients, 10 patients demonstrated a three step increase in daptomycin MIC.

Recently, eight reports have indicated the development of daptomycin resistant organisms in clinical settings. The data from these reports are summarized in Table D.

Table D. Recent Reports from the Literature on Daptomycin Resistance.

Organism	Condition	Source	Dose (mg/kg)	Highest MIC (µg/ml)	Reference
Enterococcus faecium	bacteremia	blood	6	>32	(97)
MRSA	bacteremia	blood	4	2	(98)
Enterococcus faecalis	bacteremia	blood	*	16	(99)
Enterococcus faecalis	febrile neutropenia	blood	??	??	(100)
MRSA	osteomyelitis	blood	6	4	(101)
Enterococcus faecium	fever	blood	none	4	(102)
MRSA	bacteremia	blood	8	4	(103)
MRSA	bacteremia	blood	6	4	(104)

*400 mg q48h

The first demonstration of daptomycin resistance was reported by Sabol et al. (97). This report was the first description of a clinical and bacteriological failure of an invasive VRE infection due to the emergence of high-level daptomycin resistance during therapy for a patient with bacteremia caused by *Enterococcus faecium*. Isolates of *E. faecium* ultimately demonstrated MIC values of greater than 32 µg/ml, considered to be non-susceptible. Daptomycin was dosed at 6 mg/kg.

In the second report, Mangili et al. describes a patient who developed daptomycin resistance while experiencing failure of therapy for high-grade MRSA bacteremia (98). The resistance developed during a prolonged course of daptomycin therapy. Initially, isolates had been found to be daptomycin susceptible but subsequently demonstrated a MIC of 2 µg/ml, considered to be non-susceptible. This may be the first well-documented report of the development of daptomycin resistance in a clinical isolate of MRSA that was associated with bacteriologic treatment failure.

In the third report, Munoz-Price et al. describe the emergence of resistance to daptomycin in *Enterococcus faecalis* during treatment of a vancomycin-resistant *E. faecalis* infection associated with an intravenous catheter (99). While PFGE of chromosomal DNA from isolates taken at various stages of the infection demonstrated indistinguishable patterns from all the isolates, the MICs of the various isolates did change. While isolates taken earlier in the infection presented MICs of 1 µg/ml, the final isolate had an increased MIC of 16 µg/ml (nonsusceptibility to daptomycin). This may be the first case of *E. faecalis* infection reported in which resistance to daptomycin developed while the patient was receiving therapy.

Long et al. described the case of a patient with febrile neutropenia treated with daptomycin (100). The patient later developed daptomycin-resistant *Enterococcus faecium* infection. The dosage and highest MIC were not provided in the abstract of the publication.

Hayden et al. described the development of daptomycin resistance during therapy in methicilin-resistant *S. aureus* isolated from two patients (101). The first patient had

bacteremic MRSA prosthetic knee septic arthritis. After bacteremia developed following vancomycin treatment, the therapy was discontinued and daptomycin was initiated at 6 mg/kg/day. Infection relapsed with MRSA bacteremia. Blood cultures yielded MRSA. The second patient had MRSA bacteremia and sternal osteomyelitis complicating heart surgery. The infection resolved after six weeks of vancomycin therapy but relapsed four weeks later with MRSA bacteremia and osteomyelitis. Symptoms resolved again after six weeks of daptomycin dosed at 6 mg/kg/day but MRSA bacteremia recurred one week later. In both cases, the highest daptomycin MIC of the MRSA was 4 µg/ml.

A very disturbing article comes from Lesho et al. (102). These investigators report a case of non-daptomycin-susceptible *Enterococcus faecium* bloodstream infection in a patient with no previous exposure to daptomycin. The patient had a progressively debilitating weakness and fever with a past medical history including chronic renal insufficiency, compensated congestive hear failure, urinary incontinence, and anemia. The patient had no skin lesions or rashes and no stigmata of endocarditis. Blood cultures were positive for Vancomycin-resistant *Enterococcus faecium* and *Enterococcus gallinarum*. An echocardiogram revealed echogenic material on the aortic valve consistent with the presence of a vegetation. Epsilometer test (Etest) was performed on the *Enterococcus faecium* isolate resulting in a MIC of 4 µg/ml. No Etest for daptomycin susceptibility was performed on the *Enterococcus gallinarum* isolate.

Skiest reported the development of daptomycin resistance after prolonged therapy on the drug that resulted in clinical failure (103). A patient developed septic arthritis and bacteremia due to MRSA following a bimalleolar left ankle fracture. Initial treatment was with Vancomycin but the patient was switched to linezolid. Linezolid was discontinued due to severe nausea and thus daptomycin therapy was initiated for six weeks at 8 mg/kg. Subsequently, after clinical failure with daptomycin, the patient underwent left below the knee amputation. However, a stump infection due to MSSA ensued and the patient was treated with daptomycin dosed at 6 mg/kg/day for three weeks with resolution of the infection. The MIC of the MRSA isolate was confirmed twice to be 4 µg/ml. The investigator hypothesized that the resistance developed while on therapy, since the patient initially improved while receiving daptomycin only to eventually worsen after receiving prolonged daptomycin. Preexisting daptomycin resistance cannot be ruled out. The patient received prolonged daptomycin (total of 28 weeks) over two years. The investigator states that it is likely that the prolonged course of daptomycin was a risk factor fro the acquisition of resistance.

Recently, Marty et al. reported the emergence of a daptomycin-resistant MRSA isolate during the treatment of MRSA bacteremia and osteomyelitis (104). The breakthrough isolate was indistinguishable from the pretreatment daptomycin-susceptible isolates by PFGE. Dosing was 6 mg/kg/day. Daptomycin resistance was confirmed by a MIC = 4 µg/ml.

The results of these eight reports are significant since daptomycin has been welcomed as a novel and alternative agent for the treatment of infection with drug-resistant Gram-positive bacteria.

INTERACTION WITH OTHER ANTIBIOTICS

An early *in vitro* interaction study of daptomycin with 25 other antimicrobials against 70 clinical isolates demonstrated that most effects were additive or indifferent (Original NDA 21-572\micro\pubs\adamcp.pdf). Synergistic interactions occurred most frequently with

gentamicin (37% of isolates tested) and amikacin (23%). Among the bacterial strains tested, the enterococci showed the greatest propensity for synergistic effects between daptomycin and other drugs. No antagonism was observed in this study.

In earlier published studies, daptomycin showed synergy *in vitro* against some strains of staphylococci and enterococci when combined with aminoglycosides, imipenem, ampicillin, or phosphomycin [84-88, 105-109].

Using an agar dilution method, Rand and Houck [110] have shown striking synergy between daptomycin and rifampin. Rifampin resistant VRE strains became inhibited at < 1 mg/L rifampicin in the presence of 1/4 or 1/8 MIC of daptomycin. The observation was confirmed by time-kill studies with agreement for 89.5% of isolates.

Synergy between daptomycin and rifampin was also demonstrated with an *in vivo* experimental model of MRSA endocarditis [111]. Daptomycin was administered at a dose corresponding to a human dose of 4 to 6 mg/kg q24h and was comparable to or better than therapy with vancomycin and the combination of rifampin with daptomycin was superior to daptomycin alone.

Daptomycin interaction studies were also undertaken with the Gram-negative spectrum antibiotics to allow for possible combination treatment of mixed infections due to Gram-positive and Gram-negative bacteria during the clinical trials. No *in vitro* interactions were seen between daptomycin and aztreonam when tested against a panel of Gram-positive and Gram-negative bacteria (Original NDA # 21-572\ micro\ pubs\ silvermancp. pdf).

PRECLINICAL EFFICACY—*IN VIVO*

PHARMACOKINETICS AND PHARMACODYNAMICS

Background

A pharmacodynamic analysis of daptomycin determined that the efficacy and safety of daptomycin was optimized with a once daily dosing regimen [112]. Both *in vitro* and *in vivo* studies established that daptomycin is effective in a concentration dependent manner, has a long half-life (8- 9 hours), and demonstrates a prolonged post-antibiotic effect from 4.8 to 10.8 hours [113]. In clinical pharmacokinetic studies, daptomycin demonstrated linear pharmacokinetics over the clinical i.v. dosages of 4 to 6 mg/kg. In normal volunteers administered the clinical dosage of 6 mg/kg q24h, the steady-state Cmax was 98.6 µg/mL and AUC_{0-24} was 747 µg x hr/mL [8]. The half- life in plasma was 8.9 hours. Once daily dosing of daptomycin results in linear pharmacokinetics with minimal drug accumulation [112]. In addition, daptomycin is primarily renally excreted, with the majority of the drug remaining intact in the urine. For a summation of daptomycin ADME studies, see Section 2.7.2.2, this submission.

Preclinical pharmacokinetics studies were conducted in mice, rats, rabbits, guinea pigs, dogs, and monkeys. Tissue distribution and accumulation of daptomycin were characterized in rats whereas metabolism and excretion were characterized in multiple animal species. Cmax and AUC were dose-proportional and predictable.

Binding to plasma proteins across a variety of animal species was 87-94%, which is comparable to binding in humans [114-116]. Protein binding in mouse serum and human serum was independent of daptomycin concentration between 2.5 and 80 µg/mL [116, 117]. Binding is primarily to albumin, although binding to α-1 acid glycoprotein is also observed [117]. The binding of daptomycin to albumin appears to be readily reversible, as evident by the dissociation constant (Kd) of 90.3 µM, equal to 146 µg/mL [see Report 0902]. The protein binding of daptomycin resulted in a 2- to 3-fold increase in the MIC [118].

Total clearance (CLTB) was low in comparison with the hepatic blood flow rates due in part to concentration- independent plasma protein binding. The volume of distribution (Vd) was low, consistent with distribution in the extracellular space. Daptomycin distributes primarily in the plasma, with penetration to vascular tissues (Table 12). Daptomycin, like most antibiotics, does not cross the blood- brain barrier and has limited penetration into the cerebrospinal fluid (CSF) of normal individuals. There was a 6% penetration (relative to serum) of daptomycin into the CSF of rabbits with *Streptococcus pneumoniae* meningitis, resulting in clearance of the bacterial infection in this model [119].

Daptomycin undergoes limited metabolism and is eliminated primarily as non-metabolized active drug. Daptomycin did not inhibit or induce human hepatocyte cytochrome P450 isoenzymes. In animal studies, daptomycin was eliminated primarily by renal excretion. For a summation of animal ADME studies, see Section 2.7.2.2, this submission.

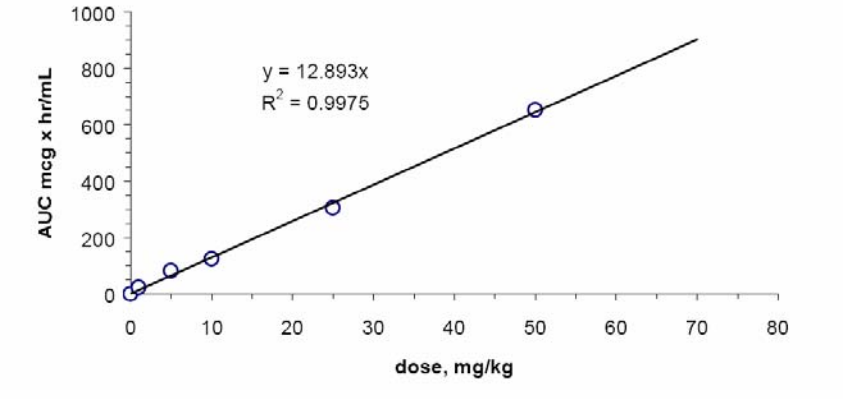
Table 12: Daptomycin Tissue Penetration

Tissue	Species	Maximal Concentration	Percent Relative to Serum	Reference
Blister fluid	Human	27.6 mg/l	68.40%	[62]
Blood clot--tissue	Rat, Rabbit	3.5 µg/g	72.70%	[63]
Peritoneal tissue chamber	Rat, Rabbit	11.8 mg/l	35.10%	[64]
Lung	Mouse, Rat	5 g/l	9.30%	[65]
BAL-ELF	Mouse, Rat, Sheep	1 g/l	2%	[65]
CSF	Rabbit	5.2 mg/l	5.97%	[61]

Source: Table 2.7.2- 30, this submission

The pharmacokinetics of daptomycin was studied extensively in mice to support the pharmacodynamic studies. The dose to exposure correlation was determined for subcutaneous (s.c.) dosing in normal mice. The equation AUC = 12.893 x [dose] was generated for dose to exposure correlations in mice (Figure 6) [Figure 2.7.2-15, this submission].

Figure 6: Correlation of Dose to AUC for Daptomycin Following Subcutaneous Dosing in Mice



Source: Figure 2.7.2- 15, this submission
Reference: Alder, 2003 [120]

***In Vivo* Pharmacodynamic Modeling**

Four different pharmacodynamic studies were conducted using a severely neutropenic mouse thigh model. The pharmacodynamic parameters that best correlated with efficacy were AUC/MIC or Cmax/MIC; time above MIC did not correlate to efficacy [113, 114, 116]. Daptomycin produces concentration-dependent bactericidal activity *in vitro* but also has an inoculum effect. Therefore, it is consistent for both AUC and Cmax to correlate with efficacy. Whereas both Cmax and AUC were predictive of efficacy, the AUC value was chosen for use in calculations. The AUC value is more accurately determined in pharmacokinetic studies due to the multiple time points utilized in the calculations, whereas Cmax determinations are dependent upon a single time critical data point. The total drug AUC/MIC ratios needed to achieve a static response against a *S. aureus* thigh infection in immunosuppressed mice for three of the studies can be found in Table 13 [113,

116, 121]. The AUC/MIC concentrations calculated to produce a therapeutic response against *S. aureus* varied from 120 to 537 µg x hr/mL.

Table 13: AUC/MIC to Achieve a Static Effect against *S. aureus* in Neutropenic Mouse Thigh Infection

Reference	Daptomycin	Total
***S. aureus* strain**	**MIC (µg/ml)**	**AUC/MIC**
Safdar, et al. 2004 [113]		
25923	0.5	388
33591	0.5	537
29213	0.5	420
6538p	0.5	409
Louie, et al. 2001 [116]		
29213	0.2	272 *
Dandekar, et al. 2003 [121]		
43300	0.25	120 **
494	0.25	360 **

* Static dose converted to AUC using the equation AUC = 7.53[dose] + 1.22 as listed in Figure 2B of reference.
** Assuming a protein binding rate of 90%
Source: Table 2.7.2- 31, this submission

A fourth pharmacodynamic study was undertaken to resolve the differences in the previous three studies. This study utilized clonally derived *S. aureus* isolates with MIC values that ranged from 1 to 16 µg/mL [see Report DAP.026.MC]. This study utilized the neutropenic mouse thigh model with five different *S. aureus* isolates of MIC value 1 – 16 µg/mL, derived from *in vitro* serial passage. Neutropenic mice were inoculated with 7.3 log10 CFU of *S. aureus* and then treated with three daily doses of daptomycin ranging from 2.5 mg/kg to 100 mg/kg once daily. There were three dose levels for each isolate, and five mice per dosage group. A more severe criterion of a 3 log10 reduction in CFU from starting inoculum to 4.3 log10 was used as the criterion for efficacy. This stricter 3 log10 reduction criterion was used because the pharmacodynamic model is applied against the requirement for bactericidal activity in bacteremia and endocarditis.

Daptomycin produced a clear dose-response against the *S. aureus*, with isolates of MIC = 1 µg/mL and 2 µg/mL responding to AUC values ≤ 275 µg x hr/mL of daptomycin, whereas the isolate of MIC = 4 required an AUC of 453 µg x hr/mL, and isolates of MIC 8 and 16 µg/mL required > 1,000 µg x hr/mL. The resulting AUC/MIC ratios required for 3 log10 reduction were relatively steady at MIC values ≥ 2 µg/mL.

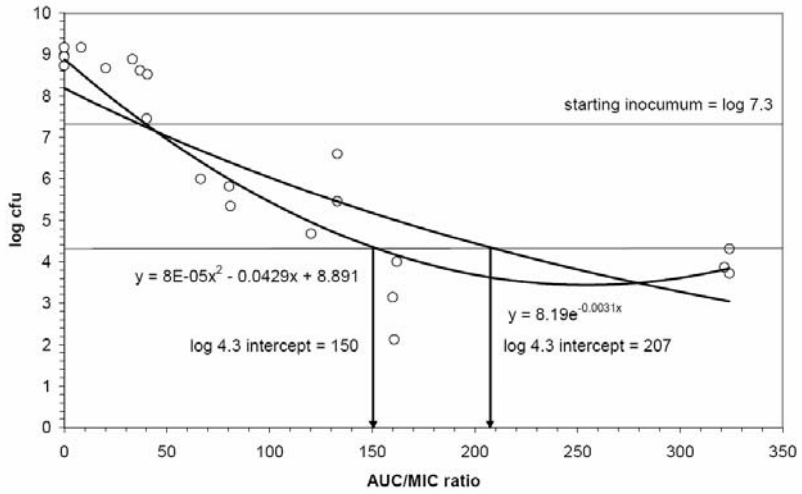
Table 14: AUC/MIC to Achieve a 3 log10 Reduction in *S. aureus* Count in Neutropenic Mouse Thigh Infection

S. aureus Strain	Daptomycin MIC (µg/mL)	Total AUC for 3 log10 reduction (µg x hr/mL)	AUC/MIC for 3 log10 reduction
MW2	1	275	275
1694	2	250	125
1695	4	453	113.2
1615	8	1031	128.9
1616	16	1766	110.3

Source: **Table 2.7.2—32, this submission**

To calculate overall AUC/MIC required for 3 log10 reduction in CFU, a model utilizing each dose and corresponding log CFU count for each isolate was used. This analysis (Figure 7) [Figure 2.7.2—16, this submission] shows the AUC/MIC and corresponding log10 CFU count for each dosage used against the five isolates.

Figure 7: Correlation of AUC/MIC to log10 CFU of *S. aureus* in Neutropenic Mouse Thigh Experiments



Source: Figure 2.7.2—16, this submission

There was an inflection point in AUC values to produce a therapeutic response at MIC = 4 µg/mL. Two different regression analyses were performed to calculate overall AUC/MIC ratio to produce a 3 log10 response.

The first analysis was a second order polynomial and weighted all data points equally. The AUC/MIC ratio was calculated at 150 based on the solution of:

$y = 8 \times 10^{-5} [x^2] - 0.0429x + 8.891$; where y = 4.3 and x = AUC/MIC ratio to achieve log 4.3 (3 log10 reduction).

The second analysis weighted the MIC = 1 and 2 value isolates more heavily, since these are the isolates closest to the breakpoint. The AUC/MIC was calculated as 207 based on the solution of:

y = 8.19e-0.0003x: where y = 4.3 and x = AUC/MIC ratio to achieve a log 4.3 (3 log10 reduction).

ANIMAL MODELS OF EFFICACY

The efficacy of daptomycin was demonstrated against both MRSA and MSSA in several animal models of infection, including models of endocarditis and bacteremia. Efficacy was measured by increase in survival or by multi-log10 reductions in bacterial burden in the target tissue. Daptomycin was efficacious against *S. aureus* at dosages that produced AUC_{0-24} exposures attainable at the clinical dosages of 6 mg/kg q24h in humans. The efficacy of daptomycin in these investigations generally paralleled *in vitro* activity and typically compared favorably with vancomycin efficacy.

In Vivo *Bacteremia Models*

Daptomycin was effective in treating a variety of drug-resistant and -susceptible Gram-positive bacterial strains in lethal bacteremia challenge models. The efficacy of daptomycin was consistent with the *in vitro* potency demonstrated against *S. aureus* (MIC90 = 0.5 µg/mL). Treatment of infections was achieved against wild type *S. aureus* at effective dosage (50% effective dosage, PD50) values of < 10 mg/kg [122]. Against laboratory-derived resistant isolates, the PD50 values ranged from 5.0 to 11.3 mg/kg.

In a murine model of *S. aureus* bacteremia, 10 and 5 mg/kg daptomycin treatments increased survival when compared with the control group, and was equally effective as vancomycin treatment [123]. In addition, blood and organ cultures demonstrated sterilization of *S. aureus* in a greater percentage of daptomycin-treated mice (55 to 73%) versus untreated controls (16%). The therapeutic effectiveness of daptomycin was equal to or superior to vancomycin as evaluated by both survival and clearance of bacteremia.

The rapid bactericidal activity of daptomycin was also demonstrated *in vivo* against MRSA in mice [124]. Mice were infected intraperitoneally with *S. aureus* Xen- 1, an MRSA isolate with a luciferase plasmid construct, which causes the bacteria to appear luminescent as long as they are producing ATP. Lack of fluorescence is associated with bacterial cell death. Using this system, viable bacteria were viewed non- invasively inside the mouse at varying intervals. A dosage of 50 mg/ kg of daptomycin (human equivalent exposure to between 6 and 8 mg/ kg) resulted in a reduction of approximately 90% in signal over two hours. Vancomycin at a dosage of 50 mg/ kg resulted in a reduction of 60 – 70% (Figure 2.7.2- 17, this submission) [124].

In Vitro *Bacteremia Models*

Daptomycin has demonstrated efficacy against *S. aureus* in *in vitro* models of bacteremia [125]. This model used infusion pumps to simulate clinical dosing of 0 mg/kg to 9 mg/kg against a *S. aureus* culture contained in a biochamber. Daptomycin produced a 3 log10 reduction in *S. aureus* CFU count at a mean simulated clinical dosage of 1.9 mg/kg, and a 5 log10 reduction [ED80 dose] at a dosage of 3.1 mg/kg against two different MRSA

isolates. The 5 log10 reduction at 3.1 mg/kg simulated dosage represented the ED80 of maximal effect.

In Vivo *Models of* S. aureus *Endocarditis*

There are six published or completed reports examining the effect of daptomycin in rat or rabbit models of *S. aureus* endocarditis [see Report Miro 2005] [111, 115, 126-128]. These studies all modeled endocarditis by placing a catheter across the aortic valve of the animal causing endothelial damage and thereby permitting consistent seeding of the valve following an i.v. inoculum of *S. aureus*. Antibiotic treatment was typically initiated 24 hours after infection and continued for two to six days. Comparator antimicrobials used in these studies included vancomycin, gentamicin, teicoplanin, imipenem, penicillin, and semi-synthetic penicillins. Table 15 presents the relevant experimental details and pharmacokinetic data for these studies. The *in vivo* efficacy of an antibiotic in the treatment of endocarditis is dependent upon the gradient-driven penetration and distribution of the drug within infected cardiac valve vegetations and upon the ability of the antibiotic to kill metabolically inactive bacteria within these vegetations [129]. In a model of *Enterococcus faecium* endocarditis in rabbits, ^{14}C-daptomycin penetrated and was homogeneously distributed throughout all aortic valve vegetations at 30 minutes post- dose [105].

Table 15: Animal Models of Daptomycin Treatment of *S. aureus* Endocarditis including Dosing and Pharmacokinetics

Species	Interval Infection to Treatment	Duration of Treatment (days)	Dosing	Peak	Trough	$T_{1/2}$	Reference
Rabbit	24h	3--10	10 mg/kg iv q24h	49	3.1	6	[72]
Rabbit	18h	4	8 mg/kg iv q8h	76	20	ND	[57]
Rat	8h, 15h 8h, 15h	3 6	5 mg/kg q24h 5 mg/kg q12h 10 mg/kg q24h 10 mg/kg q12h	25 25 60 60	< 1 ~2 < 1 7	ND	[73]
Rat	24h	5	5 mg/kg SC q12h 10 mg/kg SC q24h	31 85	1 1	1.7	[74]
Rat	4h	3	25 mg/kg SC q24h 40 mg/kg SC q24h	64 91		2.1 4.3	[53]
Rabbit	16h	2	Pump simulating human 5 mg/kg q24h	86	15	3.57 ± 0.19	[76]

Source: Table 2.7.2—33, this submission

There were multiple differences between the six studies, including the animal species, route of administration, interval between inoculation and first dose, dosing and schedule, and duration of treatment. These differences resulted in different pharmacokinetic characteristics of daptomycin between the six trials as evidenced by the differences in Cmax and trough (Cmin) values. Most of these models did not achieve the Cmax value of 98 µg/mL attained in normal volunteers dosed at 6 mg/kg. In addition, the half-life of daptomycin is markedly shorter in animals (rabbits 3.57 to 6 hours; rats 1.7 to 4.3 hours) than in humans, resulting in prolonged periods of low drug levels. The interval from the injection of the inoculum to initiation of treatment affected the size and bacterial burden of

the vegetations [127]. The duration of treatment varied from three to ten days, which is significantly shorter than the clinical treatment period of four weeks. Therefore, the animal models of endocarditis present a challenging infection model for antibiotic treatment.

Table 17 presents the quantitative experimental results of the six models. Daptomycin treatment produced efficacy in both rat and rabbit models of endocarditis. Daptomycin treatment produced increases in the percent of sterile vegetations relative to untreated controls. In rats, the effective daptomycin dose was 5 to 10 mg/kg once or twice daily by s.c. injection, which provided Cmax values of 30 µg/mL and AUC_{0-24} values of = 200 µg x h/mL (Li, unpublished data on file reported in original NDA 21-572: micro\microsum. pdf, Table 7- 4) [130]. Daptomycin achieved sterilization of cardiac vegetations in up to 100% of animals infected with staphylococcus [111, 115, 126-128, 131, 132]. The efficacy of daptomycin was consistently greater than that of other antimicrobials, including vancomycin, penicillin, ampicillin, and gentamicin. Daptomycin was significantly more effective than nafcillin against MSSA and comparable to vancomycin against MRSA.

In the most recent rabbit endocarditis model, the pharmacokinetics of daptomycin is the closest pharmacokinetic performance to the clinical values obtained in man [133]. Infusion pumps inserted in infected rabbits were used to produce the Cmax, half- life, and AUC values achieved by a 6 mg/kg dose in humans. The peak and trough levels for daptomycin were 86 and 15 mg/L and for vancomycin were 46 and 6 mg/L, respectively. In the Miro study, daptomycin produced greater reductions in bacterial burden than vancomycin against both MRSA and GISA endocarditis infections. In addition, daptomycin treatment produced a greater proportion of sterile vegetations than did vancomycin (Table 16). Therapy with daptomycin was more effective than vancomycin ($p < 0.05$) in sterilizing the endocardial vegetations and reducing the log10 CFU/g of vegetation [see Report Miro 2005] [133].

Table 16: Efficacy of Daptomycin and Vancomycin in the Treatment of MRSA and GISA Endocarditis in Rabbits Dosed Using Infusion Pumps to Simulate Clinical Dosages

Group	# Surviving at Day3/ total	# Sterile Vegetations/ Total	Log10 Mean +SD CFU/g vegetation
GISA			
Saline	0/17	0/17	9.1 ± 0.9
Vancomycin	20/23 (87%)	4/20 (20%)	6.0 ± 204
Daptomycin	19/19 (100%)	12/19 (63%)	4.8 ± 3.5
MRSA			
Saline	0/20	0/20	8.9 ± 0.6
Vancomycin	20/20 (100%)	7/20 (35%)	4.4 ± 2.6
Daptomycin	18/19 (95%)	13/18 (72%)	3.3 ± 2.3

Reference Garcia de la Maria [133] and Report Miro 2005
Source: Table 2.7.2—34, this submission

Table 17: Results of Treatment with Daptomycin and Comparator in Animal Models of *S. aureus* Endocarditis

Organism	Onset/Duration Treatment	Daptomycin Dose	Vegetation log CFU/g*	% Sterile Vegetation**	Comparator Treatment	Vegetation log CFU/g*	% Sterile Vegetation**	Vegetation log CFU/g*	Reference
MSSA	24h/ 3-10d	10mg/kg q24h	0.7 ± 0.9	NA	nafcillin	2.7 ± 3.2	NA	6.7 ± 3.2	[72]
MRSA	24h/ 3-10d	10mg/kg q24h	3.9 ± 2.4	NA	vancomycin	3.5 ± 1.8	NA	8.8 ± 0.6	[72]
MSSA 1	18h/4d	8mg/kg q8h	3.3 ± 1.9	69%	vancomycin	5.2 ± 2.2	14%	9.7 ± 0.5	[57]
MSSA 2	18h/4d	8mg/kg q8h	4.1 ± 1.1	19%	vancomycin	4.6 ± 2.4	31%	9.0 ± 0.7	[57]
MRSA	18h/4d	8mg/kg q8h	2.4 ± 0.3	94%	vancomycin	3.0 ± 1.6	78%	8.8 ± 0.9	[57]
MSSA	8h 3d	10mg/kg q12h	< 2 (< 2--4.4)	89%	vancomycin	< 2 (< 2--9.8)	67%	5.8 (< 2--8.6)	[73]
					cloxacillin	< 2 (< 2--3.6)	93%		
MSSA	15h 3d	10mg/kg q12h	< 3.6 (< 2--7.0)	35%	vancomycin	< 8.7 (< 2--10.7)	12%	9.1 (6.4--10.3)	[73]
MRSA	15h 3d	10mg/kg q12h	< 5.2 (< 2--9.4)	14%	vancomycin	< 9.0 (< 4.2--10.4)	0%	8.5 (6.5--9.5)	[73]
MSSA	15h 6d	5mg/kg q24h	< 8.3 (< 5.2--9.8)	0%	vancomycin	< 3.37 (< 2--9.6)	33%	9.1 (6.4--10.3)	[73]
		5mg/kg q12h	< 2.6 (< 2--10)	50%					
		10mg/kg q24h	< 2 (< 2--10)	60%					
		10mg/kg q12h	< 2 (< 2--4.4)	81%					
MRSA	15h 6d	5mg/kg q12h	< 7.12 (< 2--10.2)	29%	vancomycin	< 2 (< 2--10.1)	53%	8.5 (6.5--9.5)	[73]
		10mg/kg q24h	< 2 (< 2--10.3)	75%					
		10mg/kg q12h	< 2 (< 2--9.5)	61%					
MSSA	24h 5d	5mg/kg q12h	3.4 ± 0.9	31%	vancomycin	5.2 ± 2.0	27%	9.9 ± 0.6	[74]
		10mg/kg q24h	7.3 ± 2.64	10%					
MRSA	4h 3d	25mg/kg q24h	5.5 ± 1.7	85%	vancomycin	7.1 ± 2.5	78%	10.6 ± 0.8	[53]
		40mg/kg q24h	4.2 ± 1.5	92%					
MRSA	16h 2d	simulating human 6mg/kg q24h	3.3 ± 2.3	72%	vancomycin	4.4 ± 2.6	35%	8.9 ± 0.6	[76]
GISA	16h 2d	simulating human 6mg/kg q24h	4.8 ± 3.5	63%	vancomycin	6.0 ± 2.4	20%	9.1 ± 0.9	[Report Miro 2005]

*log10 colony forming units per gram of vegetation
**percentage of animals with sterile vegetations (below limit of detection)
Results are shown as presented in publication and reflect mean + standard deviation or median (range).
For reference 5, % survival is shown; NA = not available.
Source: Table 2.7.2—35, this submission

The efficacy of daptomycin was evaluated in rats dosed to approximate clinical AUC values against MRSA in a model of aortic valve endocarditis (Table 18) [111]. For the 40 mg/kg dose of daptomycin in rats, the mean peak levels in serum were 90.9 µg/mL, and the AUC was 605 µg x hr/mL, similar to the Cmax of 98.6 µg/mL and AUC of 747 µg x hr/mL produced in healthy human volunteers dosed with daptomycin at 6 mg/kg. The 25 mg/kg dose produced lower Cmax and AUC values of 64 µg/mL and 278 µg x hr/mL, respectively. Daptomycin treatment at both 25 and 40 mg/kg in rats increased the survival of the rats and decreased the bacterial burden of the vegetations compared to either vancomycin treatment or the saline control. Moreover, the 40 mg/kg daptomycin dosage (closer to 6 mg/kg human equivalent) produced significantly ($p < 0.05$) greater efficacy than did vancomycin at 150 mg/kg, whereas the 25 mg/kg dosage (closer to the 4 mg/kg human equivalent) was not statistically different from vancomycin. Table 18 describes the rat pharmacokinetic profiles and resulting efficacy in this trial. These results support the higher daptomycin clinical dosage of 6 mg/kg for treatment of endocarditis.

Table 18: Efficacy of Daptomycin in the Rat Model of Endocarditis

Group	Cmax (µg/mL)	AUC 0-24 (µg x hr/mL)	Log10 Mean ±SD CFU/g Vegetation
Daptomycin*			
25mg/kg s.c.	63.6	278.4	5.5 ± 1.7
45mg/kg s.c.	90.9	605.4	4.2 ± 1.7
Vancomycin			
150mg/kg**	ND	ND	7.1 ± 2.5
Saline	--	--	10.6 ± 0.8

*Administered as a 30-min infusion
**Administered as a continuous infusion
ND=not determined
Source: Table 2.7.2—36, this submission

Fibrin Clot Models

The efficacy of an antibiotic in the treatment of endocarditis is dependent upon the penetration and distribution of the drug within infected vegetations. Aortic valve vegetations that occur in endocarditis are not vascularized; therefore, antibiotic diffusion into the infected site is gradient driven. This has been modeled both *in vitro* and *in vivo*.

In Vivo Fibrin Clot Model

Treatment of endocarditis is dependent on antibiotic penetration and activity into sequestered vegetations. The efficacy of daptomycin was studied in a *S. aureus* fibrin clot model simulating endocarditis vegetations in rats [134]. Fibrin clots containing fibrinogen, thrombin, and bacteria were formed in vitro and surgically implanted subcutaneously in the backs of rats. The rats were treated for three to six days and the clots were harvested, homogenized, and evaluated for CFUs.

Daptomycin dosed at 33 mg/kg twice daily (66 mg/ kg/day) for six days resulted in a significant reduction (5 log10) of bacterial counts [135]. Vancomycin dosed at 100 mg/kg twice daily (200 mg/kg/day) for six days produced a 2 log10 reduction in MRSA counts.

This model demonstrates penetration and bactericidal activity of daptomycin against *S. aureus* in fibrin clots *in vivo* (Table 19).

Table 19: Efficacy of Daptomycin in a Rat Model of *S. aureus* Infection of Fibrin Clots

Group	log10 CFU
Daptomycin	
10mg/kg bid	7.42
22mg/kg bid	4.41
33mg/kg bid	3.81
Vancomycin	
25mg/kg s.c.	6.74
Saline	8.73

Reference Mortin, 2005 [135]
Source: Table 2.7.2—37, this submission

Figure 2.7.2-18 (not shown) depicts the rapid bactericidal activity of daptomycin using bioluminescent MRSA bacteria in the s.c. implanted fibrin clots. Decrease in bacterial viability is monitored in real time by measuring the loss in bioluminescence of the bacteria. There is significant reduction in bioluminescence after the initial daptomycin dose (panel B), and after five days of dosing no bioluminescence is apparent (panel D).

In Vitro Fibrin Clot Model

Daptomycin has demonstrated efficacy using *in vitro* pharmacodynamic models of endocarditis that utilized infusion pumps to simulate clinical pharmacokinetic parameters against SEV in biochambers. Daptomycin demonstrated efficacy against a variety of drug-resistant *S. aureus* strains, including MRSA, GISA, and VRSA (Table 20) [71, 89, 90, 136-138]. Daptomycin at 6 and 10 mg/kg dosing regimens was bactericidal against all strains evaluated and produced > 6 log reduction in CFU/g of vegetation within 24h. In addition, under these simulated conditions throughout the 72h time course no daptomycin resistance developed. Daptomycin was the only antibacterial to produce bactericidal activity against stationary phase *S. aureus* in high inoculum (1×10^9) SEV models [71], whereas gentamicin, linezolid and vancomycin failed.

Table 20: Summary of Bactericidal Activity of Daptomycin against a Variety of *S. aureus* Isolates in Simulated Endocarditis Vegetations

Strains	MIC (MBC)	Simulated Dosing	Log10 CFU/g Reduction in 72h	Reference
MRSA	0.25 (0.25)	6mg/kg/day	6.73	[89]
MRSA	0.125 (0.25)	6mg/kg/day	> 6	[136]
MRSA	0.25 (0.25)	10mg/kg/day	8.14	[89]
GISA	0.5 (1)	6mg/kg/day	8.05	[89]
GISA	0.5 (1)	10mg/kg/day	8.57	[89]
VRSA	0.25 (0.5)	6mg/kg/day	> 6	[136]

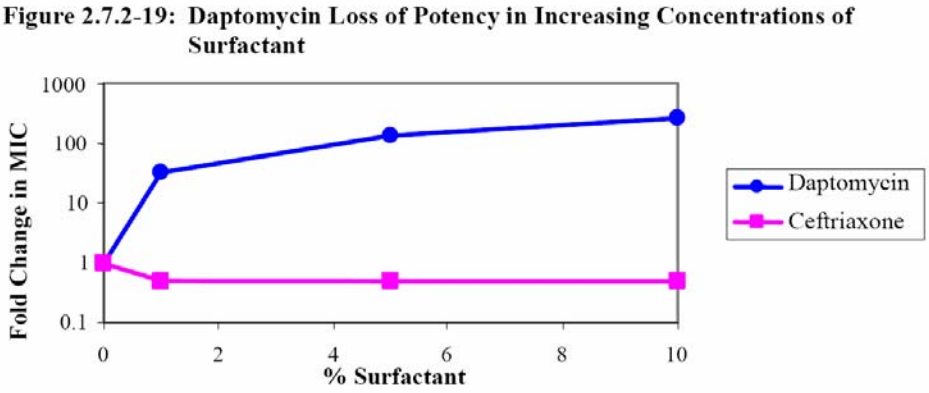
Source: Table 2.7.2—38, this submission

The Applicant asserts that the results from this SEV model demonstrate that daptomycin can penetrate vegetations and retain its bactericidal activity suggesting the potential for effective treatment of endocarditis.

In Vivo *Animal Studies of Efficacy of* S. aureus *Hematogenous Pneumonia*

S. aureus pneumonia from a hematogenous source is a common metastatic complication of right-sided infective endocarditis. Hematogenous pneumonia was of potential concern for daptomycin, based on previous clinical results. As detailed in NDA # 21- 572, daptomycin failed to meet the statistical end point of non-inferiority against ceftriaxone therapy for the treatment of hospitalized community-acquired pneumonia. Clinical efficacy in the pneumonia trial was 79% for daptomycin at 4 mg/kg q24h and 87% for ceftriaxone at 2 g q24h in the clinically evaluable population. The potential reasons for this outcome were investigated in rodent models and in a novel *in vitro* susceptibility assay. The activity of daptomycin was sharply reduced by low concentrations of pulmonary surfactant Survanta® as shown in Figure 8 (Figure 2.7.2- 19, this submission) [139]. Inhibition of daptomycin by surfactant is likely due to daptomycin binding to phosphatidylcholine and fatty acid aggregates in Survanta®, resulting in sequestration of the antibiotic. Clinical results may be due in part to both daptomycin inactivation by pulmonary surfactant and to somewhat lower concentrations in bronchial-alveolar fluid during mild lung infection compared to concentrations achieved in other body sites [139].

Figure 8: Daptomycin Loss of Potency in Increasing Concentrations of Surfactant



Reference Silverman, 2005 [139]
Source: Figure 2.7.2—19, this submission

Daptomycin failed to reduce bacterial counts in lung tissue in mouse models of *Streptococcus pneumoniae* bronchial- alveolar pneumonia (BAP) (Table 21). Infection was induced by intratracheal inoculation of the bacteria into the bronchial- alveolar space.

Table 21: Comparative Efficacy of Daptomycin in the Treatment of *S. pneumoniae* in a Mouse Model of Bronchial-Alveolar Pneumonia

Treatment Group	N	Mean Log10 CFU
Daptomycin 25 mg/kg	5	7.6
Daptomycin 50 mg/kg	5	7.7
Daptomycin 100 mg/kg	5	7.5
Ceftriaxone 50 mg/kg	5	2.9
Saline	5	7.4

Reference: Alder, 2004 [140]
Source: Table 2.7.2—39, this submission

Daptomycin produced significant efficacy in rodent models of hematogenous pneumonia [139]. Mice or rats were inoculated i. v. with 2 to 5 x 10^7 *S. aureus* cells microencapsulated in agarose beads (50 µm in diameter). The beads lodged into the capillaries in the lungs causing a hematogenous embolic pulmonary infection with significant lung pathology. Twenty-four hours post-infection the animals were treated for 6 to 14 days [140, 141].

Daptomycin, at doses simulating a once daily human dose of 6 mg/kg, was effective in promoting survival, in eliminating bacteremia, and in lowering the bacterial burden in the lungs of mice and rats challenged with either MRSA or MSSA (Table 22) [124].

Table 22: Efficacy of Daptomycin and Vancomycin against a Hematogenous MRSA Pneumonia Infection in Rats

Group	Dose	Bacterial Count (Log10) ± SD
Daptomycin	50mg/kg s.c., QD x 6	2.94 ± 0.57
Vancomycin	100mg/kg s.c., QD x 6	3.7 ± 1.18
Saline	NA	5.03 ± 0.98

Reference: Mortin, 2004 [124]
Source: Table 2.7.2—40, this submission

The Applicant asserts that these data are supportive of daptomycin efficacy against hematogenous pneumonia as a potential complication of right-sided endocarditis. Whereas daptomycin lacked comparable efficacy in BAP, data show that daptomycin decreases bacterial levels in hematogenous pneumonia in both mouse and rat lung.

In Vivo *Animal Studies of Efficacy of* S. aureus *Meningitis*

S. aureus meningitis can occur as a complication of endocarditis, as well as after neurosurgical procedures, head trauma or in individuals with CSF shunts. Cottagnoud et al evaluated the efficacy of daptomycin against experimental *S. aureus* meningitis in rabbits [142]. Daptomycin bactericidal activity was superior to vancomycin against an MSSA strain in experimental meningitis (Table 23). In a second trial, daptomycin treatment of *S. aureus* meningitis in infant rats was shown to cause less inflammation and brain damage than ceftriaxone [see Report Grandgirard-Cottagnoud 2005] [119].

Table 23: Daptomycin and Vancomycin Monotherapy against MSSA Experimental Meningitis

Groups (N=10)	Inoculum (Log10 CFU/ml)	Killing Rates/h (Δ log10 CFU/mL x h)	Killing Rates/8h (Δ log10 CFU/mL x 8h)
Daptomycin	5.50 ± 0.36	-- 0.59 ± 0.14	-- 4.54 ± 1.12
Vancomycin	5.18 ± 0.32	-- 0.43 ± 0.24	-- 3.43 ± 1.17

Reference: Cottagnoud, 2004 [88]
Source: Table 2.7.2—41, this submission

Reviewer's comments: The Applicant presents data from a number of animal models of efficacy that include bacteremia, endocarditis, fibrin clot, hematogenous pneumonia, and experimental meningitis. Models included both *in vitro* and *in vivo* models and were performed in rats, mice and rabbits. Efficacy was measured by either a log10 reduction in bacterial burden in the target tissue or by increased survival. The dosage given was a dosage that produced AUC_{0-24} exposures achievable at the human clinical dosage of 6mg/kg q24h.

The first model investigated was bacteremia in both *in vitro* and *in vivo* permutations. In an *in vivo* model of ***bacteremia in mice***, daptomycin was successful in resisting challenges with *S. aureus*. Dosages of 5 and 10 mg/kg were equally effective as vancomycin treatment. The Applicant states that blood and organ cultures showed sterilization of *S. aureus* in a significantly greater percentage of daptomycin-treated mice (55 to 73%) versus untreated controls (16%). However, the Applicant does not state the percentage of Vancomycin-treated mice that showed sterilization of *S. aureus*.

The Applicant also presents data on efficacy in a murine model in which ***mice*** were injected ***intraperitoneally*** with a MRSA stains (Xen-1) harboring a luciferase plasmid constructs. Daptomycin showed a reduction of about 90% while vancomycin showed reduction of 60—70% when both drugs were dosed at 50mg/kg (equivalent to 6—8mg/kg in humans). To this Reviewer, the significance of these results is not clear.

The Applicant also presents data from an ***in vitro*** model of ***bacteremia***. The model uses infusion pumps to simulate clinical dosing of 0—9mg/kg against a culture of *S. aureus* in a biochamber. Daptomycin produced a 3 log10 and a 5 log10 reduction of MRSA at dosages of 1.9mg/kg and 3.1mg/kg, respectively. The reason for these low dosages, relative to the proposed human dosage of 6mg/kg is unclear.

The Applicant presents data from six studies in models of ***endocarditis*** in both ***rats*** and ***rabbits***. All studies modeled endocarditis by placing a catheter across the aortic valve of the animal causing endothelial damage to permit consistent seeding of the valve following an intravenous inoculum of *S. aureus*. Comparators included Vancomycin, gentamicin, teicoplanin, imipenem, penicillin and semi-synthetic penicillins.

There were a ***variety of differences*** between the studies including the animal model, route of administration, interval between inoculation and initial dose, dosing and schedule, and duration of treatment. Most of these models did not attain the C_{max} value achieved in normal volunteers dosed at 6mg/kg. It is also pertinent that the half-life of daptomycin is markedly shorter in animals (rabbits 3.57 to 6h; rats 1.7 to 4.3h) than in humans resulting in prolonged periods of low drug levels. In addition, the period of treatment varied from 3 to 10 days, a significantly shorter period than clinical treatment of humans (4 weeks).

Consequently, extrapolation of the animal efficacy data to expected human results is not robust.

The results of the studies performed in both rats and rabbits are presented in Table 17. The results from this table are mixed but suggest that better efficacy was obtained in the rabbit model than in the rat model.

As mentioned earlier, daptomycin is more efficacious than comparators according to rabbit models of endocarditis. In the earliest report presented by the Applicant, animals dosed with daptomycin at 10 mg/kg q24h for 3—10 days had a lower cfu count of MSSA than animals treated with nafcillin. While animals dosed with the same dose of daptomycin had a slightly higher cfu count of MRSA than animals treated with Vancomycin, the daptomycin animals had a higher percentage of sterile vegetations than animals dosed with vancomycin (83% to 60%) [126]. There were no data regarding the development of antibiotic resistance.

In a second study, daptomycin was dosed at 8 mg/kg q8h for 4 days and compared to vancomycin treated rabbits. Daptomycin was more efficacious than vancomycin or teicoplanin against two strains of MSSA and one strain of MRSA as measured by percent sterile vegetations and by cfu/g per vegetation. Two animals of 16 yielded organisms resistant to daptomycin; one organism had a four-fold rise in MIC and another, an eight-fold rise in MIC [115]. ***Thus, while daptomycin was more efficacious than either teicoplanin or vancomycin, diminished susceptibility developed during therapy***. It is likely that resistant organisms were selected for by sub-inhibitory concentrations of daptomycin deep within the vegetations.

In another rabbit study, daptomycin was dosed to simulate a human dosing of 6 mg/kg q24h using a humanized pharmacokinetics model to treat rabbit endocarditis caused by MRSA. The drug was administered 16h after infection for two days. These animals were compared to animals dosed with vancomycin to simulate a 1g/12h intravenous injection. the daptomycin treated animals had a higher percentage of sterile vegetations (72%) than the vancomycin treated animals (35%) and a greater mean log reduction in cfu/g of vegetation (3.3 versus 4.4) [133]. There were no data regarding the development of antibiotic resistance.

The final rabbit study was performed recently by the Applicant. Again, daptomycin was dosed to simulate a human dosing of 6 mg/kg q24h using a humanized pharmacokinetics model to treat rabbit endocarditis caused by MRSA but also GISA. Once again, the daptomycin treated animals had a higher percentage of sterile vegetations (MRSA 72%; GISA 63%) than the vancomycin treated animals (MRSA 35%; GISA 20%) and a greater mean log reduction in cfu/g of vegetation [Report Miro 2005]. Once again, there were no data regarding the development of antibiotic resistance.

The last two references that utilize the rabbit model of endocarditis most closely resemble a simulation of human pharmacokinetics parameters. In both cases, daptomycin was more efficacious than vancomycin in treating MRSA and GISA infective endocarditis. One rabbit study examined the development of resistance to daptomycin. Since the dosing (8 mg/kg q8h) was below the simulated human level, the concentrations may have been below the optimal level and consequently, the presence of sub-inhibitory levels of daptomycin may have allowed selection resistant organisms. ***However, these animal studies suggest that proper dosing is critical to the avoidance of resistant organisms during therapy***.

One of the most pressing concerns to this Reviewer concerning this submission is the inability of daptomycin to penetrate endocarditis vegetations. As these vegetations are not vascularized and since the biofilm formed on these valves secrete an exopolysaccharide, these vegetations are resistant to the entry of antibiotics. Penetration into the vegetation is gradient driven and thus is dependent on sufficient concentrations of antibiotic available in the external environment (relative to the vegetation). Because daptomycin reportedly is so highly protein bound, concentrations *in vivo* may have to exceed by several fold the bactericidal concentrations measured *in vitro* for daptomycin to be effective for endocarditis. To address this concern, the Applicant presents data from both *in vitro* and *in vivo* models of fibrin clots.

In an ***in vivo* model in rats**, fibrin clots containing fibrinogen, thrombin, and *S. aureus* were formed *in vitro* and surgically in planted subcutaneously in the backs of rats. Rats were treated for 3—6 days and the clots were harvested, homogenized, and evaluated for CFUs. Daptomycin was dosed at 33 mg/kg twice a day for 6 days resulting in a 5 log10 reduction of CFUs. Vancomycin dosed at 100mg/kg twice daily for 6 days produced a 2 log10 reduction in MRSA counts.

In an ***in vitro model*** using infusion pumps to simulate clinical PK parameters against SEV in biochambers, daptomycin showed efficacy against MRSA, GISA and VRSA strains. At 6 and 10 mg/kg dosing regimens, daptomycin was bactericidal against all strains and demonstrated > 6 log10 reduction in CFU/g of vegetation within 24h. No resistance was seen throughout the 72h. Daptomycin was the only antibacterial to produce bactericidal activity against stationary phase *S. aureus* in high inoculum (1 x 10^9) SEV models while gentamicin, linezolid and vancomycin failed. It should be noted that the S. aureus strains used in these experiments demonstrated relatively low MICs (0.125—0.5 μg/ml).

The data presented from the fibrin clot experiments are encouraging. However, several aspects of the experiments imply that the data should be viewed with caution. The *in vivo* models utilized artificially generated fibrin clots which may or may not replicate vegetations produced *in vivo*. In addition the *in vitro* models are just that, the entire model is artificial. It is also not clear as to the significance of the log reductions seen in the vegetations. ***However, the Applicant does seem to show proof of concept that daptomycin is capable of penetrating cardiac vegetations.*** Longer term experiments may have been more useful to demonstrate sterilization of the vegetations.

The Applicant also presents data from animal studies of efficacy in *S. aureus* hematogenous pneumonia and *S. aureus* meningitis. Both of these conditions may arise as complications from endocarditis. The hematogenous pneumonia data showed that daptomycin failed in its clinical efficacy when tested against ceftriaxone, presumably due to inhibition of activity due to pulmonary surfactant. Daptomycin was superior to vancomycin against a MSSA strain in experimental meningitis. However, the reader should be aware that daptomycin does not cross the blood-brain barrier and has limited penetration into cerebrospinal fluid (CSF). A strain of MRSA was not tested. As neither complication is the primary indication for this application, these data have a diminished value in comparison to the endocarditis and fibrin clot data.

A discussion of the role of biofilms in infective endocarditis is pertinent to the results of the animal studies.

The evidence for pathogenesis of biofilms in infective endocarditis is strong. Once developed, vegetations manifest biofilm-like antibiotic resistance that cannot be

completely explained by poor penetration of antimicrobials. This was demonstrated in a study in which radiolabeled penicillin, tobramycin, and teicoplanin were given to rabbits with endocarditis (50). Astonishingly, the concentration of radioactivity was higher in the vegetations than in the blood. Another study showed that bacterial killing within vegetations require antibiotic levels 220-fold greater than the concentrations required to kill planktonic bacteria (51).

Studies show that the composition of the valve biofilm has direct bearing on clinical outcomes. In one study, valve-injured rabbits were treated with warfarin, which inhibits fibrin-platelet matrix formation (47). Vegetation formation was altered even though the treatment did not affect the bacterial counts on the valve. The resulting illness was characterized by high fever, constant bacteremia, and increased mortality. However, antibiotic treatment was more effective in the warfarin-treated rabbits. Thus, interfering with biofilm formation on the valve both produced a more explosive disease and reduced the resistance of the bacteria.

In another study, inhibiting platelet aggregation by aspirin treatment also significantly altered the disease course (44). Taken together, these experiments demonstrate an association between the biofilm composition and its clinical manifestations, and support the concept that infectious endocarditis can be manipulated by targeting biofilm development.

However, the role of protein binding of the antibiotic should not be ignored. It has been noted that 60% of daptomycin penetrates into cardiac vegetations, however, 90% of daptomycin is protein-bound, therefore only 10% of the daptomycin is biologically active in the vegetations.

CLINICAL EFFICACY

CLINICAL LABORATORY SUSCEPTIBILITY TEST METHODS

Methodologies

The activity of daptomycin requires the presence of a physiological concentration of free calcium ions (Ca^{2+}) to exert its full activity; this level of Ca^{2+} (50 µg/mL) are critical for accurate *in vitro* antimicrobial susceptibility testing (AST) results.

(b) (4)

The wide variation in Ca content that is seen in commercial lots of Mueller- Hinton agar (MHA) has been associated with inaccurate testing results with both the disk diffusion and agar dilution methodologies.

Daptomycin Agar Dilution

Agar dilution testing with daptomycin is not recommended as commercial lots of MHA exhibit a wide variation in Ca^{2+} content. The use of the agar dilution method has not been validated with daptomycin.

***Note**: The Applicant is requesting a notation in the Microbiology section of the proposed Package Insert that the use of the agar dilution method has not been validated with daptomycin.*

Daptomycin Disk Diffusion

During development of the daptomycin (30 µg) disk, very few isolates with non-susceptible MIC values were available for testing. Current interpretative criteria for disk diffusion were based primarily on the wild-type population of each organism. Since the launch of Cubicin®, a small number of matched clinical isolates (daptomycin susceptible and non-susceptible) have become available for validating the disk diffusion test [see Section 2.7.4.7, this submission].

An early report by Jevitt and colleagues at the Centers for Disease Control and Prevention (CDC) suggested that the daptomycin (30 µg) disk might not reliably detect daptomycin non-susceptible isolates [69]. Based on these reports, a collaborative study between the CDC, the Clinical Microbiology Institute (CMI), and the Applicant was undertaken. The results of this larger, two site study demonstrated that the daptomycin disk does not reliably detect daptomycin non-susceptible isolates [see Report CMI- Brown 2005, this submission].

***Note**: The Applicant has previously submitted a labeling supplement requesting removal of daptomycin disk interpretative criteria and QC ranges from the Microbiology section of the proposed Package Insert [NDA 21-572 SN007].*

(b) (4)

(b) (4)

(b) (4)

Note: (b) (4)

Quality Control Ranges

Approved Daptomycin Quality Control Ranges

QC ranges for daptomycin broth dilution MIC values have been previously approved by the Agency and are shown in Table 24 [114a]. Since receiving Agency approval, daptomycin's MIC value QC range for *Enterococcus faecalis* ATCC 29212 was changed by the Clinical Laboratory Standards Institute (CLSI) Subcommittee on Antimicrobial Susceptibility Testing from the previous range of 1 to 8 µg/mL to a new range of 1 to 4 µg/mL [145, 146]. This modification was made for two reasons. The first is so that the QC range does not cross the interpretative criteria line of = 4 µg/mL (i.e., a susceptible QC strain would not test as non-susceptible). The second reason is that narrowing the QC range to 3 dilution tubes more accurately indicates low Ca^{2+} content in the MHB.

Note: *The Applicant is requesting a change to the Agency-approved broth dilution MIC value QC range for E. faecalis ATCC 29212 from the previously approved range of 1 to 8 µg/mL to the proposed range of 1 to 4 µg/mL (Table 25).*

Table 24: Agency- Approved Broth Dilution MIC Value QC Ranges

QC Strain	MIC Value QC Range (µg/mL)*
S. aureus ATCC 29213	0.25--1
Enterococcus faecalis ATCC 292121	1--8**
Streptococcus pneumoniae ATCC 49619	0.06--0.5

*Approved QC ranges are for tests performed in broth containing 50 µg/ mL Ca^{2+} [114a]
**The Applicant is proposing a range of 1 to 4 µg/mL.
Source: Table 2.7.2- 42, this submission

(b) (4)

[redacted]

Table 25: Proposed Acceptable Quality Control Ranges for Daptomycin to be Used in Validation of Susceptibility Test Results

(b) (4)

[redacted]

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Daptomycin Interpretative Criteria

Proposed Changes to the Daptomycin Interpretative Criteria

Interpretive criteria for daptomycin were previously approved by the Agency [114a]. The Applicant requests two changes to the interpretative criteria section in the Microbiology section of the proposed Package Insert. These changes are enumerated below and depicted in Table 26.

• The first is removal of the daptomycin disk diffusion interpretative criteria. This request was previously submitted as a labeling supplement.
• The second is (b) (4)

(b) (4)

Table 26: Proposed Interpretive Criteria for Susceptibility to Daptomycin

(b) (4)

Reviewer's comments: The Applicant makes two requests for changes to the package insert. In the ***first request***, the Applicant proposes the removal of daptomycin disk interpretative criteria and QC ranges from the Microbiology section of the proposed Package Insert as requested in submission NDA 21-572 SN007 (a previously submitted labeling supplement).

Resistance data from the literature supports this request. The first demonstration of daptomycin resistance was reported by Sabol et al. (97). This report was the first description of a clinical and bacteriological failure of an invasive VRE infection due to the emergence of high-level daptomycin resistance during therapy for a patient with bacteremia caused by *Enterococcus faecium*. Isolates of *E. faecium* ultimately demonstrated MIC values of greater than 32 µg/ml, considered to be non-susceptible. Daptomycin was dosed at 6 mg/kg.

In addition, while the results of the MIC methodology reflected resistance to daptomycin, the zone of inhibition for the disk diffusion procedure was within the range indicative of susceptibility (i.e., ≥ 11 mm) by the recently published CLSI breakpoints (147). Thus, the Sponsor should be aware that the present breakpoints for the disk diffusion test do not appear to be reliable for the detection of resistance. ***Consequently, this Reviewer strongly recommends that the broth microdilution method be used to generate MIC values for determining daptomycin susceptibility of clinical isolates.***

The Applicant's ***second request*** is for the (b) (4)

(b) (4)

APPEARS THIS WAY
ON ORIGINAL

CLINICAL AND MICROBIOLOGICAL OUTCOMES

Clinical Overview

The primary efficacy results in support of the proposed indication for Cubicin® in the treatment of patients with *S. aureus* bacteremia, including those with known or suspected endocarditis caused by methicillin-susceptible and methicillin-resistant strains are derived from the pivotal study DAP-IE-01-02. An overview of the critical study design features, patient population and efficacy results from this study are provided in the following sections. No other studies have been conducted in this specific indication sought in this sNDA; an overview of efficacy results from other previously conducted Applicant- and Lilly-sponsored studies that enrolled patients with bacteremia or endocarditis is provided in the ***Clinical Summary of Efficacy***.

Study Design and Conduct

Design of Study DAP-IE-01-02

Study DAP-IE-01-02 was a Phase 3, international, multicenter, randomized (1:1), open-label study comparing i.v. daptomycin with conventional i.v. therapy [SSP (nafcillin, oxacillin, cloxacillin, or flucloxacillin) or vancomycin, both with initial synergistic gentamicin] in patients with IE or bacteremia caused by *S. aureus*. The study was designed in collaboration with the Agency, and during the course of the study, ongoing dialogue between the Applicant and the Agency continued. The protocol was amended in collaboration with the Agency and led to one significant change in study conduct, namely inclusion of patients with a high likelihood of LIE in April 2004.

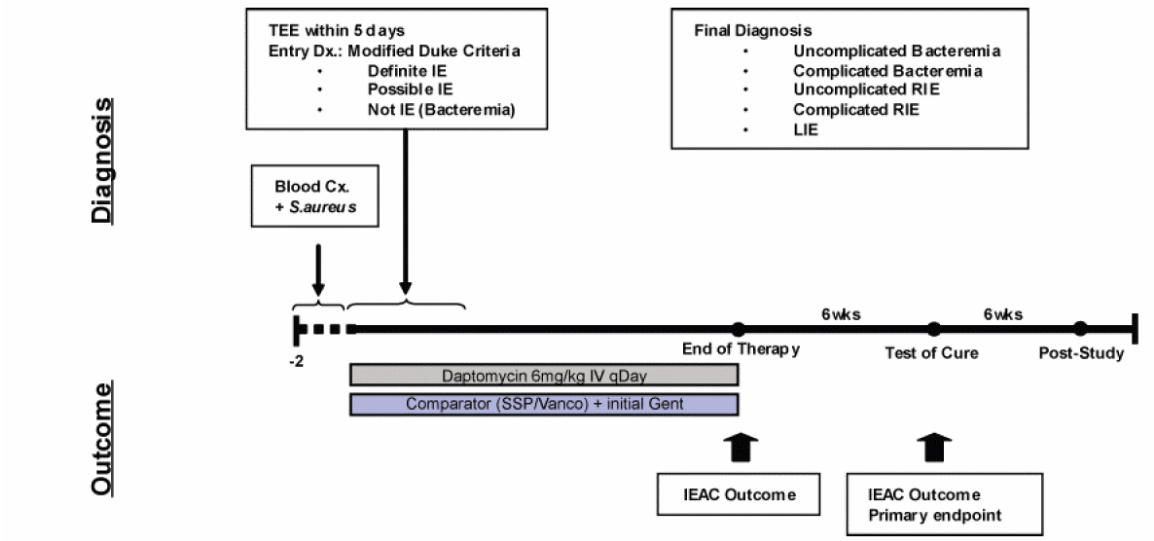
During Study DAP-IE-01-02, daptomycin was administered at 6 mg/kg q24h, the SSPs were administered at 2 g q4h and, in patients with normal renal function, vancomycin was administered at 1 g q12h. Initial synergistic gentamicin at 1 mg/kg q8h was to be administered to all patients randomized to comparator and to LIE patients randomized to daptomycin for the first four days or until blood cultures became negative.

The open-label design of the study was chosen because of ethical and safety concerns due to the high mortality of the disease and operational issues relating to the different dosing schedules. Randomization of treatment assignment was employed to avoid bias and help ensure that both known and unknown risk factors are distributed evenly between treatment groups.

Prior to a protocol amendment (Amendment 4A), patients whom the Investigator believed to have a high-likelihood of LIE were excluded. Subsequent to this amendment, patients with LIE were separately randomized to ensure an equal distribution of these patients in the 2 treatment groups.

An overview of the study design and patient populations in Study DAP-IE-01-02 is provided in Figure 11 (Figure 2.5-1, this submission).

Figure 11: Overview of Study Design and Patient Populations in DAP-IE-01-02



Source: Figure 2.5—1, this submission

All patients were required to have a single positive peripheral blood culture for *S. aureus* within 48 hours prior to randomization. If susceptibility results were unknown at the time of randomization, patients assigned to conventional therapy were to receive vancomycin. If the organism proved to be MSSA, therapy was to be changed to SSP, unless contraindicated by a documented prior history of penicillin or ß-lactam drug allergy.

Clinical efficacy assessments were conducted daily until the EOT visit with special emphasis on assessment of the signs and symptoms of worsening *S. aureus* infection. Blood cultures were repeated daily until negative for 48 hours, at EOT and during follow-up at the TOC and post-study (PS) visits. Antibiotic history was obtained for the 30 days prior to randomization and concomitant antibiotics were recorded throughout the study (to the PS visit, when applicable). All patients were to undergo transesophageal echocardiography (TEE) by Day 5 to evaluate for endocarditis; the TEE was read locally by the Investigators to guide the patient's treatment course and by an independent cardiologist who was blinded to treatment. The latter assessment was used in determination of Entry and Final diagnosis by an independent adjudication committee (see below).

Other evaluations conducted during the study included daily physical examination, chest x-ray, vital signs, electrocardiogram (ECG), and clinical laboratory tests (including hematology, clinical chemistry, coagulation, urinalysis and CPK), as well as appropriate tests to rule out metastatic foci of infection.

The duration of study treatment was based on the patient's diagnosis and the susceptibility of the *S. aureus* isolate. Baseline diagnosis by the Investigator was determined according to the Modified Duke Criteria [148] and included the categories of Definite IE, Possible IE and Not IE.

After consultation with the Agency, the Sponsor convened a DMC to review study data during the trial and to recommend continuing, modifying, or stopping the study. The trial was continued to completion; there were no significant safety findings or recommendations by the DMC to change the conduct of the study.

In addition, due to the open-label nature of the trial, the heterogeneity of the population, and the complexity of diagnosis and treatment outcome assessments in patients with *S. aureus* bacteremia and IE, an IEAC was convened to conduct a post-study review of individual patient data blinded to treatment. The IEAC was charged with determining diagnoses, both Entry (Definite, Possible, Not IE) and Final (complicated and uncomplicated RIE, complicated and uncomplicated bacteremia, LIE) diagnoses and determining treatment outcome at both TOC and EOT.

Complete details on the study design, and all study procedures can be found in the Clinical Study Report included in Module 5 of this submission [see Report DAP-IE-01-02].

Efficacy Measures and Methods

The population studied included only patients with *S. aureus* bacteremia and known or suspected infective endocarditis.

The primary efficacy endpoint, defined in collaboration with the Agency, was success based on the IEAC Outcome at TOC in the ITT and PP populations pooled across diagnostic strata, and were a composite endpoint based on clinical as well as microbiologic success. Clinical success was evaluated by measures of fever as well as clinical signs and symptoms of infection. Microbiological success was measured by achieving bacterial eradication via negative blood cultures, a sensitive measure of drug effect.

The primary outcome measure was the comparison of the success rates for the two treatment groups; the 95% confidence interval (CI) for the difference in success rates (daptomycin minus comparator) was calculated based on the normal approximation to the binomial distribution, with and without a continuity correction factor. The non-inferiority test was based upon a comparison of the lower bound of the 95% CI relative to a margin of 20% in the ITT population. Because the size of the study was not powered for the PP population, the findings in the PP population were to be logically consistent with the findings in the ITT population in order to consider the outcome of this study as positive.

In addition to the overall pooled analyses in the ITT and PP populations, the 95% CI was presented for each individual prespecified IEAC Entry and Final diagnostic strata and the following pooled groups: IEAC Entry diagnostic groups of IE (Possible IE plus Definite IE) and IEAC Final diagnostic groups of RIE (complicated plus uncomplicated) and complicated bacteremia plus RIE.

Because the comparator group was an active control and the study did not include a placebo arm, assay sensitivity of the trial was addressed by convening an IEAC to make independent, consistent assessments of diagnoses and outcomes. Their assessment included an evaluation of potentially effective non-study antibiotics (PENS) that were administered

to patients. This assessment enhanced assay sensitivity of the trial in that patients who received PENS were deemed failures by the IEAC, ensuring that successful treatment outcomes could be attributed to study drug.

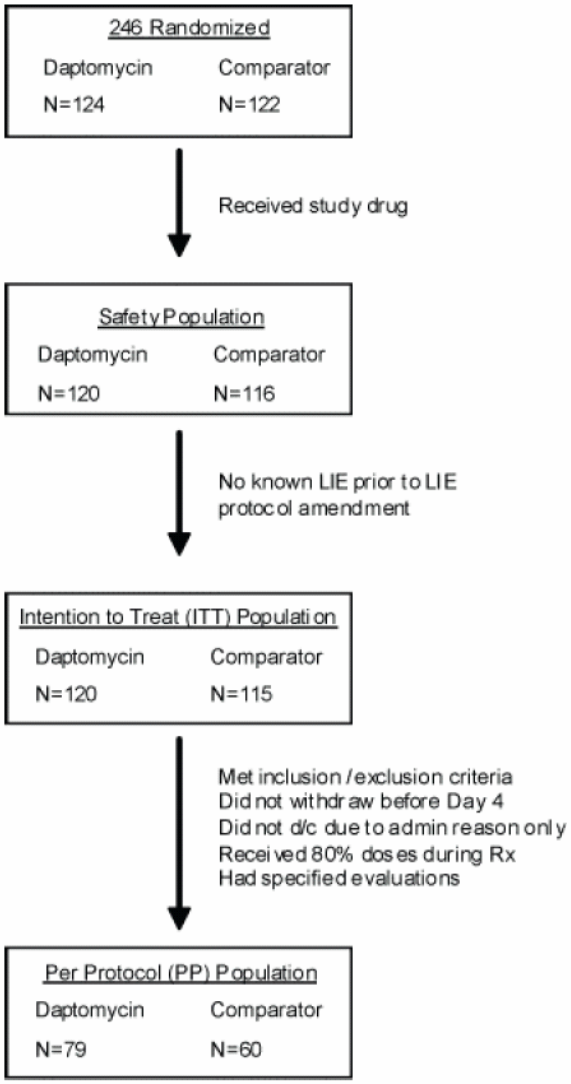
The delta of 20% was selected in collaboration with the Agency. It was recognized that *S. aureus* bacteremia and IE is a disease for which placebo has little to no effect (based on the pre-antibiotic era data demonstrating 82% mortality [149]) and therefore placebo is not an acceptable treatment option in this setting. This, together with the pressing medical need for additional agents effective against MRSA led to the decision to proceed with a 20% non-inferiority margin. The clinically acceptable loss of efficacy relative to control was to be determined by clinical review of the data, including efficacy in the relevant groups. In collaboration with the Agency, it was decided that an adequate number of patients with complicated *S. aureus* bacteremia and definite or possible IE would be needed in order to ascertain efficacy.

The secondary efficacy endpoint was time to clearance of bacteremia. Additional efficacy analyses included time to defervescence, microbiological response rates, Investigator assessment of clinical response, relapse rates, and survival.

Disposition of Patients in Study DAP-IE-01-02

A total of 246 patients were randomized into Study DAP-IE-01-02; 236 of these 246 randomized patients received at least one dose of study drug, including 120 who received daptomycin and 116 who received the comparator agent. Ten patients, including four randomized to receive daptomycin and six randomized to receive the comparator agent, were not dosed. Among the 116 comparator patients, 53 received only vancomycin and 63 received SSP with or without initial vancomycin therapy of = 3 days duration, with the exception of four patients who received a longer duration of vancomycin therapy.
An overview of patient disposition is displayed in Figure 12 (Figure 2.5- 2, this submission).

Figure 12: Overview of Patient Disposition in Study DAP-IE-01-02



Source: Figure 2.5- 2, this submission

The majority of the patients in both treatment groups completed therapy (66.7% and 67.2% in the daptomycin and comparator groups, respectively).

Over 99% of patients dosed (235 of 236) were included in the ITT population. The PP population, which included those patients in the ITT population with documented adherence to the protocol, was comprised of 139 (58.9%) of the 236 patients who received treatment. A higher proportion of patients in the daptomycin group (79 of 120, 65.8%) were included in the PP population relative to the comparator group (60 of 116, 51.7%). However, the primary reasons for exclusion from the PP population were similar between the treatment groups and included early termination from treatment for reasons other than adverse event or failure (24.2% and 29.3% in the daptomycin and comparator groups, respectively), major inclusion or exclusion criteria violations (10.0% and 12.1%,

respectively), non-evaluable per the IEAC (7.5% and 12.1%, respectively), receipt of < 4 days of therapy (7.5% and 7.8%, respectively), and non-compliant with the visit schedule (i.e., missed Baseline, EOT or TOC visits) (5.8% and 5.2%, respectively). The largest difference between the treatment groups with regard to reasons for exclusion from the PP population was lack of adherence to the study medication schedule (0% in the daptomycin group compared to 6.9% in the comparator group); this difference is likely related to the ease of once daily dosing with daptomycin.

Diagnosis and Baseline Pathogens

Entry and Final diagnoses as determined by the IEAC and Baseline Infecting pathogens are displayed in Table 27. IEAC-determined Entry diagnoses, based on the Modified Duke Criteria, and IEAC-determined Final diagnoses were similar between the treatment groups. More than 75% of the patients had suspected or proven *S. aureus* endocarditis (IEAC Entry diagnosis of Possible + Definite IE) and 74% had an IEAC Final diagnosis of complicated bacteremia or IE. MRSA was well represented in the study population, accounting for almost 40% of infections in both treatment groups, similar to a recently reported international study [150].

Table 27: Summary of IEAC Entry and Final Diagnostic Subgroups and Baseline Infecting Pathogens (Study DAP-IE-01-02, ITT Population)

Diagnostic Subgroup	Daptomycin (N=120)	Comparator (N=115)	Total (N=225)
IEAC Entry Diagnosis			
N	120	115	235
Definite IE	17 (14.2%)	20 (17.4%)	37 (15.7%)
Possible IE	73 (60.8%)	71 (61.7%)	144 (61.3%)
Not IE	30 (25.0%)	24 (20.9%)	54 (23.0%)
IEAC Final Diagnosis			
N	120	115	235
Complicated RIE	13 (10.8%)	12 (10.4%)	25 (10.6%)
Uncomplicated RIE	6 (5.0%)	4 (3.5%)	10 (4.35)
Complicated bacteremia	60 (50.0%)	61 (53.0%)	121 (51.5%)
Uncomplicated bacteremia	32 (26.7%)	29 (25.2%)	61 (26.0%)
LIE	9 (7.5%)	9 (7.8%)	18 (7.7%)
Baseline Infecting Pathogen			
N	120	115	235
MSSA	74 (61.7%)	70 (60.9%)	144 (61.3%)
MRSA	45 (37.5%)	44 (38.3%)	89 (37.9%)
No *S. aureus* isolated	1 (< 1%)	1 (< 1%)	2 (< 1%)

Source: Table 2.5- 6, this submission
(Cross references: Report DAP- IE- 01- 02, Table 11- 4 and Table 11- 5)

Complicated or uncomplicated RIE was reported in 15.8% and 13.9% of patients in the daptomycin and comparator groups, respectively, complicated bacteremia was reported in 50.0% and 53.0%, respectively, uncomplicated bacteremia was reported in 26.7% and 25.2%, respectively, and LIE was reported in 7.5% and 7.8%, respectively.

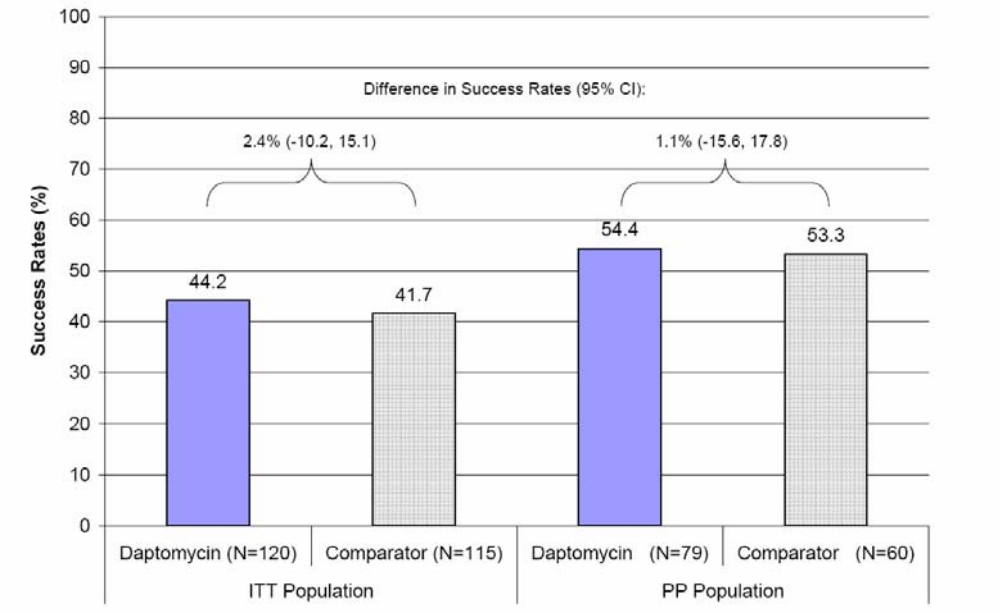
A total of 61.7% and 60.9% of patients in the daptomycin and comparator groups, respectively, had infections caused by MSSA and 37.5% and 38.3%, respectively, had infections caused by MRSA. As expected, the majority of patients in the comparator group who received vancomycin throughout the study had infections caused by MRSA (43 of 53, 81.1%) and the majority of patients who received SSP had infections caused by MSSA (60 of 61, 98.4%).

Efficacy Results

Primary Efficacy Endpoint, IEAC Outcome at Test of Cure

Daptomycin was as effective as conventional therapy in the treatment of patients with *S. aureus* bacteremia with known or suspected endocarditis. Results met the efficacy endpoint and were successful at TOC in the co-primary ITT and PP populations (Figure 13) [Figure 2.5-3, this submission].

Figure 13: IEAC Success Rates at TOC (Study DAP-IE-01-02, ITT and PP Populations)



Source: Figure 2.5- 3, this submission
(Cross references: Report DAP- IE- 01- 02, Figure 11- 1)

In the ITT population, 44.2% of 120 daptomycin-treated patients were judged by the IEAC to have a successful outcome compared to 41.7% of 115 comparator-treated patients. Within the comparator arm, the success rate was 37.7% (20 of 53 patients) for the vancomycin arm and 45.2% (28 of 62 patients) for the SSP arm. Similarly, in the PP population 54.4% of 79 daptomycin-treated patients had a successful outcome at TOC compared to 53.3% of 60 comparator-treated patients. In both populations, daptomycin met the statistically defined non-inferiority criteria; the lower bound of the 95% CI around the difference in success rates was within the pre-specified delta of - 20% for the overall pooled analysis (with and without the continuity correction) and when the results were adjusted for IEAC Entry and Final diagnostic subgroups.

Regardless of IEAC Entry diagnostic subgroup, treatment with daptomycin led to similar success rates as treatment with conventional therapy. A summary of IEAC success rates at TOC is presented by IEAC Entry and Final diagnostic subgroup in Table 28.

Table 28: Summary of IEAC Success Rates at TOC by IEAC Diagnostic Subgroups (Study DAP-IE-01-02, ITT and PP Populations)

Population Diagnostic Subgroup	Daptomycin n/N (%)	Comparator n/N (%)	Differences in Success Rates (95% CI)
Overall ITT Population	53/120 (44.2%)	48/115 (41.7%)	2.4% (--10.2, 15.1)
IEAC Entry Diagnosis			
Definite + Possible IE	41/90 (45.6%)	37/91 (40.7%)	4.9% (--9.5, 19.3)
Not IE	12/30 (40.0%)	11/24 (45.8%)	--5.8% (--32.4, 20.7)
IEAC Final Diagnosis			
cRIE + uRIE + cBAC	34/79 (43.0%)	30/77 (39.0%)	4.1% (--11.3, 19.5)
RIE (cRIE + uRIE)	8/19 (42.1%)	7/16 (43.8%)	--1.6% (--34.6, 31.3)
cRIE + uRIE + cBAC	5/13 (38.5%)	6/12 (50.0%)	--11.5% (--50.3, 27.2)
uRIE	3/6 (50.0%)	1/4 (25.0%)	25.0% (--33.3, 83.3)
cBAC	26/60 (43.3%)	23/61 (37.7%)	5.6% (--11.8, 23.1)
uBAC	18/32 (56.3%)	16/29 (55.2%)	1.1% (--15.6, 17.8)
LIE	1/9 (11.1%)	2/9 (22.2%)	--11.1% (--45.2, 22.9)
Overall PP Population	43/79 (54.5%)	32/60 (53.3%)	1.1% (--15.6, 17.8)
IEAC Entry Diagnosis			
Definite + Possible IE	32/62 (51.6%)	24/44 (54.5%)	--2.9% (--22.2, 16.3)
Not IE	11/17 (64.7%)	8/16 (50.0%)	14.7% (--18.7, 48.1)
IEAC Final Diagnosis			
cRIE + uRIE + cBAC	25/51 (49.0%)	18/37 (48.6%)	0.4% (--20.8, 21.5)
RIE (cRIE + uRIE)	6/12 (50.0%)	4/8 (50.0%)	0.0% (--44.7, 44.7)
cRIE + uRIE + cBAC	5/10 (50%)	4/6 (66.7%)	--16.7% (--65.5, 32.2)
uRIE	19/39 (48.7%)	0/2 (0%)	50.0% (--19.3, 119.3)
cBAC	19/39 (48.7%)	14/29 (48.3%)	0.4% (--23.6, 24.5)
uBAC	17/21 (81.0%)	12/17 (70.6%)	10.4% (--17.0, 37.8)
LIE	1/7 (14.3%)	2/6 (33.3%)	--19.0% (--64.8, 26.7)

Source: Table 2.5- 7, this submission
(Cross references: Report DAP-IE-01-02, Table 11-11 and Table 11-12.)

For patients presenting to the hospital with signs and symptoms consistent with definite or possible IE as determined by the IEAC based on the Modified Duke Criteria, the success rates at TOC were 45.6% for daptomycin and 40.7% for comparator in the ITT population and 51.6% and 54.5%, respectively, in the PP population. For those patients likely not to have IE, success rates were 40.0% and 45.8% for daptomycin and comparator, respectively, in the ITT population, and 64.7% and 50.0%, respectively, in the PP population.

Furthermore, for patients in the ITT population with an IEAC Final diagnosis of RIE (complicated or uncomplicated) or complicated bacteremia, treatment with daptomycin was as effective as treatment with conventional therapy with success rates of 43.0% and 39.0%,

respectively. In the PP population, the success rates for patients with RIE and complicated bacteremia were 49.0% and 48.6% in the daptomycin and comparator groups, respectively. For those patients with an IEAC Final diagnosis of uncomplicated bacteremia, success rates were 56.3% and 55.2% in the daptomycin and comparator groups, respectively, for the ITT population, and 81.0% and 70.6%, respectively, in the PP population.

A total of 18 patients in the ITT population, nine in each treatment group were determined by the IEAC to have a Final diagnosis of LIE. Three of these 18 patients in the ITT population were reported to have a successful outcome at TOC by the IEAC, one in the daptomycin group and two in the comparator group. Outcome in all patients with LIE is presented below (Outcome in Patients with LIE).

IEAC Success Rates at TOC by Oxacillin Susceptibility of the Baseline Pathogen
Similar efficacy was observed in daptomycin-treated patients irrespective of methicillin susceptibility (44.6% vs. 44.4% for MSSA vs. MRSA, respectively) (Table 29). These rates were comparable to success rates in comparator patients with MSSA (48.6%) and were numerically higher than success rates in comparator patients with MRSA (31.8%).

Table 29: Summary of IEAC Success Rates at TOC by Oxacillin Susceptibility, Overall and by IEAC Entry and Final Diagnostic Subgroups (Study DAP-IE-01-02, ITT Population)

Group/ Pathogen	Daptomycin (N=120) n/N (%)	Comparator (N=115) n/N (%)	Differences in Success Rates (95% CI)
Overall ITT Population*			
MSSA	33/74 (44.6%)	34/70** (48.6%)	--4.0% (--20.3, 12.3)
MRSA	20/45 (44.4%)	14/44*** (31.8%)	12.6% (--7.4, 32.6)
IEAC Entry Diagnosis			
Definite + Possible IE			
MSSA	26/54 (48.1%)	26/53 (49.1%)	--0.9% (--19.8, 18.0)
MRSA	15/36 (41.7%)	11/38 (28.9%)	12.7% (--8.9, 34.3)
Not IE			
MSSA	7/20 (35.0%)	8/17 (47.1%)	--12.1% (--43.7, 19.6)
MRSA	5/9 (55.6%)	3/6 (50.0%)	5.6% (--46.0, 57.1)
IEAC Final Diagnosis			
cRIE + uRIE + cBAC			
MSSA	20/49 (40.8%)	21/48 (43.8%)	--2.9% (--22.6, 16.7)
MRSA	14/30 (46.7%)	9/29 (31.0%)	15.6% (--8.9, 40.2)
uBAC*			
MSSA	12/21 (57.1%)	11/17 (64.7%)	--7.6% (--38.6, 23.5)
MRSA	6/10 (60.0%)	5/11 (45.5%)	14.5% (--27.7, 56.8)

*One patient in each treatment group did not have *S. aureus* isolated at baseline.
**A total of 60 of the 70 patients received SSP (± initial vancomycin) and 10 patients received vancomycin.
***A total of 43 of the 44 patients received vancomycin and one patient received SSP followed by vancomycin.
Source: Table 2.5- 8, this submission
(Cross reference: Report DAP-IE-01-02, Table 11-13)

Similar results were noted for analysis of success rates by oxacillin susceptibility in the PP population as were observed in the ITT population. IEAC success rates at TOC in the PP population were 55.6% and 52.9% for patients in the daptomycin group with infections caused by MSSA and MRSA, respectively, and 57.1% and 44.4%, respectively, for patients in the comparator group.

IEAC Success Rates at TOC by Duration of Treatment

Table 30 presents a summary of IEAC success rates at TOC by duration of study treatment. Across all ITT patients, success rates increased with increasing duration of treatment in both the daptomycin and comparator groups. In the daptomycin group, success rates at TOC were 37.7%, 51.7% and 64.3% for patients who received dosing for 1 to 14 days, 15 to 28 days and > 28 days, respectively; in the comparator group, success rates were 26.9%, 51.2% and 59.1%, respectively.

In the daptomycin group, an increase in success rates was noted with increasing duration of therapy for each subgroup based on IEAC Final diagnosis. Note that the only patients who received > 28 days of therapy in the daptomycin group were patients with complicated infections.

Table 30: Summary of IEAC Success Rates at TOC by Duration of Treatment and IEAC Final Diagnosis (Study DAP-IE-01-02, ITT Population)

Group	Daptomycin (N=120) 1--14 days	15--28 days	n/N (%) >28 days
Overall ITT Population	29/77 (37.7%)	15/29 (51.7%)	9/14 (64.3%)
cRIE + uRIE + cBAC	17/45 (37.8%)	9/21 (42.9%)	8/13 (61.5%)
cRIE	1/4 (25.0%)	2/6 (33.3%)	2/3 (66.7%)
uRIE	2/5 (40.0%)	1/1 (100%)	0
cBAC	14/36 (38.9%)	6/14 (42.9%)	6/10 (60.0%)
uBAC	12/25 (48%)	6/7 (85.7%)	0
LIE	0/7 (0%)	0/1 (0%)	1/1 (100%)
Group	**Comparator (N=115) 1--14 days**	**15--28 days**	**n/N (%) >28 days**
Overall ITT Population	14/52 (26.9%)	21/41 (51.2%)	13/22 (59.1%)
cRIE + uRIE + cBAC	5/34 (14.7%)	14/24 (58.3%)	11/19 (57.9%)
cRIE	0/3 (0%)	3/3 (100%)	3/6 (50.0%)
uRIE	0/1 (0%)	1/3 (33.3%)	0
cBAC	5/30 (16.7%)	10/18 (55.6%)	8/13 (61.5%)
uBAC	9/16 (56.2%)	5/11 (45.5%)	2/2 (100%)
LIE	0/2 (0%)	2/6 (33.3%)	0/1 (0%)

Source: Table 2.5-9, this submission
(Cross reference: Response to FDA Pre-submission Requests, Table 1)

IEAC Outcome at EOT

IEAC outcome was also reported for the EOT evaluation; results of this analysis are provided in Table 31. In both treatment groups, overall success rates were higher at EOT compared to those observed at TOC and were consistent with response rates reported in published literature (> 60%) [151-153]. Furthermore, as was observed at the primary

endpoint (TOC), daptomycin was as effective as conventional therapy at the EOT visit in the treatment of patients with *S. aureus* bacteremia, including those with known or suspected endocarditis (61.7% and 60.9%, respectively).

Table 31: Summary of IEAC Success Rates at EOT by IEAC Entry and Final Diagnostic Subgroups and by Oxacillin Susceptibility (Study DAP-IE-01-02, ITT Population)

Group Pathogen	Daptomycin (N=120) n/N (%)	Comparator (N=115) n/N (%)	Differences in Success Rates (95% CI)
Overall ITT Population	74 (61.7%)	70 (60.9%)	0.8% (--11.7, 13.3)
IEAC Entry Diagnosis			
Definite + Possible IE	54/90 (60.0%)	55/91 (60.4%)	--0.4% (--14.7, 13.8)
Not IE	20/30 (66.7%)	15/24 (62.5%)	4.2% (--21.5, 29.9)
IEAC Final Diagnosis			
cRIE + uRIE + cBAC	45/79 (57.0%)	45/77 (58.4%)	--1.5% (--17.0, 14.0)
uBAC	25/32 (78.1%)	22/29 (75.9%)	2.3% (--18.9, 23.4)
LIE	4/9 (44.4%)	3/9 (33.3%)	11.1% (--33.6, 55.9)
Oxacillin Susceptibility*			
MSSA	46/74 (62.2%)	44/70 (62.9%)	--0.7% (--16.5, 15.1)
MRSA	28/45 (62.2%)	26/44 (59.1%)	3.1% (--17.2, 23.4)

*Based on 119 and 115 patients in the daptomycin and comparator groups, respectively. One patient in each treatment group did not have *S. aureus* isolated at baseline.
Source: Table 2.5- 10, this submission
(Cross references: Report DAP-IE-01-02, Table 11-16 and Table 11-17)

In addition, success rates were similar between the treatment groups across diagnostic subgroups at EOT. A successful outcome was reported at EOT for 60.0% and 60.4% of patients in the daptomycin and comparator groups, respectively, with an IEAC Entry diagnosis of definite or possible IE. For IEAC Final diagnostic subgroups, a successful outcome was reported at EOT for the ITT population in 57.0% and 58.4% of patients in the daptomycin and comparator groups, respectively, with a diagnosis of RIE (complicated or uncomplicated) or complicated bacteremia and in 78.1% and 75.9% of patients, respectively, for patients with a diagnosis of uncomplicated bacteremia.

Furthermore, similar success rates at EOT were noted in the daptomycin and comparator groups for patients with infections caused by MSSA and MRSA. At the EOT evaluation, 62.2% and 62.9% of patients in the daptomycin and comparator groups, respectively, with infections caused by MSSA had a successful outcome, as did 62.2% and 59.1% of patients, respectively, with infections caused by MRSA.

Investigator Assessment of Response

Efficacy as assessed by the IEAC was consistent with efficacy as assessed by the Investigators. Based on Investigator assessment, daptomycin was as effective as conventional therapy in the treatment of patients with *S. aureus* bacteremia with known or suspected endocarditis. Success (cure or improvement) at TOC was reported by the

Investigators in 64 (53.3%) of 120 daptomycin patients and in 58 (50.4%) of 115 comparator patients.

Time to Clearance and Time to Defervescence

Time to clearance of *S. aureus* bacteremia was the secondary efficacy endpoint in this study. Median times to clearance were five and four days in the daptomycin and comparator groups, respectively, in the ITT population. For patients with infections caused by MSSA, median times to clearance were four and three days, respectively, and for patients with infections caused by MRSA, eight and nine days, respectively.

In the ITT population, median time to defervescence was three days in both treatment groups overall, and for patients with infections caused by MSSA and by MRSA.

Survival Analyses

The Kaplan-Meier survival curve, including all available survival data, is provided in Figure 2.5-4 (this submission, not shown). As of last follow-up, a total of 18 (15.0%) of the 120 patients in the daptomycin group and 19 (16.4%) of 116 patients in the comparator group had died.

Reasons for Treatment Failure

A total of 134 patients in the ITT population were reported by the IEAC as not achieving treatment success (i.e., were failures or non-evaluable), including 67 (55.8%) of 120 patients in the daptomycin group and 67 (58.3%) of 115 patients in the comparator group. The IEAC was to provide all reasons for each failure or non-evaluable case. No differences were noted between the treatment groups in the proportion of patients who were reported as failures for receipt of non-study antibiotics that may have influenced outcome (16.7% and 13.9% in the daptomycin and comparator, respectively) or in the number of patient deaths (10.8% and 11.3%, respectively). As well, no difference was observed in the proportion of patients who were reported by the IEAC as microbiologic failure (23.3% in the daptomycin group and 20.0% in the comparator group); however, *patients in the daptomycin group were more likely to be reported as failures at TOC due to persisting or relapsing S. aureus infections*. Patients in the comparator group were more likely to be reported as failures due to premature discontinuation due to adverse events (6.7% and 14.8%, respectively).

S. aureus *Isolates with Decreased Susceptibility to Daptomycin*

A review of *S. aureus* susceptibility data over time was conducted. Overall, eight patients had *S. aureus* isolates that demonstrated increasing daptomycin MICs on study, seven patients in the daptomycin treatment group and one patient in the comparator group who received vancomycin. All baseline isolates had daptomycin MICs of 0.25 to 0.5 µg mL and rose to 2 or 4 µg/mL. Six of the seven daptomycin-treated patients were determined to be microbiologic failures at TOC by the IEAC and one patient was reported as a success. Two of the six patients who failed to respond had LIE due to MRSA, three had complicated bacteremia due to MRSA, and one had MSSA complicated RIE.

Thus, a total of 6 (5.0%) of 120 daptomycin-treated patients were reported as treatment failures by the IEAC at TOC in the setting of *S. aureus* isolates with increasing daptomycin

MICs. A total of 60 (50.0%) of 120 daptomycin patients were reported as failure/non-evaluable by the IEAC at TOC who did not have *S. aureus* isolates with increasing daptomycin MICs on study.

Outcome in Patients with LIE

Although initially excluded from entry into the study, a total of 19 patients with IEAC Final diagnoses of LIE were treated in this study, including nine patients in the daptomycin group and 10 in the comparator group; one of these 10 patients entered the study with a high likelihood of LIE prior to Amendment 4A and was thus excluded from the ITT population in accordance with the Statistical Analysis Plan.

Among the 19 patients with an IEAC Final diagnosis of LIE, 10 had infections caused by MSSA, including four patients in the daptomycin group and six in the comparator group, and nine had infections caused by MRSA, including five in the daptomycin group and four in the comparator group. Among those patients with LIE caused by MSSA, one of four daptomycin-treated patients and two of six comparator-treated patients had successful outcomes at TOC. None of the nine patients with LIE caused by MRSA had successful outcomes at TOC.

It is noteworthy that so many of these patients (15 of 19) did not receive surgical therapy as several studies have demonstrated improved outcomes with early valve replacement surgery [154-159].

A total of 9 of the 19 patients with LIE died, including three (33.3%) of nine patients in the daptomycin group and six (60.0%) of 10 patients in the comparator group.

PK/PD Association with Efficacy

Several animal models of infection have demonstrated that the parameters Cmax/MIC and AUC_{0-24}/MIC are those most closely correlated with *in vivo* efficacy. These observations are consistent with daptomycin concentration-dependent bactericidal activity noted *in vitro*. A population PK model (see Section 2.5.3, this submission) conducted on the data from the pivotal trial provided estimates for each patient's steady- state daptomycin PK parameters, specifically Cmax and AUC_{0-24}; and susceptibility testing of the patient's baseline *S. aureus* provided daptomycin MIC values. Given these data, the relationship between daptomycin PK/PD parameters and efficacy was examined.

No relationship was noted between the daptomycin PK/PD parameters and IEAC outcome or pathogen eradication rates at EOT. Similar Cmax, AUC_{0-24}, and resulting Cmax/MIC and AUC_{0-24}/MIC values were observed in both patients with success and failure at EOT as determined by the IEAC.

Critical Appraisal of Study Design, Conduct and Efficacy Outcome Measures

Study Design

Patient selection: More than 5,000 patients with *S. aureus* bacteremia from 76 sites in the US and Western Europe were screened in order to enroll a total of 246 patients [101]. By including patients from such a large number of sites and geographic regions, the patient

population in the study reflects the varying standards of care in the places in which the drug will ultimately be used. The presence of multiple exclusion criteria intended to ensure the inclusion of a population reflective of the patients most in need of therapy for SAB/SAIE led to the large number of screen failures. However, in spite of these factors, the treatment groups were well balanced with regard to most demographic and baseline characteristics (see Section 2.5.4.3.1, this submission).

Inability to stratify at randomization by diagnosis: Patients with complicated bacteremia and definite or possible endocarditis are at the greatest risk of developing metastatic foci of infection and relapse compared to those with uncomplicated SAB. Many complications, including metastatic foci and endocarditis are not diagnosed until days to weeks following treatment initiation despite the fact that they may have been present prior to randomization. Clinicians are faced with extremely ill patients with *S. aureus* bacteremia and must make empirical treatment decisions urgently, frequently before completing a full diagnostic work-up. In an effort to standardize diagnostic evaluation, all patients in the SAB/SAIE study were to undergo TEE within five days of treatment start to assess for endocarditis at baseline and were diagnosed according to the Modified Duke criteria as having definite, possible or no endocarditis [148]. In spite of the lack of stratification, the treatment groups were well- balanced with regard to the diagnostic strata (see Section 2.5.4.3.2, this submission).

Duration and timing of follow-up: The need to follow severely ill patients during long courses of therapy (minimum duration from 2-6 weeks) and to a late TOC visit for the evaluation of the primary endpoint, six weeks following EOT, led to operational challenges, including difficulty in ensuring full follow-up of all patients. There is no precedent for such long-term follow-up in a prospective study of SAB/SAIE in the literature. Therefore the response rates at TOC may be lower than that reported in the literature.

Choice of active control: The study was designed with an active control arm; placebo-control was not considered an acceptable option. Without treatment, IE is uniformly fatal and treatment of inadequate intensity or duration is often followed by clinical and microbiological relapse. The mortality rate of SAB/SAIE without antibiotics in the pre-antibiotic era was 82% [149], so clinical success with placebo is extremely unlikely. Thus, it was deemed appropriate to compare daptomycin with standard of care in this study. It was anticipated that the active control would perform as expected based on historical data [160-166]. This expectation was met in view of the EOT success rate of > 60% in the comparator arm.

Choice of comparator agents: Standard therapy is dictated by *S. aureus* susceptibility, with MRSA patients receiving vancomycin and MSSA patients receiving SSP unless allergic to ß-lactam antibiotics. Initial synergistic gentamicin is added to both vancomycin and SSPs based on American Heart Association recommendations [167*]. Thus, two control groups (SSP and vancomycin) were required for this study.

Open- label design: despite the potential bias inherent in an open-label study, an open-label design was selected due to the life-threatening nature of SAB/SAIE and operational issues surrounding the different study medications (different activity vs. MRSA of the comparator agents; different dosing regimens and infusion times for daptomycin and comparators; the potential need to monitor plasma vancomycin concentrations). The effect of this potential bias was minimized by including an objective microbiologic endpoint as part of the criteria for success and by convening the IEAC to assess outcome.

Study Conduct and Possible Implications
Study conduct: All (100%) of the daptomycin- treated patients and 93% of those treated with comparator met pre-specified criteria for adherence to the drug regimen. A total of 5.5% of patients were non-compliant with visits at major time points.

External committees: A DMC was convened to monitor ongoing safety data and make recommendations regarding study conduct. The trial was continued to completion; there were no significant safety findings or recommendations by the DMC to change the conduct of the study. Therefore the interpretation of trial results were not confounded by major changes in study conduct except for the addition of patient with LIE.

An IEAC was convened to make blinded, independent, consistent assessments of diagnoses and outcomes. The IEAC assessment of outcome added rigor to the evaluation of treatment effect in this study. Furthermore, the magnitude of the treatment difference was similar based on IEAC outcome and Investigator assessment.

Concomitant therapy: The receipt of PENS was assessed by the IEAC as part of the independent review and was defined as a criterion for failure, thus ensuring that effect of study drug would not be unduly influenced by other concomitant therapies.

Applicant's Conclusions and Relevance
Study DAP-IE-01-02 was a comparative study of *S. aureus* endocarditis and bacteremia conducted in a seriously ill patient population. The population studied had documented evidence of infection with the disease of interest. In the ITT population, all but one patient in each arm had documented *S. aureus* bacteremia at baseline.

Although a large number of patients were screened from many international sites, the population included in this study reflects the population currently in greatest need of therapy for SAB/SAIE. In general, this was an elderly, severely ill, hospitalized, patient population with underlying complications as reflected by the high numbers of patients with SIRS, diabetes, indwelling devices and prior surgery. Importantly, 38% of patients in this study had infections due to MRSA. These data are consistent with data reviewed in two recent large epidemiologic studies of endocarditis [150, 168].

Daptomycin 6 mg/kg administered as monotherapy (once daily i.v.) was as effective as standard of care (SSP or vancomycin 2-6 times daily i.v., both with initial synergistic gentamicin) in the treatment of *S. aureus* endocarditis or bacteremia. Non-inferiority criteria were met in both the ITT and PP populations, and daptomycin demonstrated

efficacy irrespective of methicillin susceptibility. Notably, in MRSA infections, the response to daptomycin was higher than that observed in the comparator group. The Applicant contends that the efficacy results were robust with demonstrated efficacy across pre-specified diagnostic strata (complicated bacteremia, uncomplicated bacteremia, RIE), at different time points (TOC and EOT) and according to both IEAC and Investigator assessments. Across all ITT patients success rates increased with increasing duration of treatment in both the daptomycin and comparator groups.

The overall success at TOC in the daptomycin group in the ITT population was 44.2% and 41.7% in the comparator group. In the PP population, 54.4% of daptomycin and 53.3% of comparator patients had success to TOC. These overall success rates at TOC, six weeks following the last dose of study drug, were lower than the predicted rate of 65% that was used to establish sample size and likely reflect the long-term follow-up required by the TOC visit. The 65% assumed efficacy rate was based on recent studies that demonstrated increasing MRSA rates along with increasing mortality, with reports of up to 64% mortality among patients with MRSA bacteremia or *S. aureus* infections with noneradicable foci or both [160-166] and 20% to 50% among patients with IE [31, 33, 150, 154]. Of note, outcome in these studies is often assessed at the end of therapy or shortly thereafter. IEAC success at EOT was similar to that reported in the literature with success rates of 61.7% for daptomycin and 60.9% for comparator in the ITT population and 67.1% and 66.7% for daptomycin and comparator, respectively, in the PP population.

More daptomycin patients failed due to persisting or relapsing *S. aureus* infection relative to comparator patients. A total of six (5.0%) of 120 daptomycin patients failed in the setting of increasing MICs while 60 (50.0%) of 120 patients failed without associated increased MICs. In contrast, more comparator patients failed due to adverse events associated with drug discontinuation, including hypersensitivity reactions and renal failure.

Patients with LIE had poor response in both treatment groups, high mortality, and no patient with LIE due to MRSA had a successful outcome. This emphasizes the high morbidity and mortality associated with this disease and it is noteworthy that 15 of these 19 patients did not receive surgical therapy as several studies have demonstrated improved outcomes with early valve replacement surgery [154-159].

Reviewer's comments: After viewing the clinical data supplied by the Applicant, the question arises, ***do patients treated with daptomycin for endocarditis or bacteremia due to* S. aureus *develop resistant organisms during therapy?***

The Applicant has provided patient report forms that contain MIC data for patients given daptomycin or comparators to treat endocarditis or bacteremia. Table E was constructed to show the numbers and percentages of patients in both study arms showing number of patients with increases in daptomycin and vancomycin MICs and those who developed daptomycin or vancomycin resistance.

Table E. Frequency of Increased MICs and Resistance to Daptomycin and Vancomycin in Patients during Therapy.

	N, % increased daptomycin MIC	N, % increased vancomycin MIC	N, % developed daptomycin resistance	N, % developed vancomycin resistance
clinical successes				
daptomycin arm	***17/53 (32.1%)****	12/53 (22.6%)*	0/53 (0%)*	0/53 (0%)*
comparator arm	10/46 (21.7%)	11/46 (23.9%)	1/46 (2.2%)	0/46 (0%)
clinical failures				
daptomycin arm	***21/60 (35.0%)***	14/59 (23.7%)*	***6/60 (10.0%)***	0/59 (0.0%)*
comparator arm	11/50 (22.0%)*	14/51 (27.5%)*	0/50 (0.0%)**	0/50 (0.0%)**

*determination of MICs not done for one patient
**determination of MICs not done for two patients
Source: patient report forms, CRT electronic file, this submission

The data from Table E show that patients in the daptomycin arm, whether they were clinical successes or clinical failures, were *more likely* to demonstrate *increased MICs* to daptomycin than patients in the comparator arm. Also, patients in the daptomycin arm that were clinical failures were more likely to develop resistance to daptomycin (6/60, 10%) than clinical successes or patients treated with the comparator. The data also showed that increases in daptomycin MICs and daptomycin resistance are not correlated with increases in vancomycin MICs or vancomycin resistance.

Table F was constructed from the patient report forms and shows more detailed data from the patients in whom isolates developed at least a two dilution step increase with in daptomycin MIC.

Table F: Clinical Failures in Daptomycin Arm with Increased Daptomycin MICs

Case #	Final Diagnosis	Organism	Baseline MIC	High MIC	MIC Step Increase
(b) (6)	complicated bacteremia	MRSA	0.25	2	3
	complicated RIE	MSSA	0.25	4	4
	complicated bacteremia	Both	0.25	2	3
	left IE	Both	0.25	2	3
	left IE	MRSA	0.5	2	2
	complicated bacteremia	MRSA	0.5	2	2
	left IE	MRSA	0.25	1	2
	left IE	MRSA	0.25	1	2

Note: Data is not limited to baseline MICs. At baseline, case# (b) (6) had only MRSA in the blood and MSSA was not isolated until Day 20P. The baseline pathogen was MRSA for case # (b) (6) and MSSA was not isolated from blood until Day 04.
Source: patient report forms, CRT electronic file, this submission.

All cases demonstrated a MIC step increase of at least two steps with the exception of two patients (b) (6) and (b) (6) All cases demonstrated a highest level of MIC of at least 1 µg/ml and 6/8 patients had MICs of 2 µg/ml or greater.
Data from patient report forms were used to construct the following table. Table G presents the MIC distributions (by dilution) for patients with bacteremia or endocarditis in the ITT population.

Table G. Distribution of MICs for Daptomycin Treated Patients (ITT) by Clinical Outcome

Clinical success	MIC (µg/mL) 0.12	0.25	0.5	1	2	4
(N=53)	1/53 (1.9%)	36/53 (67.9%)	14/53 (26.4%)	2/53 (3.8%)	1/53 (1.9%)	0/53 (0%)
bacteremia						
uncomplicated	1/53 (1.9%)	11/53 (20.7%)	3/53 (5.7%)			
complicated		18/53 (33.9%)	9/53 (16.9%)	2/53 (3.8%)		
RIE						
uncomplicated		3/53 (5.7%)	1/53 (1.9%)			
complicated		3/53 (5.7%)	1/53 (1.9%)			
LIE		1/53 (1.9%)				
Clinical failure	**MIC (µg/ml) 0.12**	**0.25**	**0.5**	**1**	**2**	**4**
(N=59)	1/59 (1.7%)	34/59 (57.6%)	15/59 (25.4%)	3/59 (5.1%)	***5/59 (8.5%)***	***1/59 (1.7%)***
bacteremia						
uncomplicated		9/59 (15.3%)	4/59 (6.8%)			
complicated	1/59 (1.7%)	19/59 (32.2%)	6/59 (10.2%)	1/59 (1.7%)	3/59 (5.1%)	
RIE						
uncomplicated		1/59 (1.7%)	2/59 (3.4%)			
complicated		3/59 (5.1%)	2/59 (3.4%)			1/59 (1.7%)
LIE		2/59 (3.4%)	1/59 (1.7%)	2/59 (3.4%)	2/59 (3.4%)	
total	**2/112 (1.8%)**	**70/112 (62.5%)**	**29/112 (25.9%)**	**5/112 (4.4%)**	**5/112 (4.5%)**	**1/112 (0.9%)**

Source: patient report forms, CRT electronic file, this submission

Data from Table G indicate there were more patients with daptomycin MICs of ≥ 1 µg/ml among clinical failures than among clinical successes. Six patients with complicated bacteremia, one patient with complicated RIE, and four patients with LIE had pathogens demonstrating MICs ≥ 1 µg/ml. Six patients who were clinical failures developed resistance (MIC >1µg/ml) during treatment with daptomycin. These data indicate that greater than 10% of clinical failures had a MIC =2 µg/ml or greater.

Table H shows data from patients with relapsing or persistent bacteremia. The table shows clinical failures associated with MSSA, MRSA, MICs equal to or greater than 1 µg/ml, and MICs that increased by ≥ 2-fold dilutions.

Table H: Changes in MICs for Relapsing or Persistent Bacteremia Patients

	MIC ≥ 1	≥ 2 steps	MRSA	MSSA
daptomycin arm (N=20)	***9/20 (45.0%)***	***9/20 (45.0%)***	12/2 (60.0%)*	11/20 (55.0%)*
comparator arm (N=11)	1/11 (9.1%)	0/11 (0%)	8/11 (72.7%)	2/11 (18.2%)
Total (N=31)	10/31 (32.2%)	9/31 (29.0%)	20/31 (64.5%)	13/31 (41.9%)

*3 patients had both MSSA and MRSA
Source: patient report forms, CRT electronic file, this submission

Data from Table H indicate that patients with relapsing or persistent bacteremia in daptomycin arm were more likely to have pathogens with a MIC ≥ 1 µg/ml and demonstrate a two or more increase in MIC dilution steps than relapsing or persistent bacteremia patients treated with comparator.

To summarize, bacteremia/infective endocarditis patients on daptomycin therapy who were clinical failures were more likely to demonstrate increased daptomycin MICs and develop non-susceptibility to daptomycin than those patients who were clinical successes. Many of these clinical failures had MIC values ≥ 1 µg/ml, the criterion for non-susceptibility. Patients with relapsing or persistent bacteremia were more likely to have increased MICs if treated with daptomycin rather than comparator. This was irrespective of whether *S. aureus* demonstrated oxacillin susceptibility or resistance.

INTERPRETATIVE CRITERIA

The Applicant asserts that the data generated from surveillance studies, *in vivo* animal modeling, and study DAP-IE-01-02 support the current daptomycin interpretative criteria for *S. aureus*. Key data are presented below in support of the current interpretative criteria for *S. aureus*, including:

- recent global surveillance results;
- clinical susceptibility of *S. aureus* from study DAP-IE-01-02;
- pharmacodynamics in animal models;
- human pharmacokinetic data from study DAP-IE-01-02;
- Monte Carlo simulations, where human PK data and surveillance data are applied to the pharmacodynamic targets; and
- clinical and microbiological outcome data correlated to susceptibility.

Global Surveillance Studies

Applicant-sponsored global surveillance trials were run concurrently with study DAP-IE-01-02. The first study was conducted by (b) (4) in 2000-2001 and was (b) (4) Subsequent studies in 2002, 2003, and 2004 were conducted by (b) (4) and have been previously reported [62, 169-172].

A pooled, multi-year analysis was performed that stratified staphylococcal isolates by study year, oxacillin susceptibility, and geographic region (i.e., US and European Union [EU]) [Report DAP.022.MC]. The top level summaries of daptomycin MIC values for *S. aureus* and coagulase-negative staphylococci are shown in Table 32. Consistent MIC90 values and MIC value ranges for each category were obtained regardless of the subset of the data examined (i.e., collection year, oxacillin susceptibility, geographic region), allowing the conclusion that daptomycin MIC value distributions for staphylococci have remained consistent since 2001.

Table 32: Daptomycin MIC Value Distribution Against Staphylococci (Combined US and EU Surveillance)

Combined US and EU 2001 to 2004 Surveillance	Daptomycin MIC Value (µg/mL)				
	≤ 0.12	0.25	0.5	1	2
Staphylococcus aureus					
Count (n=13,398)	734	8711	3846	103	4
%	5.5	65	28.7	0.8	0
cumulative %	5.5	70.5	99.2	100	100
Coagulase-negative staphylococci					
Count (n=15,239)	648	2746	1702	138	5
%	12.4	52.4	32.5	2.6	0.1
cumulative %	12.4	64.8	97.3	99.9	100

(MIC90 value is shaded)
Source: Table 2.7.2- 45, this submission

In addition to the global surveillance studies, special collections of rare *S. aureus* isolates have been tested, including h-GISA, GISA, and DSV isolates, and confirm the potency and bactericidal activity against these atypical *S. aureus* isolates. These collections include a higher proportion of isolates with daptomycin MIC values of 1 and 2 µg/mL, as well as a handful of isolates at 4 and 8 µg/mL. Additionally, daptomycin retains potency against the four reported VRSA strains with MIC values of = 1 µg/mL. These data are summarized in Table 2.7.2-25 and Table 2.7.2-26 (this submission).

S. aureus isolates from clinical studies have included a small number of strains from daptomycin- treated patients that have shown an increase in daptomycin MIC values while on-therapy. This included one patient in the Lilly AVAM study whose *S. aureus* went from 0.5 µg/mL to 12.5 µg/mL (4 µg/mL when tested in the presence of the correct calcium concentration), one patient in the compassionate use study DAP-EAP-02-01 whose isolate went from 0.25 µg/mL to 2 µg/mL, six patients in the DAP-IE-01-02 study whose isolates increased from a baseline value of 0.25 to 0.5 µg/mL to 2 µg/mL, and one patient in the DAP-IE-01-02 study whose isolate went from 0.25 µg/mL to 4 µg/mL.

In Study DAP-IE-01-02, seven daptomycin patients (7 of 120, 5.8%) had *S. aureus* isolated that demonstrated increased daptomycin MIC values on study. Additional information about these isolates can be found in the Clinical Summary of Efficacy [see Section 2.7.3.2.1.7 and Section 2.7.3.5.2]. Six of the seven isolates were from patients assessed as microbiological failures. In contrast to these six patients, 60 patients in the daptomycin group (60 of 120, 50.0%) had baseline *S. aureus* daptomycin MIC values of = 0.5 µg/mL who were IEAC failures at TOC without developing a non-susceptible *S. aureus* isolate on study.

Cases of daptomycin resistance in *S. aureus* have been reported during post- marketing (Section 2.7.2.4.5.2, this submission). In nine cases where a susceptible parent strain and its non- susceptible derivative strain have been available for testing, the daptomycin non-susceptible MIC values were primarily 2 and 4 µg/mL with one isolate confirmed with an MIC value of 8 µg/mL (Table 2.7.2-29).

Daptomycin surveillance studies continue to demonstrate a unimodal MIC value distribution with a MIC90 value of 0.5 µg/mL and a maximum MIC value of 2 µg/mL for *S. aureus*. Special populations of *S. aureus* isolates (e.g., GISA, DSV) contain more isolates with daptomycin MIC values of 1 and 2 µg/mL, and a maximum MIC value of 8 µg/mL. Nine patients from Cubist and Lilly-sponsored clinical trials have had *S. aureus* isolates develop non- susceptible isolates with daptomycin MIC values of 2 and 4 µg/mL.

These data support a daptomycin susceptible interpretative criteria of = 1 µg/mL.

Pharmacodynamics for S. aureus

The neutropenic mouse model of thigh infection has been used previously to determine dose response parameters of antibacterial compounds [see Report DAP. 026.MC]. The model is based on the reduction in tissue bacterial load following treatment. PK data is then correlated with the dose response data to produce an exposure- response determination.

For daptomycin, both C_{max} and AUC $_{0\text{-}24}$ have been shown to be predictive of efficacy in animal models of infection [113, 114, 116, 121, 173]. To further investigate the pharmacodynamics of daptomycin, the AUC $_{0\text{-}24}$ value was chosen as the parameter to be modeled in the mouse neutropenic thigh infection model [see Report DAP.026.MC]. The study rationale and methodology are reviewed in Section 2.7.2.4.7.2, this submission. The isolates used in the study were a set of clonal community- acquired MRSA (CA-MRSA) strains with increasing daptomycin MIC values, ranging from 1 to 16 µg/mL, derived from the virulent parental strain MW2 [174]. There was a clear inflection point in the drug-exposure required to treat isolates with a daptomycin MIC value of = 2 µg/mL, compared to isolates with a daptomycin MIC value = 4 µg/mL. The criterion for efficacy was a 3-log10 reduction in bacterial counts relative to saline-treated, control mice following a 3-day course of daptomycin therapy. The resulting AUC $_{0\text{-}24}$ /MIC ratios for efficacy ranged from 110 to 275, with an overall regression curve fit of 150 to 207, depending upon whether a second order polynomial (emphasis on all data points) or a logarithmic curve fit (emphasis on isolates with a daptomycin MIC value of 1 or 2 µg/mL) was used (Figure 2.7.2-11). The more stringent criteria, an AUC $_{0\text{-}24}$ /MIC ratio of = 207, was selected as the target criteria for daptomycin efficacy.

Human Pharmacokinetics and Pharmacodynamic Calculations

In Study DAP-IE-01-02, the daptomycin dose of 6 mg/kg q24h resulted in an AUC $_{0\text{-}24}$ range of 242 to 2210 µg · hr/mL, with a mean ± SD of 622 ± 304 µg · hr/mL. All daptomycin- treated patients who underwent PK sampling (106 of 120; 88.3%) attained a serum AUC $_{0\text{-}24}$ /MIC ratio of = 207.

The correlation of daptomycin PK/PD parameters with efficacy were examined [see Section 2.7.3.5.3]. No correlations were observed between any daptomycin PK/PD parameter examined and clinical (IEAC outcome at EOT) or microbiological (pathogen eradication at EOT) efficacy. Since all patients attained the more stringent target $AUC_{0\text{-}24}$ /MIC criteria for efficacy of = 207, this lack of correlation between the PK/PD parameters studied and clinical and microbiological efficacy would be predicted based on the animal model data.

The lowest AUC $_{0\text{-}24}$ observed in study DAP-IE-01-02 was 242.0 µg · hr/mL. The AUC$_{0\text{-}24}$ /MIC ratio for this patient given a hypothetical *S. aureus* at the susceptible breakpoint of 1 µg/mL would be 242. The human PK data from study DAP-IE-01-02 indicates that the daptomycin susceptible interpretative criteria of = 1 µg/mL is a conservative estimate for *S. aureus*.

Monte Carlo Simulations and Calculations

A Monte Carlo simulation was performed on potential efficacy against *S. aureus*. The daptomycin MIC values from the pooled global surveillance studies (Table 2.7.2-45) and the human AUC $_{0\text{-}24}$ values from patients in study DAP-IE-01-02 (modeled using a three-parameter log normal distribution) were used as variables, applied to an AUC $_{0\text{-}24}$ /MIC target criterion of 207 for efficacy against *S. aureus*. This simulation yielded a > 99.9% probability of efficacy against *S. aureus* [see Report DAP.030.MC].

Five additional Monte Carlo simulations were performed using five theoretical *S. aureus* populations, each with uniform daptomycin MIC values of 0.5, 1, 2, 4, and 8 µg/mL [see Report DAP.030.MC]. Each simulation used the human AUC $_{0\text{-}24}$ value distribution from patients in study DAP-IE-01-02 applied against an AUC $_{0\text{-}24}$ /MIC target criterion of either 207 or 150 for efficacy against *S. aureus* (Table 33). There was a probability of > 99% for daptomycin achieving the required target criteria for efficacy against populations of *S. aureus* with daptomycin MIC values of = 1 µg/mL. For isolates with a daptomycin MIC value of 2 µg/mL, there was a high probability of achieving the target criteria of 150 (94.1%) and a slightly lower probability of achieving the target criteria of 207 (74.5%). The probability of daptomycin achieving either the 207 or 150 target criteria for efficacy decreased significantly against *S. aureus* populations with daptomycin MIC values of 4 µg/mL (16.4% and 40.5%, respectively) and 8 µg/mL (0.5% and 3.3%, respectively).

The results of these simulations indicate that the current susceptible interpretative criteria for *S. aureus* of = 1 µg/mL is conservative.

Table 33: Summary of Target Attainment Rates for Monte Carlo Simulations using Theoretical Populations of *S. aureus* with Identical, Fixed Daptomycin MIC Values

Target attainment rates using an AUC$_{0\text{-}24}$/MIC criteria for efficacy of:		
Daptomycin MIC value (µg/mL)	207	150
0.5	> 99.9%	> 99.9%
1	99.70%	> 99.9%
2	74.50%	94.10%
4	16.40%	40.50%
8	0.50%	3.30%

(Cross Reference: Report DAP.030.MC)
Source: Table 2.7.2- 46, this submission

Correlation of Daptomycin Susceptibility to Efficacy in Study DAP-IE-01-02

The least susceptible baseline *S. aureus* isolate among daptomycin- treated patients in study DAP-IE-01-02 was 0.5 µg/mL. The efficacy of daptomycin showed no pattern of decreased therapeutic or microbiologic success rates with increasing daptomycin MIC

values up to 0.5 µg/mL [see Section 2.7.3.5.1]. This lack of correlation was consistently observed across relevant diagnostic subgroups, MSSA/MRSA subgroups, and susceptibility testing methodologies (b) (4)

The lack of correlation between efficacy and susceptibility up to a daptomycin MIC value of 0.5 µg/mL for *S. aureus* supports the current susceptible interpretative criteria for *S. aureus* of = 1 µg/mL. These analyses demonstrate that the current interpretative criteria for *S. aureus* performed well for determining susceptibility to daptomycin in study DAP-IE-01-02.

Rationale for Interpretive Criteria for S. aureus

Data obtained from non-clinical investigations performed since the approval of daptomycin in September 2003 and from study DAP-IE-01-02 are supportive of daptomycin's current interpretative criteria for *S. aureus* (methicillin-susceptible and -resistant strains) = 1 µg/mL as susceptible and = 2 µg/mL as non-susceptible. This is based upon:

• Daptomycin multi-year surveillance studies continue to demonstrate a unimodal MIC value distribution with a MIC90 value of 0.5 µg/mL and a maximum MIC value of 2 µg/mL (< 0.03% of the population) for *S. aureus*;

• Studies of special populations of *S. aureus* (e.g., GISA, DSV) have shown a greater number of isolates with daptomycin MIC values of 1 and 2 µg/mL, against which daptomycin maintains its bactericidal activity;

• A mouse neutropenic thigh infection study that used clonal, derivative strains of the virulent CA-MRSA parent strain MW2 with increasing daptomycin MIC values demonstrated that similar drug exposure was needed to treat *S. aureus* isolates with daptomycin MIC values = 2 µg/mL and increased drug exposure was required for isolates with daptomycin MIC values = 4 µg/mL;

• Monte Carlo simulations that utilized the daptomycin AUC_{0-24} values from patients in study DAP-IE-01-02 demonstrated a > 99.5% probability of attaining the more stringent target AUC_{0-24} /MIC criterion of 207 when applied against a theoretical *S. aureus* population with daptomycin MIC values of 1 µg/mL;

• Monte Carlo simulations demonstrated a 94.1 to 74.5% probability of attaining sufficient drug exposure for efficacy against a theoretical *S. aureus* population with daptomycin MIC values of 2 µg/mL using a target AUC_{0-24} /MIC criterion of 150 (best curve fit) to 207 (most stringent criterion); and

• The efficacy of daptomycin showed no pattern of decreased therapeutic success rates or pathogen eradication rates with increasing daptomycin MIC values up to 0.5 µg/ml, the least susceptible baseline *S. aureus* isolate among daptomycin-treated patients.

These data support the conservative interpretative criteria of = 1 µg/mL (susceptible) and = 2 µg/mL (non- susceptible) for *S. aureus* (including methicillin-resistant strains) and

demonstrate that the current interpretative criteria for *S. aureus* perform well for determining susceptibility to daptomycin in the proposed indication of *S. aureus* bacteremia including those patients with known or suspected endocarditis caused by methicillin-susceptible and methicillin-resistant strains.

Reviewer's comments: Generally, the determination of susceptibility criteria for a pathogen relies on:

- *In vitro* spectrum of activity including surveillance results, clinical susceptibilities, comparison studies with other antimicrobials and MICs of organisms having characterized resistance genes.
- *In vivo* animal studies (e.g. rabbit endocarditis model), pharmacodynamics in animals and Monte Carlo analysis.
- Clinical results and failure analysis.

The Applicant's data from surveillance studies in North America and Europe from 2000 to 2004 are shown in Table 4. According to the Applicant, Table 4 illustrates that daptomycin susceptibility has remained consistent throughout the last four years. However, careful examination of these data suggests otherwise.

Data from the studies performed between 2000 and 2004 show that when the percentages of isolates for each MIC dilution are calculated, the percentage of the isolates with MICs of ≤ 0.12 and 0.25 µg/ml ***decrease*** over time while the percentage of isolates with MICs of 0.5, 1, and 2 µg/ml ***increase*** over time. This trend occurs for both MSSA and MRSA. Clearly, the vast majority of isolates have a MIC = 0.25 µg/ml with the next largest group of isolates having a MIC = 0.5 µg/ml. Thus, ***daptomycin MICs of clinical isolates of S. aureus, regardless of methicillin susceptibility, have increased over time.*** Thus, an increase in non-susceptibility may follow.

Since daptomycin belongs to a unique class of antimicrobial, it was not informative to compare the susceptibilities of daptomycin to other antimicrobials.

There has been limited experience with resistance to daptomycin. While the Applicant has provided data showing an association of certain mutated gene and increased MICs, the mechanism of resistance has not been clearly defined. However, eight recent publications have reported daptomycin non-susceptibility and "resistance".

These publications report "resistance" to daptomycin in clinical isolates from patients on therapy (see Table D). Four of these publications reported on MRSA isolates. Of these, three were associated with bacteremia and one was associated with osteomyelitis. All samples were from blood and dosages ranged from 4mg/kg to 8 mg/kg. MICs ranged from 2 µg/ml to 4 µg/ml. Clearly, all four isolates exceeded the susceptible criterion of ≤ 1 µg/ml. *Thus*, ***although there are limited numbers of isolates at this MIC, a MIC ≥ 2 µg/ml could potentially serve as a breakpoint for a new criterion of "resistance".***
The Applicant provides an overview of isolates with treatment associated failures and decreases in daptomycin susceptibility following commercial availability (see table 2.7.2—29, this submission). This table shows that 15 patients developed MICs to daptomycin ≥ 1 µg/ml since daptomycin was approved by the Agency. (Isolates with a MIC ≤ 1 µg/ml are considered susceptible to daptomycin). Of these 15 patients, nine patients had *S. aureus* isolated from blood. Of these nine, eight patients demonstrated isolates with a three step increase in daptomycin MIC. Final MICs for the *S. aureus* isolates ranged from 1—8 µg/ml.

From these data, it is evident that isolates with a MIC as low as 1 μg/ml may be associated with treatment failures.

The Applicant cites pharmacodynamic data from the mouse neutropenic thigh model. However, this model is limited and does not adequately serve as a model for endocarditis or bacteremia. As the rabbit model of infective endocarditis serves as the "gold standard", results from such a model should be more predictive of results that would be expected in a clinical trial.

The Applicant cites only one reference to an *in vitro* model of bacteremia. Several references are made to the rat and rabbit models of endocarditis; the Applicant does not provide MIC data from such models. Instead, the Applicant provides data on log reduction of bacteria in vegetations and percentages of sterile vegetations. The more pertinent measure of percentage of sterile vegetations ranged from 0—92%. While the upper level of this range is impressive, one would expect that any percentage of sterilization less than 100% would be troublesome as any remaining live bacteria could easily initiate a new infection.

One report did provide MIC data; Silverman et al, (2001) showed that two of 16 rabbits yielded organisms resistant to daptomycin; one organism had a four-fold rise in MIC and another, an eight-fold rise in MIC.

As was seen with the original application, Monte Carlo simulations coupled with animal PK/PD data present conflicting data. Consequently, these data are de-emphasized in the determination of breakpoints.

The most important data to consider for the determination of breakpoints are the data derived from the pertinent clinical study.

When considering all-comers in the trial, MICs to daptomycin increased as well as non-susceptibility to daptomycin in both arms of the treatment while on therapy. Table E shows that the patients in the daptomycin arm, whether they were clinical successes or clinical failures, were more likely to demonstrate increased MICs to daptomycin than patients in the comparator arm. Patients in the daptomycin arm that were clinical failures were more likely to develop non-susceptibility or "resistance" to daptomycin (eight patients) than patients who were clinical successes or patients treated with comparator. Of the clinical failures, six patients had a baseline MIC = 0.25 μg/ml while two patients had a baseline MIC = 0.5 μg/ml (Table F). The highest level MIC attained ranged from 1 μg/ml (two patients) to 4 μg/ml (one patient); the other five patients had a MIC = 2 μg/ml. **Again*, as seen with the reports of treatment failures after commercial availability provided by the Applicant, it is evident that isolates with a MIC as low as 1 μg/ml may be associated with treatment failures.***

When a particular group of patients are examined, the patients with persistent or relapsing bacteremia showed increasing MICs and non-susceptibility to daptomycin (Table H). Data from this table indicate that patients with relapsing or persistent bacteremia in daptomycin arm were more likely to have pathogens with a MIC ≥ 1 μg/ml and demonstrate a two or more increase in MIC dilution steps than relapsing or persistent bacteremia patients treated with a comparator.

Taken together, the *in vitro*, *in vivo* and clinical data, demonstrate that isolates with a MIC = 1 μg/ml are associated with increased non-susceptibility or resistance and with clinical

failure. By nature, a final MIC cannot be predictive of clinical outcome while a patient is on therapy. However, what can patient baseline MICs tell us?

Table I is a compilation of data from the Applicant's clinical trial sorted by clinical outcome for both daptomycin and comparator treated patients by baseline daptomycin MIC.

Table I. Clinical Outcome (IEAC Success) by Baseline MIC

	MIC (μg/ml)				
	0.12	**0.25**	**0.5**	**1**	**ALL-Comers**
Daptomycin					
clinical success (N=54)	7/12 (58.3%)	41/86 (47.7%)	6/15 (40.0%)	0 (0%)	54/113 (47.8%)
clinical failure (N=59)	5/12 (41.7%)	45/86 (52.3%)	9/15 (60.0%)	0 (0%)	59/113 (52.2%)
Comparator					
clinical success (N=54)	10/18 (55.6%)	31/63 (49.2%)	5/10 (50.0%)	0 (0%)	46/92 (50.0%)
clinical failure (N=59)	8/18 (44.4%)	32/63 (50.8%)	5/10 (50.0%)	1/1 (100%)	46/92 (50.0%)

Note: patients without a recorded baseline MIC were excluded.

When clinical outcome is examined in the patients from the daptomycin arm, clinical success occurred in 47.8% of patients and clinical failure occurred in 52.2% of patients regardless of baseline MIC.

However, when clinical success and clinical failure rates are examined for patients from the daptomycin arm at individual baseline MIC steps, the rates differ from the overall rates. Clinical success was greater in patients with a MIC = 0.12 μg/ml (58.3%) than patients overall (47.8%) in the daptomycin arm. Success rates were similar between the patients with a baseline MIC = 0.25 μg/ml (47.7%) and the patients overall (47.8%) in the daptomycin arm. However, patients with a MIC = 0.5 μg/ml had significantly lower success rate (40.0%) than patients overall (47.8%) in the daptomycin arm. The corresponding changes in clinical failure rates ensued.

Interestingly, clinical success rates were similar among patients in the comparator arm regardless of baseline daptomycin MIC (0.12, 0.25, or 0.5 μg/ml). This would be expected as these patients were treated with an alternative antibiotic and not exposed to daptomycin.

These data suggest that to increase the chance of clinical success, the attending physician may want to use the baseline daptomycin MIC as a factor in his decision for the choice of antibiotic for bacteremia. Thus, if the baseline daptomycin MIC is 0.12 μg/mL or less, there is greater chance of success in treating the patient. If the baseline daptomycin is 0.5 μg/ml or greater, the physician may want to discontinue daptomycin therapy and use an alternative antibiotic.

It is worth noting that the current susceptibility breakpoint for *S. aureus* (MIC ≤ 1 μg/ml) was established based on data derived from two cSSSI clinical trials. This disease is not as severe and does not require the extensive adjunct therapy as that of the current disease (bacteremia/endocarditis) for which an indication is sought. Consequently, a modified susceptibility breakpoint may be necessary and beneficial to determine if daptomycin therapy should be initiated in patients diagnosed with bacteremia/endocarditis.

Consequently, this Reviewer recommends that the breakpoint for daptomycin susceptibility for S. aureus, regardless of oxacillin susceptibility, be set at 0.25 μg/ml for bacteremia due

to S. aureus infection. This breakpoint would increase the probability of clinical success regardless of indication, bacteremia or endocarditis. Note that 89.9% (48/54) patients in the daptomycin arm demonstrating clinical success had a baseline MIC ≤ 0.25 μg/ml. Both indications were included despite the recommendation that only the bacteremia indication be granted. This was due to the realization that off-label treatment is likely and has occurred for endocarditis due to *S. aureus* infection.

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MICROBIOLOGY PORTION OF THE PACKAGE INSERT

Note: This Reviewer indicates recommended changes to the Microbiology portion of the Package Insert as follows. Deletions are in ~~red and strikethrough font~~; additions are in blue and underlined font.

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4 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

Peter Coderre
3/22/2006 11:28:05 AM
MICROBIOLOGIST

Frederic Marsik
3/23/2006 07:18:57 PM
MICROBIOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021572Orig1s008

CLINICAL PHARMACOLOGY REVIEW(S)

NDA#	21-572
PRODUCT	Daptomycin (Cubicin™)
FORMULATION	Sterile lyophilized powder for injection
DOSAGE STRENGTH	500 mg vials
SUBMISSION DATES	9/22/05, 1/24/06, 1/26/06, 2/3/06, 2/21/06
SUBMISSION TYPE	NDA Supplement, SE1-008
SPONSOR	Cubist Pharmaceuticals, Inc., Lexington, MA 02421
OCPB DIVISION	Division of Clinical Pharmacology 4
MEDICAL DIVISION	Division of Anti-Infective and Ophthalmology Products
REVIEWER	Charles R. Bonapace, Pharm.D.
PM REVIEWER	Dakshina Chilukuri, Ph.D.
TEAM LEADER	Venkat R. Jarugula, Ph.D.
PM TEAM LEADER	Joga Gobburu, Ph.D.

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

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1. EXECUTIVE SUMMARY

Cubist Pharmaceuticals, Inc. submitted a supplemental New Drug Application for Cubicin™ (daptomycin for injection) for the treatment of *Staphylococcus aureus* bacteremia including those with known or suspected endocarditis (SAB/SAIE). This NDA was granted a priority review status. The proposed dosage regimen is 6 mg/kg IV q24h administered over 30 min. The duration of treatment is based on the treating physician's working diagnosis (b) (4) Daptomycin is currently approved for the treatment of complicated skin and skin structure infections and the approved dosage regimen is 4 mg/kg IV q24h infused over 30 min. The duration of therapy for complicated skin and skin structure infections is 7 to 14 days.

The sponsor submitted the results from two Phase 1 clinical studies and an *in vitro* study evaluating the *in vitro* metabolism of daptomycin by human liver microsomes. Study DAP-ADT-04-02 characterized the pharmacokinetics of daptomycin when administered at doses up to 12 mg/kg q24h for 14 days to healthy subjects. Study DAP-REN-02-03 characterized the pharmacokinetics of daptomycin 8 mg/kg loading dose followed by 6 mg/kg following hemodialysis three times weekly in subjects with end-stage renal disease receiving hemodialysis. The *in vitro* study (PKR-05-007) assessed whether daptomycin is a substrate of CYP P450 isoenzymes since this information was not included with the original NDA submission. An additional study (PKR-05-006) was performed to provide metabolic profiling of select plasma and urine samples obtained from study DAP-ADT-04-02.

The supplemental NDA for daptomycin for injection was discussed at the Anti-Infective Drugs Advisory Committee Meeting on March 6, 2006. The advisory committee members were asked to respond to the following two questions: Do data from the pivotal study provide substantial evidence of safety and efficacy of daptomycin in the treatment of *S. aureus* bacteremia? Do data from the pivotal study provide substantial evidence of safety and efficacy of daptomycin in the treatment of patients with infective endocarditis? The advisory committee members responded unanimously in favor of the first question (9 yes, 0 no) and the majority responded in favor of the second question (5 yes, 4 no).

1.1 Recommendations:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 4 (OCP/DCP4) has reviewed NDA 21-572. The submission is acceptable from a Clinical Pharmacology point of view.

The labeling comments outlined in the annotated label should be conveyed to the sponsor.

1.2 Phase IV Commitments:

No Phase IV commitments are recommended.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings:

Drug Metabolism
In the original NDA submission, the sponsor performed *in vitro* studies to provide evidence that daptomycin does not inhibit or induce the activities of CYP P450 isoenzymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4. In the current submission, the sponsor evaluated the potential of daptomycin to act as a substrate of CYP P450 isoenzymes using human liver microsomes. The results of the *in vitro* study support that daptomycin is not a substrate of CYP P450 isoenzymes.

A mass balance study submitted with the original NDA 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. However, it was unknown if active metabolites of daptomycin are present in serum and/or urine. Metabolic profiling of plasma and urine samples from six healthy subjects following the administration of daptomycin 6 mg/kg IV revealed the absence of metabolites from plasma but the presence of four minor metabolites from urine (<5% of the daptomycin UV response). Three of the metabolites appear to be oxidative metabolites and the structure of the fourth compound was not identified.

Pharmacokinetics in healthy subjects
The pharmacokinetics of daptomycin were assessed in 36 healthy subjects who received daptomycin IV 6 mg/kg q24h or 8 mg/kg q24h for 4 days, 10 mg/kg q24h for 14 days, or 12 mg/kg q24h for 14 days. Following single dose administration, the mean C_{max} and $AUC_{0-\infty}$ increased nearly proportional to dose and the mean CL_T, V_{SS}, and $t_{1/2}$ remained unchanged with increasing dose. The single dose pharmacokinetic parameters were predictive of the steady-state pharmacokinetics. The pharmacokinetics of daptomycin are linear up to 12 mg/kg.

Pharmacokinetics in subjects with renal impairment
A population pharmacokinetic analysis was performed in the Phase 3 clinical study supporting the use of daptomycin for the treatment of *Staphylococcus aureus* bacteremia (SAB) including those with known or suspected endocarditis (SAIE) to determine the pharmacokinetics of daptomycin 6 mg/kg in patients with renal impairment. The mean steady-state AUC_{0-24} increased 17% and 59% in patients with mild (n=29) and moderate (N=15) renal impairment compared to patients with normal renal function (N=62). The decrease in total clearance with increasing renal impairment was similar among patients in the Phase 3 study receiving daptomycin 6 mg/kg compared to healthy subjects and patients with complicated skin and skin structure infections receiving daptomycin 4 mg/kg in the current label. The results of the population pharmacokinetic analysis support the proposed dosage adjustment of daptomycin 6 mg/kg q24h for patients with $CL_{CR} \geq 30$ mL/min and 6 mg/kg q48h for patients with CL_{CR} <30 mL/min, including those receiving hemodialysis or CAPD.

The effect of low-flux and high-flux hemodialysis membranes on the pharmacokinetics of daptomycin was assessed after administration of a 8 mg/kg loading dose of daptomycin followed by 6 mg/kg maintenance doses three times weekly after the completion of hemodialysis for 21 days (nine doses) to 26 subjects with end-stage renal disease. The dose normalized C_{max} and $AUC_{0-\tau}$ values were statistically significantly higher on day 17 compared to day 1 for the low-flux dialyzer and high-flux dialyzer groups, although the dose normalized $AUC_{0-\tau}$ increased to a greater extent (among subjects in the low-flux group. There was no statistical difference between the dose normalized $AUC_{0-\tau}$ values and C_{max} values on day 8 compared to day 1. Thus, greater accumulation was observed in subjects receiving hemodialysis with low-flux membranes (approximately 120%) compared to those receiving hemodialysis with high-flux membranes (approximately 25%).

Population pharmacokinetics
The mean plasma clearance and volume of distribution of daptomycin were 11% and 20% higher, respectively in patients with *S. aureus* bacteremia with known or suspected endocarditis compared to healthy subjects receiving daptomycin IV 6 mg/kg. The changes in the pharmacokinetics of daptomycin in patients with bacteremia were similar to those previously reported in patients with complicated skin and skin structure infections (cSSSI). In these patients, the mean plasma clearance of daptomycin was unchanged and the volume of distribution was 28% higher compared to healthy subjects receiving daptomycin IV 6 mg/kg.

Exposure-response
An exposure-response analysis was performed to assess the relationship between measures of daptomycin exposure (C_{max}, C_{min}, and AUC_{0-24}) and PK/PD metrics (C_{max}/MIC, C_{min}/MIC, and AUC_{0-24}/MIC) and the IEAC success and microbiological outcome. While the results of the analyses indicate that a relationship may exist in a subpopulation of patients, no clinically relevant relationship was observed due to the limited number of patients and heterogeneity in the population.

Exposure-toxicity
An exposure-toxicity analysis was performed for patients with *S. aureus* bacteremia with available CPK data and steady-state C_{min} concentrations to assess the relationship between daptomycin exposure and CPK elevation. The proportion of patients with elevated CPK values (≥500 IU/L and ≥1000 IU/L) significantly increased as the C_{min} increased.

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Charles R. Bonapace, Pharm.D.
Office of Clinical Pharmacology
Division of Clinical Pharmacology 4

RD/FT Initialed by Venkat R. Jarugula, Ph.D._____
Team Leader

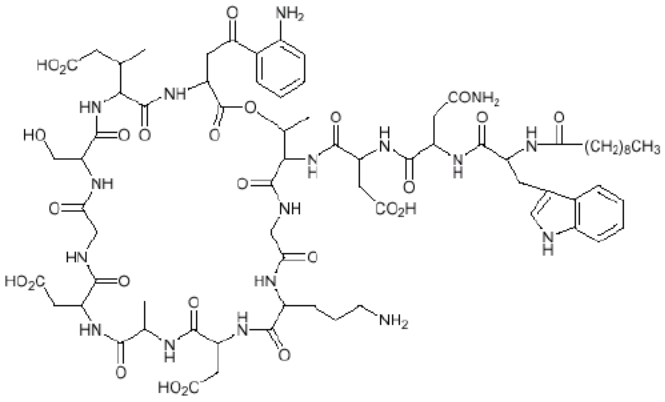
cc:
Division File: NDA 21-572
HFD-520 (CSO/Davi)
HFD-520 (MO/Nambiar, Sorbello, Cooper)
HFD-520 (Microbiology/Marsik, Coderre)
HFD-880 (Division File, Lazor, Selen, Jarugula, Bonapace)
CDR (Clin. Pharm.)

2. QUESTION-BASED REVIEW

2.1. General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Daptomycin is a cyclic lipopeptide antibiotic derived from the fermentation of a strain of *Streptomyces roseosporus*. It is a cyclic 13-amino acid peptide with a decanoic acid side-chain attached to the terminal L-tryptophan. 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.

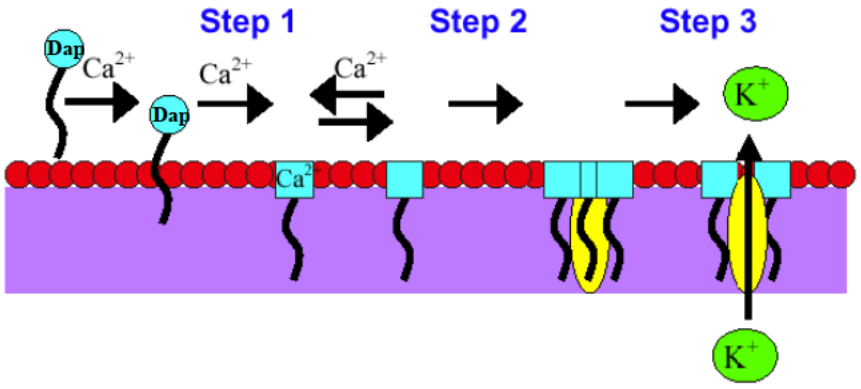
Table 1. Components and quantitative formulation of the unit dosage form - drug product

Component	Function	Quantity/500 mg vial
Daptomycin	Active ingredient	500 mg (b) (4)
Sodium hydroxide, NF	pH adjustment	(b) (4)
		(b) (4)
		(b) (4)

2.1.2 What is the proposed mechanism(S) of drug action and therapeutic indication(s)?

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). 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.

Figure 1. Model for the mechanism of action of daptomycin



Daptomycin demonstrates *in vitro* activity against aerobic and facultative Gram-positive organisms. Daptomycin demonstrates poor *in vitro* activity (b) (4) against Gram-negative organisms and anaerobes.

Daptomycin is currently approved for the treatment of complicated skin and skin structure infections caused by susceptible strains of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae* subsp. *equisimilis* and *Enterococcus faecalis* (vancomycin-susceptible strains only).

The sponsor is seeking an indication for the treatment of *Staphylococcus aureus* bacteremia including those with known or suspected endocarditis caused by methicillin-susceptible and methicillin-resistant strains.

2.1.3 What is the proposed dosage(s) and route(s) of administration?

The approved dosage regimen of daptomycin for the treatment of complicated skin and skin structure infections is 4 mg/kg IV q24h administered over 30 min for 7 to 14 days. The proposed dosing regimen of daptomycin for the treatment of *Staphylococcus aureus* bacteremia including those with known or suspected endocarditis is 6 mg/kg IV q24h administered over 30 min. The duration of treatment should be based on the treating physician's working diagnosis (b) (4)

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The sponsor performed two Phase 1 clinical studies (DAP-ADT-04-02 and DAP-REN-02-03) and one Phase 3 clinical study (DAP-IE-01-02) with the current application evaluating the safety and efficacy of daptomycin 6 mg/kg IV to support the dosing of daptomycin in patients with *Staphylococcus aureus* bacteremia including those with known or suspected endocarditis. Study DAP-00-02 (submitted with the original NDA) also supports the pharmacokinetics of daptomycin 6 mg/kg. Two additional Phase 2/3 clinical studies (B8B-MC-AVAM and DAP-EAP-02-01) were submitted to provide supportive safety and efficacy data of daptomycin in the treatment of infective endocarditis/bacteremia (B8B-MC-AVAM) or the treatment of infections due to Gram-positive bacteria that cannot be adequately treated with currently available therapy (study DAP-EAP-02-01).

DAP-ADT-04-02: This study was a Phase 1, single center, randomized, double-blind, placebo-controlled, multiple-dose, safety, tolerability, and pharmacokinetic study of ascending doses of daptomycin. Thirty-six healthy subjects were randomized to receive daptomycin IV 10 mg/kg q24h or placebo for 14 days, daptomycin IV 12 mg/kg q24h or placebo for 14 days, daptomycin IV 6 mg/kg q24h for 4 days, or daptomycin IV 8 mg/kg q24h for 4 days administered over 30 min.

DAP-REN-02-03: This study was a Phase 1, two center, randomized, double-blind study to evaluate the tolerability and pharmacokinetics following multiple-dose IV administration of daptomycin in subjects with end-stage renal disease (ESRD) receiving hemodialysis with low-flux and high-flux dialysis membranes. Subjects were randomized to receive daptomycin IV as a single loading dose of 8 mg/kg on study day 1 followed by 8 additional doses of daptomycin IV 6 mg/kg, given after every dialysis on Study Days 3, 5, 8, 10, 12, 15, 17, and 19 for a total of 9 doses over 21 days or placebo. Subjects randomized to placebo were to receive normal saline on the same dosing schedule as that of daptomycin.

DAP-00-02: This study was a Phase 1, single center, double-blind, randomized, multiple-dose study in 32 healthy male and female subjects randomized to receive daptomycin IV 4 mg/kg q24h for 7 days, 6 mg/kg q24h for 7 days, or 8 mg/kg q24h for 14 days administered over 30 min. This study evaluated the single- and multiple-dose pharmacokinetics of daptomycin.

DAP-IE-01-02: This study was a Phase 3, multicenter, randomized, open-label, comparative study to assess the safety and efficacy of daptomycin (n=120) compared to conventional therapy (n=116) in the treatment of patients with infective endocarditis or bacteremia due to *Staphylococcus aureus*. Patients were randomized to receive either daptomycin IV 6 mg/kg q24h or comparator drug for 28 to 42 days. Comparators consisted of vancomycin and antistaphylococcal penicillins (i.e., nafcillin, oxacillin, cloxacillin, or flucloxacillin). Initial synergistic gentamicin was to be administered to patients randomized to comparator and to patients with left-sided infective endocarditis randomized to daptomycin. Patients with CL_{CR} <30 mL/min were excluded from the study.

The daptomycin dose of 6 mg/kg q24h selected for the treatment of *S. aureus* bacteremia and endocarditis (study DAP-IE-01-02) was based upon animal models of endocarditis, animal toxicology data, clinical data from earlier studies, and *in vitro* and *in vivo* PK/PD modeling. Data submitted and reviewed with the original NDA suggest that daptomycin is a concentration-dependent, bactericidal antibiotic. Thus, the C_{max}/MIC and/or AUC/MIC ratios appear to be most closely correlated with efficacy. Clinical data from two early studies showed that there was no advantage in dose fractionation of daptomycin in patients with complicated infections and that daptomycin exposure at multiples of the MIC_{90} (unbound C_{max} is approximately 15× MIC_{90} and the unbound concentration at 6 hrs is approximately 4× MIC_{90}) of *S. aureus* could be attained with the 6 mg/kg q24h dose in patients with serious *S. aureus* infections. These data support the daptomycin dose of 6 mg/kg q24h selected for the pivotal *S. aureus* bacteremia and infective endocarditis study.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy endpoint in study DAP-IE-01-02 was the Independent External Adjudication Committee (IEAC) outcome at the test of cure (TOC) visit. Patients were classified as a success, failure, or non-evaluable. The definitions of success, failure, and non-evaluable are defined below.

Patients were classified as success if they met all of the following criteria:

- Were judged as cured or improved by the IEAC at TOC.
- Had a negative blood culture at TOC.

- Did not receive a potentially effective non-study (PENS) antibiotic that could have altered the therapeutic outcome at TOC (as defined by the IEAC).
- Received at least the minimum amount of study medication as defined in the protocol.

Patients were classified as a failure if they met any one of the following criteria:

- Were judged a clinical failure by the IEAC at EOT or TOC.
- Had persisting or relapsing bacteremia or no blood culture at TOC.
- Died.
- Received a PENS antibiotic that influenced therapeutic outcome (as defined by the IEAC).
- Discontinued study medication prematurely.

Patients who were classified by the IEAC as "Non-Evaluable" at EOT were considered "Non-Evalubale" by the IEAC at TOC.

A secondary efficacy endpoint in study DAP-IE-01-02 was the time to microbiological clearance in the overall ITT population.

The microbiological outcome by patient was part of the IEAC outcome. The pathogen-level microbiological responses at the TOC visit are defined below.

Documented eradication - Blood culture results obtained within the TOC analysis window were negative for the baseline infecting pathogen.

Presumed eradication – A baseline infecting pathogen meeting either of the following criteria:

- the patient did not have a *S. aureus* baseline infecting pathogen and the patient was deemed an IEAC success at TOC; or
- a blood culture result was negative but was outside of the TOC analysis window and the patient was deemed an IEAC success at TOC based on a review of all available data blinded to treatment.

Documented persistence - The baseline infecting pathogen was present within the TOC analysis window as determined by an isolate from a blood culture classified as "Persisting Pathogen".

Presumed persistence – A baseline infection pathogen meeting one of the following criteria:

- the patient did not have a *S. aureus* baseline infecting pathogen and the patient was deemed an IEAC failure at TOC;
- a blood culture result was missing from the TOC analysis window and the patient was deemed an IEAC failure at TOC;
- the patient was an IEAC Failure at EOT (i.e., failure carried forward).

Non-evaluable - A baseline infecting pathogen from a patient who was deemed non-evaluable by the IEAC at TOC or no baseline infecting pathogen was isolated.

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

The concentration of the active moiety of daptomycin was appropriately identified and measured in plasma and urine to assess pharmacokinetic parameters. The concentration of daptomycin in plasma and urine was determined using HPLC with UV detection and represents the concentration of the parent compound. Although the sponsor has identified several minor inactive metabolites of daptomycin in urine, metabolites of daptomycin (active or inactive) have not been identified in plasma.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to onset and offset of the desirable pharmacological response or clinical endpoint.

The exposure-response relationship of daptomycin has previously been evaluated using *in vitro* time-kill studies and in vivo animal models of infection. Please refer to the daptomycin review for the original NDA submission dated September 12, 2003 for complete information.

The pharmacometrics reviewer performed an exposure-response analysis to assess the relationship between measures of daptomycin exposure (C_{max}, C_{min}, and AUC_{0-24}) and PK/PD metrics (C_{max}/MIC, C_{min}/MIC, and AUC_{0-24}/MIC) and the IEAC success and microbiological outcome. While the results of the analyses indicate that a relationship may exist in a subpopulation of patients, no clinically relevant relationship was observed due to the limited number of patients and heterogeneity in the population. Please refer to the pharmacometrics review in Appendix 4.3 for further details.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to onset and offset of the desirable pharmacological response or clinical endpoint.

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. 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 creatine phosphokinase (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.

The pharmacometrics reviewer performed an exposure-toxicity analysis based on patients with *S. aureus* bacteremia with available CPK data and steady-state C_{min} concentrations. The proportion of patients with elevated CPK values (≥500 IU/L and ≥1000 IU/L) increased as the C_{min} increased. The relationship between proportion of patients with elevated CPK values and C_{min} was statistically significant ($p=0.007$ for ≥500 IU/L and $p=0.012$ for ≥1000 IU/L). Please refer to the pharmacometric review in Appendix 4.3 for further details.

2.2.4.3 Does this drug prolong the QT or QTc interval?

The sponsor previously assessed the impact of daptomycin on cardiac repolarization in study DAP-QTNC-01-06 submitted and reviewed with the original NDA submission (see review dated September 12, 2003 for further details). In summary, 120 healthy male and female subjects were randomized to received daptomycin IV 6 mg/kg q24h or placebo for 14 days. 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 (ΔQTc) 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. There was no apparent relationship between daptomycin plasma concentration and ΔQTc. It

appears that daptomycin IV 6 mg/kg q24h does not impact cardiac repolarization in a clinically relevant manner.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The dose and dosing regimen selected for study DAP-IE-01-02 is consistent with the known relationship between dose-concentration-response for efficacy and safety. Since daptomycin appears to be a concentration-dependent antibiotic, administration of a single daily dose maximizes the C_{max}/MIC ratio and increases the probability of a successful clinical outcome. The 6 mg/kg dose was selected for evaluation in the clinical study since it represents the highest dose supported by safety data. The degree of skeletal myopathy in dogs and in limited data from humans appears to be primarily related to the dosing frequency (time between doses) 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.

2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose PK parameters?

The sponsor assessed the single-dose and multiple-dose pharmacokinetics of daptomycin in 36 healthy subjects following the administration of daptomycin IV 10 mg/kg q24h or placebo for 14 days (n=12) daptomycin IV 12 mg/kg q24h or placebo for 14 days (n=12), daptomycin IV 6 mg/kg q24h for 4 days (n=6), or daptomycin IV 8 mg/kg q24h for 4 days (n=6).

Single dose pharmacokinetics:

The mean plasma concentration-time profiles following the administration of daptomycin IV 6 mg/kg q24h, 8 mg/kg q24h, 10 mg/kg q24h, and 12 mg/kg q24h on day 1 are shown in Figure 2. The mean pharmacokinetic parameters following administration of the four regimens of daptomycin on day 1 are shown in Table 2. In general, the mean C_{max}, AUC_{0-24}, and $AUC_{0-\infty}$ increased nearly proportional to dose across all doses. The mean CL_T, V_{SS}, and $t_{1/2}$ remained unchanged with increasing dose. The mean CL_R and Fe % were higher with the 8 mg/kg, 10 mg/kg, and 12 mg/kg doses compared to the 6 mg/kg dose. The unbound fraction of daptomycin was 9%, 10%, 7%, and 10% with the 6 mg/kg, 8 mg/kg, 10 mg/kg, and 12 mg/kg dose, respectively and was relatively unchanged over the dosing range.

Figure 2. Mean daptomycin plasma concentration-time profiles following administration of daptomycin IV 6 mg/kg q24h, 8 mg/kg q24h, 10 mg/kg q24h, and 12 mg/kg q24h on <u>day 1</u>

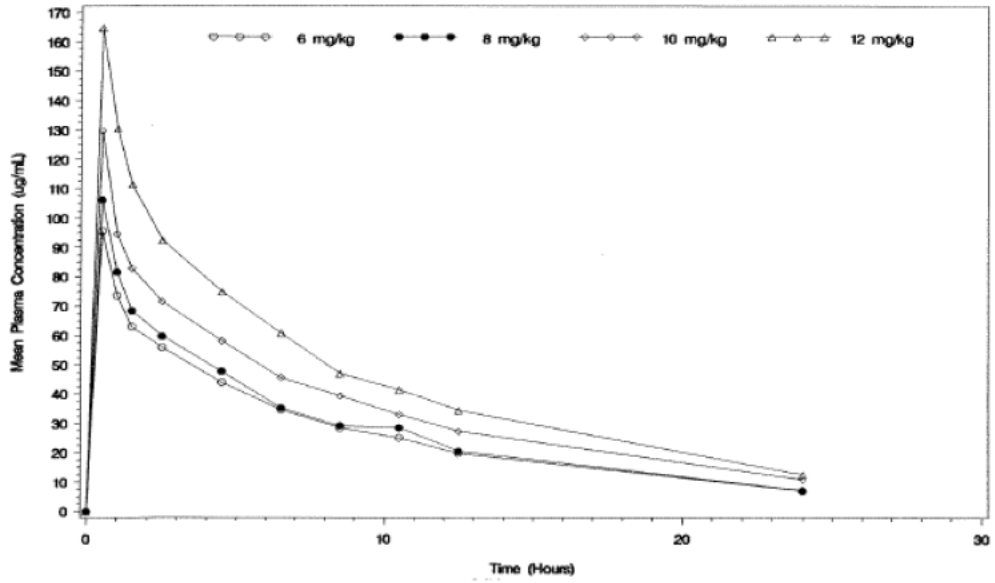


Table 2. Mean (CV%) pharmacokinetic parameters following administration of daptomycin IV 6 mg/kg q24h, 8 mg/kg q24h, 10 mg/kg q24h, and 12 mg/kg q24h on <u>day 1</u>

Dose (mg/kg)	C_{max} (μg/mL)	AUC_{0-24} (μg*hr/mL)	$AUC_{0-\infty}$ (μg*hr/mL)	Vss (mL/kg)	CL_T (mL/hr/kg)	CL_R (mL/hr/kg)	$t_{1/2}$ (hrs)	Fe (%)
6	95.7 (32%)	653.5 (31%)	729.8 (32%)	97.0 (13%)	9.89 (12%)	3.97 (27%)	7.5 (11%)	36.9 (37%)
8	106.2 (20%)	694.9 (19%)	773.3 (20%)	94.0 (10%)	10.11 (24%)	5.65 (48%)	7.3 (18%)	49.0 (34%)
10	129.7 (11%)	880.1 (14%)	1013.5 (16%)	106.6 (12%)	9.92 (21%)	5.12 (40%)	8.3 (12%)	47.4 (50%)
12	164.8 (7%)	1122.5 (20%)	1269.2 (22%)	98.9 (11%)	10.04 (24%)	5.55 (30%)	7.8 (12%)	50.3 (30%)

<u>Multiple dose pharmacokinetics:</u>

The mean plasma concentration-time profiles of daptomycin IV 6 mg/kg q24h, 8 mg/kg q24h, 10 mg/kg q24h, and 12 mg/kg q24h on day 4 are shown in Figure 3. The mean pharmacokinetic parameters of daptomycin on day 4 are shown in Table 3 for all four dose groups. The mean pharmacokinetic parameters on days 7 and 14 are shown in Table 4 for the 10 mg/kg and 12 mg/kg dose groups.

On day 4, the daptomycin mean C_{max} and $AUC_{0-\tau}$ increased proportional to dose. No accumulation of daptomycin was observed with the 6 mg/kg dose following four days of administration based on C_{max} or AUC. The accumulation index of daptomycin for the other three doses ranged from 1.14 to 1.24 based on AUC and 1.09 to 1.16 based on C_{max}.

Figure 3. Mean daptomycin plasma concentration-time profiles following administration of daptomycin IV 6 mg/kg q24h, 8 mg/kg q24h, 10 mg/kg q24h, and 12 mg/kg q24h on day 4

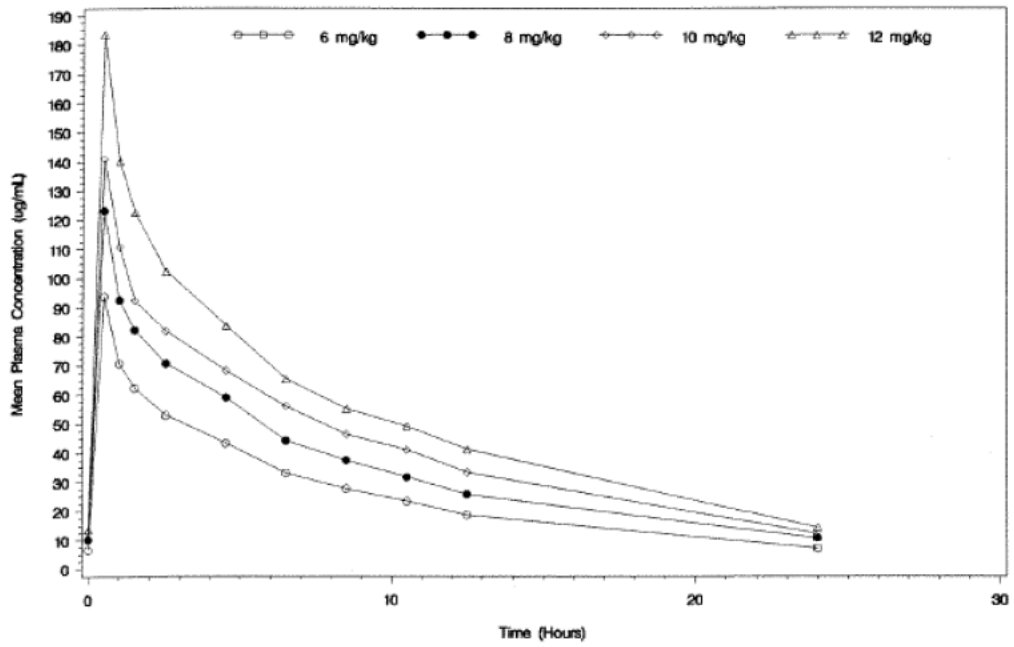


Table 3. Mean (CV%) pharmacokinetic parameters following administration of daptomycin IV 6 mg/kg q24h, 8 mg/kg q24h, 10 mg/kg q24h, and 12 mg/kg q24h on day 4

Dose (mg/kg)	C_{max} (µg/mL)	$AUC_{0-\tau}$ (µg*hr/mL)	CL_T (mL/hr/kg)	$t_{1/2}$ (hrs)
6	93.9 (6%)	631.8 (12%)	9.07 (17%)	7.9 (13%)
8	123.3 (13%)	858.2 (25%)	9.03 (33%)	8.3 (26%)
10	141.1 (17%)	1038.8 (17%)	8.76 (25%)	7.9 (8%)
12	183.7 (14%)	1277.4 (20%)	9.03 (30%)	7.7 (13%)

The mean daptomycin C_{max} and $AUC_{0-\tau}$ values on days 7 and 14 (daptomycin IV 10 mg/kg q24h and 12 mg/kg q24h) were similar to day 4. The mean CL_T was similar on day 7 or day 14 compared to day 1.

Table 4. Mean (CV%) pharmacokinetic parameters following administration of daptomycin IV 10 mg/kg q24h and 12 mg/kg q24h on days 7 and 14

Dose (mg/kg)	C_{max} (μg/mL)	$AUC_{0-\tau}$ (μg*hr/mL)	CL_T (mL/hr/kg)	CL_R (mL/hr/kg)	$t_{1/2}$ (hrs)	Fe (%)
Day 7						
10	138.9 (9%)	1015.9 (18%)	8.83 (25%)	5.89 (73%)	8.0 (9%)	56.1 (47%)
12	184.2 (12%)	1311.6 (19%)	8.75 (28%)	6.79 (46%)	7.9 (12%)	67.5 (34%)
Day 14						
10	139.3 (15%)	1082.1 (15%)	7.52 (19%)	5.53 (35%)	7.9 (6%)	64.4 (25%)
12	181.7 (13%)	1290.5 (22%)	8.96 (32%)	6.98 (45%)	7.9 (14%)	68.2 (33%)

No subject had an elevation in serum CPK above 500 U/L (normal range of CPK values up to 174 U/L) at any dose level. Thus, there was no exposure-response relationship between dose of daptomycin and elevation of CPK within three times the upper limit of normal in this study.

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The sponsor performed a population pharmacokinetic analysis to describe the pharmacokinetics of daptomycin in healthy subjects and patients with bacterial infections as well as identify sources of inter-individual variability in the pharmacokinetics of daptomycin. Compared to healthy subjects receiving daptomycin IV 6 mg/kg (study DAP-ADT-04-02), the mean plasma clearance and volume of distribution of daptomycin were 11% and 20% higher, respectively in patients with *S. aureus* bacteremia. The changes in the pharmacokinetics of daptomycin in patients with bacteremia were similar to those in patients with complicated skin and skin structure infections (cSSSI). In these patients, the mean plasma clearance of daptomycin was unchanged and the volume of distribution was 28% higher compared to healthy subjects. Please refer to the pharmacometrics review in Appendix 4.3 for further details.

2.2.5.6 What are the characteristics of drug metabolism?

In vitro studies with human hepatocytes indicate that daptomycin does not inhibit or induce the activity of the following human cytochrome (CYP) P450 isoenzymes: 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4. It is unlikely that daptomycin will inhibit or induce the metabolism of drugs metabolized by the CYP P450 system.

In the current submission, the sponsor assessed the *in vitro* metabolism of daptomycin using pooled human liver microsomes. Daptomycin was not metabolized by human liver microsomes and the results support that there is no significant involvement of CYP P450 enzymes in the metabolism of daptomycin.

The sponsor also assessed the metabolism of daptomycin in vivo using human urine and plasma samples from the Phase 1 study DAP-ADT-04-02 (6 mg/kg dose group only). No metabolites of daptomycin were observed in any plasma sample from any subject. Four metabolites of daptomycin were detected in urine at low concentrations with each of them contributing to <5% of daptomycin based on the daptomycin UV response, of which three are likely oxidative metabolites. Three metabolites were observed in the urine from all subjects, whereas the fourth metabolite was observed in the urine from 4/6 subjects.

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

In study DAP-ADT-04-02, the pharmacokinetics of daptomycin were linear up to 12 mg/kg and the plasma clearance was similar across the dose range.

2.2.5.9 How do the PK parameters change with time following chronic dosing?

The mean plasma clearance was modestly higher on day 1 (range 9.92 to 10.04 mL/hr/kg) compared to day 14 (range 7.52 to 8.96 mL/hr/kg) although the $AUC_{0-\infty}$ on day 1 predicted the $AUC_{0-\tau}$ at steady state. The mean half-lives were unchanged between day 1 (7.8 to 8.3 hrs) and day 14 (7.91 to 7.94 hrs).

2.2.5.10 What is the inter- and intra-subject variability of PK 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 and subjects with end-stage renal disease. The greatest inter-subject variability was observed with CL_R in subjects who were able to produce urine. The CV% of CL_R for subjects assigned to the low-flux and high-flux dialysis membrane groups were 159% and 52%, respectively.

2.3 Intrinsic factors

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The impact of end-stage renal disease (ESRD) on the pharmacokinetics of daptomycin was assessed in a Phase 1 study submitted with the current submission. The impact of hepatic impairment and obesity as well as covariates such as age, gender, weight, and race on the pharmacokinetics of daptomycin was assessed in the original NDA submission. Please refer to the review dated September 12, 2003 for further details.

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

2.3.2.5 Renal impairment

In the Phase 3 clinical study supporting the use of daptomycin for the treatment of *Staphylococcus aureus* bacteremia (SAB) including those with known or suspected endocarditis (SAIE) caused by methicillin-susceptible and methicillin-resistant strains, all patients with CL_{CR} ≥30 mL/min received daptomycin IV 6 mg/kg q24h. Patients with a CL_{CR} <30 mL/min were excluded from the study. The sponsor's proposed dosage regimens of daptomycin is 6 mg/kg q24h for patients with CL_{CR} ≥30 mL/min and 6 mg/kg q48h for patients with CL_{CR} <30 mL/min, including those receiving hemodialysis or CAPD (Table 5).

Table 5. Dosage regimens of daptomycin by indication for patients with creatinine clearance ≥30 mL/min and <30 mL/min

Creatinine Clearance (mL/min)	cSSSI	SAB/SAIE
≥30 mL/min	4 mg/kg q24h	6 mg/kg q24h
<30 mL/min, including hemodialysis* or CAPD	4 mg/kg q48h	6 mg/kg q48h

*Daptomycin should be administered following hemodialysis on hemodialysis days

The mean population pharmacokinetic parameters of daptomycin following administration of a single 4 mg/kg dose infused over 30 min in non-infected subjects and patients (cSSSI) with varying degrees of renal function are shown in Table 6. The mean population pharmacokinetic parameters of daptomycin at steady-state following administration of 6 mg/kg q24h infused over 30 min in patients (SAB/SAIE) with varying degrees of renal function are shown in Table 7.

The exposure of daptomycin (AUC) among patients with SAB/SAIE and normal renal function receiving daptomycin 6 mg/kg q24h is 545 μg*hr/mL. In comparison, the exposure of daptomycin (AUC) among patients with SAB/SAIE and moderate renal impairment receiving daptomycin 6 mg/kg q24h is 868 μg*hr/mL. The exposure of daptomycin in patients with moderate renal impairment is 1.59-fold the exposure of daptomycin in patients with normal renal function. The increased exposure is equivalent to daptomycin IV 9.6 mg/kg q24h.

Table 6. Mean (SD) population daptomycin pharmacokinetic parameters following a single 30-minute infusion of 4 mg/kg to infected patients with complicated skin and skin structure infections and non-infected subjects with varying degrees of renal function

Renal function	$AUC_{0-\infty}$ (μg*hr/mL)	$t_{1/2}$ (hrs)	V_{SS} (L/kg)	CL_T (mL/hr/kg)
Normal renal function CL_{CR} >80 mL/min N=165	417 (155)	9.39 (4.74)	0.13 (0.05)	10.9 (4.0)
Mild impairment CL_{CR} 50-80 mL/min N=64	466 (177)	10.75 (8.36)	0.12 (0.05)	9.9 (4.0)
Moderate impairment CL_{CR} 30-<50 mL/min N=24	560 (258)	14.70 (10.50)	0.15 (0.06)	8.5 (3.4)
Severe impairment CL_{CR} <30 mL/min N=8	925 (467)	27.83 (14.85)	0.20 (0.15)	5.9 (3.9)
Hemodialysis and CAPD N=21	1244 (374)	29.81 (6.13)	0.15 (0.04)	3.7 (1.9)

Table 7. Mean (SD) population daptomycin pharmacokinetic parameters at steady-state in patients with *Staphylococcus aureus* bacteremia dosed at 6 mg/kg q24h with varying degrees of renal function

Renal function	AUC_{0-24} (μg*hr/mL)	$t_{1/2}$ (hrs)	V_{SS} (L/kg)	CL_T (mL/hr/kg)	C_{max} (μg*hr/mL)	C_{min} (μg*hr/mL)
Normal renal function CL_{CR} >80 mL/min N=62	545 (296)	9.0 (2.86)	0.15 (0.07)	13.2 (5.0)	108 (143)	6.9 (3.5)
Mild impairment CL_{CR} 50-80 mL/min N=29	637 (215)	12.0 (2.26)	0.17 (0.04)	10.5 (3.5)	80 (41)	12.4 (5.6)
Moderate impairment CL_{CR} 30-<50 mL/min N=15	868 (349)	16.1 (3.62)	0.17 (0.05)	8.2 (3.6)	114 (24)	19.0 (9.0)
Severe impairment CL_{CR} <30 mL/min N=2	1050, 892	25.8, 16.0	0.20, 0.15	5.7, 6.7	97, 83	25.4, 21.4

Seventeen patients with moderate renal impairment were evaluated for safety and efficacy in the Phase 3 clinical trial DAP-IE-01-02. Pharmacokinetic data are available from 15 of the patients. The IEAC outcome at TOC (ITT population) stratified by baseline creatinine clearance is shown in Table 8. Patients were classified as non-evaluable at TOC if they were classified as non-evaluable at EOT.

Similar to the findings from the original NDA submission for complicated skin and skin structure infections, the success of daptomycin (based on IEAC outcome) was lower among patients with renal impairment, especially moderate renal impairment. The success of daptomycin was statistically significantly lower than comparator for patients with moderate renal impairment. Since the percentage of non-evaluable patients in the comparator arm exceeded those in the daptomycin arm at all categories of renal function, the lower daptomycin IEAC success with increasing renal impairment was not due to an increase in the number of non-evaluable patients.

Table 8. IEAC outcome at TOC by baseline creatinine clearance (ITT population)

Baseline renal function	Daptomycin (n=120)	Comparator (n=115)	Difference in success rates (C.I.)
Overall			
Success	44.2% (53/120)	41.7% (48/115)	2.4%
Failure	48.3% (58/120)	46.1% (53/115)	(-10.2 to 15.1)
Non-evaluable	7.5% (9/120)	12.2% (14/115)	
Normal renal function			
Success	56.7% (38/67)	42.4% (25/59)	14.3%
Failure	34.3% (23/67)	47.5% (28/59)	(-3.0 to 31.7)
Non-evaluable	9.0% (6/67)	10.2% (6/59)	
CL_{CR} ≤80 mL/min			
Success	28.3% (15/53)	41.1% (23/56)	-12.8%
Failure	66.0% (35/53)	44.6% (25/56)	(-30.5 to 4.9)
Non-evaluable	5.7% (3/53)	14.3% (8/56)	
Mild renal impairment			
Success	38.2% (13/34)	41.2% (14/34)	-2.9%
Failure	52.9% (18/34)	44.1% (15/34)	(-26.2 to 20.3)
Non-evaluable	8.8% (3/34)	14.7% (5/34)	
Moderate renal impairment			
Success	11.8% (2/17)	47.4% (9/19)	-35.6%
Failure	88.2% (15/17)	36.8% (7/19)	(-62.8 to -8.4)
Non-evaluable	0% (0/17)	15.8% (3/19)	
Severe renal impairment			
Success	0% (0/2)	0% (0/3)	0.0%
Failure	100% (2/2)	100% (3/3)	(0.0 to 0.0)
Non-evaluable	0% (0/0)	0% (0/3)	

The pathogen eradication at TOC (ITT population) stratified by baseline creatinine clearance is shown in Table 9. Patients were classified as non-evaluable at TOC if they were classified as non-evaluable at EOT. Patients were classified as not assessed at TOC if they were classified as failures at EOT.

Similar to the results of IEAC outcome at TOC, the pathogen eradication at TOC was lower among patients with renal impairment, especially moderate renal impairment compared to patients with normal renal function. However, the large percentage of patients with moderate renal impairment not assessed in the daptomycin arm (64.7%) relative to comparator (26.3%) may account for the lower eradication rate for patients with moderate renal impairment randomized to daptomycin, and consequently the lower IEAC success rate.

Table 9. Pathogen eradication at TOC by baseline creatinine clearance (ITT population)

Baseline renal function	Daptomycin (n=120)	Comparator (n=115)	Difference in success rates (C.I.)
Overall			
Eradicated	51.7% (62/120)	49.6% (57/115)	2.1%
Persisted	10.0% (12/120)	11.3% (13/115)	(-10.7 to 14.9)
Not assessed	30.8% (37/120)	27.0% (31/115)	
Non-evaluable	7.5% (9/120)	12.2% (14/115)	
Normal renal function			
Eradicated	62.7% (42/67)	52.5% (31/59)	10.1%
Persisted	6.0% (4/67)	13.6% (8/59)	(-7.1 to 27.4)
Not assessed	22.4% (15/67)	23.7% (14/59)	
Non-evaluable	9.0% (6/67)	10.2% (6/59)	
Mild renal impairment			
Eradicated	50.0% (17/34)	44.1% (15/34)	5.9%
Persisted	11.8% (4/34)	14.7% (5/34)	(-17.8 to 29.6)
Not assessed	29.4% (10/34)	26.5% (9/34)	
Non-evaluable	8.8% (3/34)	14.7% (5/34)	
Moderate renal impairment			
Eradicated	17.6% (3/17)	57.9% (11/19)	-40.2%
Persisted	17.6% (3/17)	0% (0/19)	(-68.9 to -11.6)
Not assessed	64.7% (11/17)	26.3% (5/19)	
Non-evaluable	0% (0/17)	15.8% (3/19)	
Severe renal impairment			
Eradicated	0% (0/2)	0% (0/3)	NA
Persisted	50% (1/2)	0% (0/3)	
Not assessed	50% (1/2)	100% (3/3)	
Non-evaluable	0% (0/2)	0% (0/3)	

In the daptomycin group, patients with decreased renal function, in particular those with moderate renal impairment, were more likely to experience serious adverse events (SAEs) compared to patients with normal renal function or mild renal impairment (Table 10). No difference was noted in the comparator group for the incidence of SAEs in patients with normal renal function or mild to moderate renal impairment. A total of nine patients, including three in the daptomycin group (2.5%) and six in the comparator group (5.2%) experienced SAEs that were reported by the investigators as drug-related.

Table 10. Number (%) of patients reporting serious adverse event by baseline creatinine clearance (safety population)

Renal function	Daptomycin (N=120)	Comparator (N=116)
Normal renal function	40.3% (27/67)	47.5% (28/59)
$CL_{CR} \leq 80$ mL/min	66.0% (35/53)	42.1% (24/57)
Mild renal impairment	58.8% (20/34)	37.1% (13/35)
Moderate renal impairment	82.4% (14/17)	42.1% (8/19)
Severe renal impairment	50.0% (1/2)	100% (3/3)

The reviewer concurs with the sponsor's proposed dosage regimens for patients with normal renal function, mild renal impairment, severe renal impairment, and hemodialysis or CAPD. However, the mean AUC of daptomycin among patients with moderate renal impairment in Study DAP-IE-01-02 (868 μg*hr/mL) is equivalent to 9.6 mg/kg q24h compared to the mean AUC from patients with normal renal function (545 μg*hr/mL) and exceeds the highest dose of daptomycin with substantial safety data from healthy subjects and patients.

Based on the lower IEAC success and microbiological eradication of daptomycin in patients with moderate renal impairment, the reviewer does not recommend a dosage adjustment of daptomycin in patients with moderate renal impairment. The reviewer concurs with the sponsor's proposed dosage regimen of 6 mg/kg q24h for patients with moderate renal impairment and recommends wording in the label describing the potential for lower efficacy and higher incidence of adverse events in patients with moderate or severe renal impairment receiving daptomycin compared to comparator.

The pharmacokinetics of daptomycin were assessed in 26 subjects with end-stage renal disease (ESRD) receiving hemodialysis with low-flux or high-flux dialysis membranes. Subjects received a single loading dose of daptomycin IV 8 mg/kg or placebo on study day 1 followed by 8 additional doses of daptomycin IV 6 mg/kg or placebo given after every dialysis for a total of 9 doses over 21 days. The mean plasma concentration-time profiles following administration of daptomycin IV 8 mg/kg on day 1, then 6 mg/kg following hemodialysis with low-flux and high-flux dialysis membranes are shown in Figures 4 and 5.

Figure 4. Mean daptomycin plasma concentration-time profiles following administration of daptomycin IV 8 mg/kg after hemodialysis with low-flux and high-flux dialysis membranes on day 1

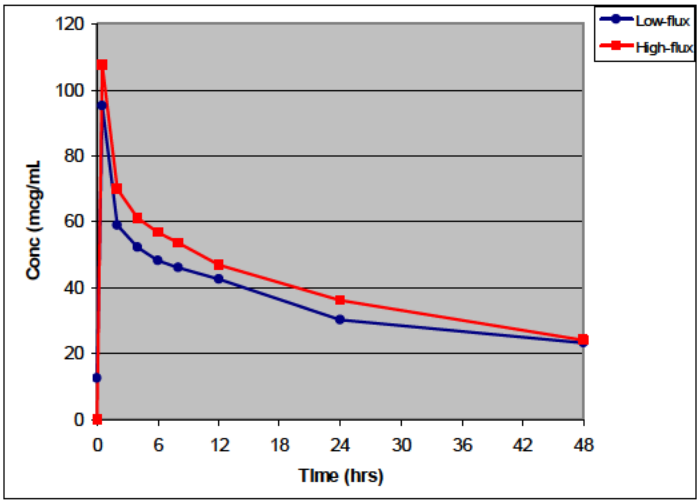
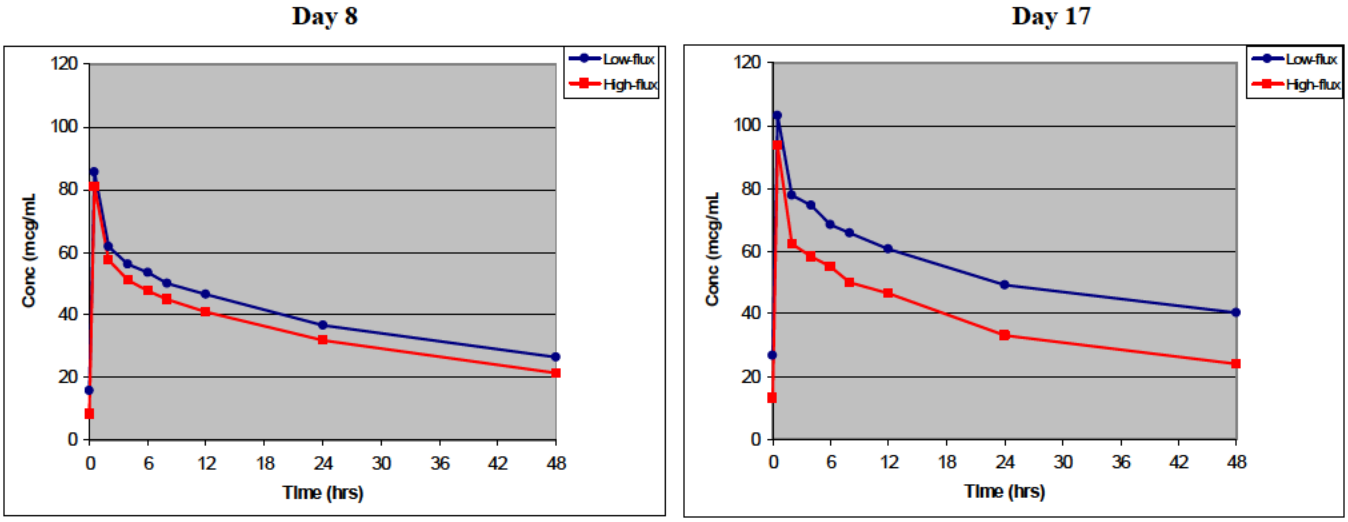


Figure 5. Mean daptomycin plasma concentration-time profiles following administration of daptomycin IV 8 mg/kg, then 6 mg/kg after hemodialysis with low-flux and high-flux dialysis membranes on days 8 and 17



On day 1, the mean plasma concentrations of daptomycin were slightly greater among subjects in the high-flux group compared to the low-flux group even though the mean V_{SS} (L/kg) was the same for both groups. On days 8 and 17, the mean plasma concentrations of daptomycin were greater among subjects in the low-flux group compare to the high-flux group.

The mean pharmacokinetic parameters following administration of daptomycin 8 mg/kg on day 1, then 6 mg/kg following hemodialysis three times weekly are shown in Table 11 with the low-flux dialyzer and Table 12 with the high-flux dialyzer. In general, the C_{max} ranged from 81 to 107 µg/mL across all subjects and the mean half-life of daptomycin ranged from 36 to 56 hours with a trend toward increasing half-life with prolonged dosing. The mean half-life increased after multiple dosing to a greater extent in the low-flux dialyzer group compared to the high-flux dialyzer group. The mean V_{SS} ranged from 0.14–0.27 L/kg, consistent with high protein binding in plasma. Although urine data were available for only seven subjects, the mean fraction of dose excreted from urine ranged from 0.45–7.2%, indicating that renal clearance was not a major pathway in the removal of intact daptomycin from the body of subjects with ESRD.

Table 11. Mean (CV%) pharmacokinetic parameters on days 1, 8, and 17 following administration of daptomycin 8 mg/kg IV (day 1), then 6 mg/kg IV after hemodialysis with a low-flux dialyzer

Parameter	N	Day 1	N	Day 8	N	Day 17
Actual dose (mg/kg)	5	7.6 (31%)	5	5.5 (16%)	4	5.3 (12%)
C_{max} (µg/mL)	6	91.0 (31%)	5	85.6 (33%)	4	103.1 (26%)
$AUC_{0-\tau}$ (µg*hr/mL)	6	1697 (33%)	5	1917 (45%)	4	2586 (35%)
$AUC_{0-\infty}$ (µg*hr/mL)	6	3067 (43%)	5	3704 (55%)	4	6263 (54%)
V_{SS} (L)	5	10.0 (30%)	5	12.7 (20%)	4	11.92 (36%)
V_{SS} (L/kg)	5	0.14 (18%)	5	0.19 (29%)	4	0.16 (20%)
CL_T (mL/hr/kg)	5	2.83 (40%)	5	3.49 (55%)	4	2.24 (34%)
CL_R (mL/hr/kg)	4	0.18 (166%)	4	0.15 (144%)	2	0.01 (141%)
$t_{1/2}$ (hrs)	6	38.5 (21%)	5	42.3 (27%)	4	55.9 (36%)
Xe (mg)	4	10.94 (130%)	4	9.81 (90%)	2	1.20 (141%)

Table 12. Mean (CV%) pharmacokinetic parameters on days 1. 8, and 17 following administration of daptomycin 8 mg/kg IV (day 1), then 6 mg/kg IV after hemodialysis with a high-flux dialyzer

Parameter	N	Day 1	N	Day 8	N	Day 17
Actual dose (mg/kg)	7	8.0 (41%)	6	5.3 (13%)	3	5.7 (14%)
C_{max} (μg/mL)	7	107.4 (39%)	6	81.1 (38%)	3	93.6 (17%)
$AUC_{0-\tau}$ (μg*hr/mL)	7	1945 (34%)	6	1672 (36%)	3	1716 (27%)
$AUC_{0-\infty}$ (μg*hr/mL)	7	3185 (33%)	6	2877 (40%)	3	3246 (9%)
V_{SS} (L)	7	11.49 (68%)	6	15.27 (47%)	3	20.91 (71%)
V_{SS} (L/kg)	7	0.14 (545)	6	0.19 (55%)	3	0.27 (85%)
CL_T (mL/hr/kg)	7	2.76 (51%)	6	3.72 (50%)	3	3.63 (44%)
CL_R (mL/hr/kg)	3	0.18 (54%)	2	0.16 (96%)	2	0.19 (8%)
$t_{1/2}$ (hrs)	7	35.7 (11%)	6	38.1 (17%)	3	45.3 (38%)
Xe (mg)	3	17.28 (70%)	2	19.33 (116%)	2	15.76 (585)

The dose normalized C_{max} and $AUC_{0-\tau}$ were statistically significantly higher on study day 17 than study day 1 for the low-flux and high-flux groups. The dose normalized $AUC_{0-\tau}$ values for subjects in both groups increased from day 1 to day 17, although the dose normalized $AUC_{0-\tau}$ increased to a greater extent among subjects in the low-flux group. Subjects receiving hemodialysis with low-flux membranes had greater accumulation than subjects receiving hemodialysis with high-flux membranes. The dose normalized C_{max} values increased from day 1 to day 17 for subjects in both the low-flux and high-flux groups to a similar extent.

There was no significant difference between the dose normalized $AUC_{0-\tau}$ values and C_{max} values on day 8 and day 1 as daptomycin may not have reached steady state by day 8.

The mean (SD) daptomycin plasma concentrations pre- and post-dialysis for study days 1, 8 and 17 by dialysis membrane are shown in Table 13. Pre- and post-dialysis blood samples were drawn within 1 hr before the start and after the end of dialysis. No statistically significant difference in daptomycin plasma concentrations were observed on study days 1, 8 and 17 for subjects on low-flux membrane dialysis. Subjects on high-flux dialysis membranes had a markedly greater reduction in daptomycin concentrations pre- to post-dialysis compared to those on low-flux dialysis membranes.

Table 13. Mean (SD) daptomycin plasma concentrations (μg/mL) pre- and post-dialysis by study day and dialysis membrane

Dialysis Membrane	Study Day 1		Study Day 8		Study Day 17	
	Pre-dialysis	Post-dialysis	Pre-dialysis	Post-dialysis	Pre-dialysis	Post-dialysis
Low-flux[a]	0.79 (1.93)	12.65 (28.38)	16.53 (8.81)	15.78 (8.39)	28.93 (11.43)	26.80 (9.85)
High-flux	0.00 (0.00)	0.00 (0.00)	13.91 (5.61)	8.15 (3.38)	21.87 (2.82)	13.00 (2.48)

[a] The pre- and post-dialysis concentrations on Study Day 1 should theoretically be 0. See the text for details.

NOTE: The post-dialysis sample for Subject (b) (6) (70.40 μg/mL), which was also the subject's C_{max}, may have been switched inadvertently with the end of infusion sample (0 μg/mL).

2.4. Extrinsic factors

2.4.2 Drug-Drug interactions

2.4.2.1 Is there an *in vitro* basis to suspect in vivo drug-drug interactions?

The sponsor assessed the potential of daptomycin to act as a substrate, inhibitor, and inducer of Cytochrome P450 isoenzymes using *in vitro* methods. The results of *in vitro* studies support that daptomycin is not a substrate, inhibitor, or inducer of CYP P450 isoenzymes.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Based on *in vitro* metabolism studies and metabolic profiling from plasma and urine samples obtained from study DAP-ADT-04-02 (6 mg/kg dosing regimen), daptomycin is not a substrate of CYP isoenzymes.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

The sponsor has previously determined that daptomycin is neither an inhibitor nor inducer of CYP isoenzymes.

2.4.2.4 Is the drug a substrate and/or inhibitor of P-glycoprotein transport processes?

The sponsor has not assessed the potential of daptomycin to act as a substrate and/or inhibitor of P-glycoprotein.

2.4.2.6 Does the label specify co-administration of another drug and if so, has the interaction potential between these drugs been evaluated?

The proposed label does not specify co-administration of another drug.

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

In addition to antibiotics with Gram-negative and anaerobic activity, medications that are likely to be co-administered to the target population consist therapeutics used to treat chronic conditions. It is unlikely that daptomycin will inhibit or induce the metabolism of drugs metabolized by the CYP P450 system.

2.5 General Biopharmaceutics

Not applicable.

2.6 Analytical Section

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

The sponsor used reverse phase high performance liquid chromatography with ultraviolet detection (HPLC/UV) to identify and measure the active moieties of daptomycin in plasma.

2.6.2 Which metabolites have been selected for analysis and why?

No metabolites have been selected for analysis from plasma and urine. Metabolic profiling was performed on selected plasma and urine samples from study DAP-ADT-04-02 (6 mg/kg dose only) to assess for the presence of metabolites since the sponsor had not previously identified metabolites of daptomycin in plasma or urine.

2.6.3 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 and urine represent total concentrations. The protein binding of daptomycin in plasma was previously determined using equilibrium dialysis and is approximately 92%. The mean unbound fraction of daptomycin in the current application is 9%, 10%, 7%, and 10% for the 6 mg/kg, 8 mg/kg, 10 mg/kg, and 12 mg/kg dosage regimens, respectively and is consistent with previous findings.

2.6.4 What bioanalytical methods are used to assess concentrations?

See the response for 2.6.1 stated above.

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The standard curves in plasma and urine ranged from 3.00 to 500 μg/mL for daptomycin. The C_{max} of daptomycin in plasma ranged from 69.4 to 155 μg/mL following the administration of 6 mg/kg and 143 to 184 μg/mL following the administration of 12 mg/kg. The C_{min} concentrations of daptomycin in plasma ranged from 3.7 to 12.2 μg/mL following the administration of 6 mg/kg and 4.8 to 20.8 μg/mL following the administration of 12 mg/kg. Thus, the plasma concentrations of daptomycin were within the standard curve.

Urine concentrations from the 12-hr collections (0-12 and 12-24 hrs) ranged from 21.4 to 242 μg/mL following administration of 6 mg/kg and 47.4 to 575 μg/mL following administration of 12 mg/kg. Urine concentrations were diluted with pooled urine when they exceeded the upper limit of quantification.

Standard curves were calculated using a linear weighted (1/concentration squared) least-squares regression algorithm.

2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

The lower limit of quantification of daptomycin for the plasma and urine assay was 3.00 μg/mL. The upper limit of quantification of daptomycin for the plasma and urine assay was 500 μg/mL.

2.6.4.3 What is the accuracy, precision, and selectivity at these limits?

The accuracy of daptomycin in plasma and urine was 100 ± 15% and the precision ranged was within -15% to +15%. Pooled human plasma and pooled human urine were used to assess for endogenous interfering substances.

2.6.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

The stability of daptomycin in plasma and urine was assessed under various conditions. Daptomycin was shown to be stable in plasma at 4°C, in extracted samples at 4°C, following long-term storage at -20°C, and following three freeze-thaw cycles. Daptomycin was shown to be stable in urine at room temperature, in urine at 4°C, in extracted samples at 4°C, and following three freeze-thaw cycles.

2.6.4.5 What is the QC sample plan?

The sponsor's QC sample plan was [redacted] (b) (4) and consisted of four quality control (QC) samples for the analysis of plasma and urine concentrations. The four QCs consisted of 3.00, 7.50, 75.0, and 400 μg/mL.

APPEARS THIS WAY ON ORIGINAL

3. DETAILED LABELING RECOMMENDATIONS

See Appendix 4.1. Proposed Package Insert

The proposed label has been updated with the sponsor's changes as well as the reviewer's proposed changes in the following sections:

CLINICAL PHARMACOLOGY
INDICATIONS AND USAGE
PRECAUTIONS, Drug Interactions
OVERDOSAGE
DOSAGE AND ADMINISTRATION

The sponsor's proposed changes are shown in **red** text whereas the reviewer's proposed changes are shown in **blue** text.

APPEARS THIS WAY
ON ORIGINAL

30 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

4.2 Clinical Pharmacology and Biopharmaceutics Individual Study Reviews

4.2.1 Pharmacokinetics and drug metabolism report no. PKR 05-007: Evaluation of *In Vitro* metabolism of daptomycin by human liver microsomes (HLM) (PKR-05-007)

OBJECTIVES:
The objectives of the study were to evaluate the *in vitro* Phase I metabolism of daptomycin and the potential of cytochrome P450 involvement using human liver microsomes.

FORMULATION:
Daptomycin lot no. 010853A

STUDY DESIGN:
Human liver microsomes were purchased from (b) (4) The microsomes were obtained from several donors.

(b) (4)

RESULTS:
Over the course of the 60 min incubations with human liver microsomes, no disappearance of daptomycin was observed either in the presence or absence of NADPH. The results of individual incubations of daptomycin with human liver microsomes with and without NADPH are shown in Tables 1 and 2. No

degradation of daptomycin was observed in the negative control (daptomycin incubation with buffer system without human liver micrsomes).

Table 1. Daptomycin peak area ratios and percentage of daptomycin remaining for human liver microsomal incubations <u>with</u> NADPH

Minute	A	B	C	Mean	SD	% CV	Remaining (%)
0	(b) (4)			1.72	0.24	14.13	100.0
10				2.05	0.25	12.06	119.3
20				1.99	0.15	7.6	115.6
30				2.18	0.18	8.24	126.4
60				2.34	0.36	15.5	135.7

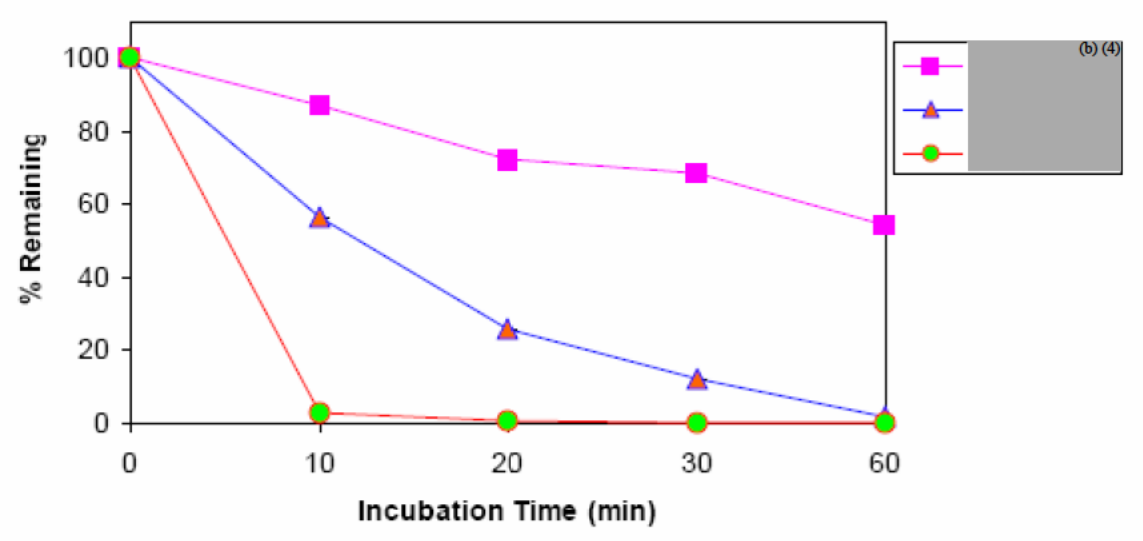
Table 2. Daptomycin peak area ratio and percentage of daptomycin remaining for human liver microsomal incubations <u>without</u> NADPH

Minute	A	B	C	Mean	SD	% CV	Remaining (%)
0	(b) (4)			1.74	0.01	0.81	100.0
10				1.72	0.07	4.1	98.8
20				1.68	0.17	9.9	96.3
30				1.85	0.04	2.0	106.1
60				2.34	0.24	10.2	134.4

In both control and microsomal incubations, the daptomycin peak area versus internal standard peak area ratio appeared to increase over the course of incubation. The reason for the increase is not clear. However, because both curves generated from microsomal incubations in the presence or absence of NADPH increased in parallel, it is plausible that there is no significant metabolism of daptomycin and that CYP P450 enzymes are likely not involved in the metabolism of the drug.

Results from incubations of the positive controls (Figure 1) demonstrated that the microsomes have normal metabolic capacity, which rendered the *in vitro* half-lives for (b) (4) (69.7 hrs). (b) (4) (9.6 hrs), and (b) (4) (3.0 hrs) consistent with historical results. Such results also suggested that the lack of daptomycin metabolism was not due to loss of the metabolic capability of the microsomes.

Figure 1. Disappearance of positive control compound in human liver microsomal incubations



CONCLUSIONS:

The results demonstrate that daptomycin was not metabolized by human liver microsomes in the study and suggest that there is no significant involvement of CYP P450 enzymes in the metabolism of daptomycin.

Since it has previously been shown that daptomycin is not an inhibitor of CYP P450 enzymes, CYP P450 mediated drug-drug interactions are unlikely with the clinical use of daptomycin.

APPEARS THIS WAY
ON ORIGINAL

4.2.2 A randomized, double-blinded, placebo-controlled, multiple dose, safety and pharmacokinetic study of ascending doses of daptomycin n healthy volunteers (DAP-ADT-04-02)

Dates: January 17, 2005 to March 29, 2005
Clinical site: Comprehensive Phase One, Clinical Studies LTD, Fort Lauderdale, FL
Analytical sites: (b) (4) (b) (4)

RATIONALE:
A previous Phase 1 study indicated that 8 mg/kg administered daily for 14 days was well tolerated in subjects, but that a modest (~20%) nonlinear PK relationship was observed at that dose (DAP-00-02). The current study was conducted to examine the pharmacokinetics of daptomycin at doses of 6, 8, 10 and 12 mg/kg/day and the safety and tolerability of daptomycin in healthy subjects at doses of 10 and 12 mg/kg daily for a period of up to 14 days. It is thought that daptomycin doses of 8, 10, or 12 mg/kg daily may be required to observe optimal benefit in the setting of serious infections (e.g., VRE bacteremia).

OBJECTIVES:
The primary objective of this study was to assess the pharmacokinetic profile of multiple doses of daptomycin in healthy volunteers at doses of 6, 8, 10, and 12 mg/kg/day. The secondary objective of the study was to assess the safety and tolerability of once daily intravenous (IV) dosing of daptomycin at 10 and 12 mg/kg in healthy volunteers for a period of 14 consecutive days.

FORMULATION:
Daptomycin 500 mg vial (lot No. 010853A)

STUDY DESIGN:
This study was a single center, randomized, double-blind, placebo-controlled, multiple-dose, safety, tolerability, and pharmacokinetic study of ascending doses of daptomycin. A total of 36 male and female subjects between the ages of 18 and 45 yrs with a creatinine clearance ≥80 mL/min were to be randomized into three separate cohorts. The planned dosing strategy is shown in the table below.

Dosing Cohort	Daily Dose (mg/kg/day)	Total Subjects (n)	Daptomycin subjects	Control Subjects	Maximum # of Dosing Days
1	10	12	9	3	14
2	12	12	9	3	14
3	6 or 8	12	12	0	4

In Cohort 1, 12 subjects were to be randomized (3:1) to receive daptomycin 10 mg/kg IV q24h or placebo infused over 30 min for 14 consecutive days. In Cohort 2, 12 subjects were to be randomized (3:1) to receive daptomycin 12 mg/kg IV q24h or placebo infused over 30 min for 14 consecutive days. Escalation to Cohort 2 was to only occur after review of the safety data obtained from Cohort 1 indicated that it was safe to proceed. Cohort 3, which was included to establish a pharmacokinetic baseline for comparison with Cohorts 1 and 2, was to include 12 subjects randomized 1:1 to receive daptomycin 6 or 8 mg/kg IV q24h infused over 30 min administered for 4 days.

If, based on the safety data from Cohort 1, a decision was made not to escalate to the 12 mg/kg dose, 12 subjects in Cohort 2 were to be randomized (3:1) receive daptomycin 8 mg/kg or placebo for 14 days and 6 subjects in Cohort 3 were to receive daptomycin at a dose of 6 mg/kg for 4 days

<u>Cohorts 1 and 2</u>
Pharmacokinetic plasma samples were to be collected on days 1, 4, 7, and 14. Samples were to be collected at -0.5, 0, 0.5, 1, 2, 4, 6, 8, 10, 12, and 24 hrs relative to the end of infusion. On day 14,

additional samples were to be collected at 36 and 48 hrs after last infusion. Trough levels were to be collected prior to dosing on days 3 and 11.

Pharmacokinetic urine samples were to be pooled for 0-12 hrs and 12-24 hrs from the start of study drug administration on days 1, 7, and 14. On day 1, a pre-dose sample also was to be obtained.

Protein binding samples were to be collected on all cohorts on day 1 at the end-of-infusion and 2 and 8 hrs post infusion.

Cohort 3
Pharmacokinetic plasma samples were to be collected on days 1 and 4. Samples were to be collected at -0.5, 0, 0.5, 1, 2, 4, 6, 8, 10, 12, 24 hrs relative to the end of infusion. In addition, trough levels were to be collected in all subjects prior to dosing on day 3.

Urine samples for pharmacokinetic analysis were to be pooled for 0-12 hrs and 12-24 hrs from the start of study drug administration on day 1. A pre-dose sample also was to be obtained on day 1.

Protein binding samples were to be collected on day 1 at the end of infusion, and 2 and 8 hrs post infusion.

Electrocardiograms:
For Cohorts 1 and 2, 12-lead ECGs were to be performed at screening, day 1 (pre-dose), day 4 (predose), day 7 (pre- and post dose), day 10 (pre- and post dose), day 14 (pre-dose), and day 3 (only if day 14 ECG was abnormal). For Cohort 3, 12-lead ECGs were to be performed at screening, day 1 (pre-dose), and day 4 (predose).

All pre-dose ECGs performed while on-therapy were to be taken within 1 hr prior to study drug administration and post-dose ECGs were to be performed 20 min following the end-of-infusion. The timing of the ECGs was to be done consistently with respect to scheduled meals. For subjects in Cohorts 1 and 2 who received study drug doses of 10 or 12 mg/kg, the ECGs were to be sent to an independent cardiologist who was to document ECG intervals and provide clinical interpretation.

Electrophysiologic Testing:
Electrophysiologic testing was to be done only for Cohorts 1 and 2. Assessments were to be performed at screening, baseline, on the final day of dosing, and once between days 12 and 16. On dosing days, testing was to be performed approximately 1 hr after dosing.

Motor nerve function was to be assessed using the NC-Stat® Nerve Conduction Monitoring System combined with a median nerve biosensor. The electrophysiology studies were designed to determine: 1) distal onset latency of the CMAP in the abductor pollicis brevis (APB) muscle of the hand following supramaximal stimulation of the median nerve at the wrist; 2) peak amplitude of the evoked CMAP, and 3) minimal latency of the associated F-wave of the non-dominant hand. Distal latency and F-wave latency reflect maximal conduction velocity and are sensitive to changes in the distal axon and myelin.

DAPTOMYCIN ASSAY METHODOLOGY:
High Performance Liquid Chromatography with ultraviolet detection (HPLC/UV)

Criterion	Plasma	Urine	Comments
Concentration range	3.00 to 500 μg/mL	3.00 to 500 μg/mL	Satisfactory
LLOQ	3.00 μg/mL	3.00 μg/mL	Satisfactory
Linearity	R^2 ≥0.9969	R^2 ≥0.9984	Satisfactory
Accuracy	94.79% to 101.86%	95.97% to 99.83%	Satisfactory
Precision	3.49% to 5.55%	1.61% to 12.54%	Satisfactory
Specificity	Satisfactory	Satisfactory	Satisfactory
Stability	Stability in matrix at 4°C, extracted samples at 4°C, freeze-thaw for 3 cycles	stability in matrix at RT, stability in matrix at 4°C, extracted samples at 4°C, freeze-thaw for 3 cycles	Satisfactory

Each standard curve was calculated using a linear weighted (1/concentration squared) least-squares regression algorithm.

DATA ANALYSIS:
Plasma daptomycin concentration data were analyzed by non-compartmental pharmacokinetic analysis. The following parameters were estimated: maximum plasma concentration (C_{max}); time at which the C_{max} occurred (T_{max}); trough concentration prior to dosing on days 3, 4, 7, 11, and 14 for cohorts 1 and 2 and on days 3 and 4 for cohort 3 (C_{min}); area under the plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$); AUC from zero to tau ($AUC_{0-\tau}$); AUC from zero to last quantifiable concentration (AUC_{0-t}); plasma clearance (CL_T); unbound plasma clearance (CL_{UT}); renal clearance (CL_R); unbound renal clearance (CL_{UR}); percent of daptomycin dose excreted unchanged in urine over the dosing interval (Fe %); terminal volume of distribution (Vz); volume of distribution at steady-state (V_{SS}); mean residence time (MRT); and terminal elimination half-life ($t_{1/2}$).

The protein binding of daptomycin in serum was assessed using equilibrium dialysis.

STATISTICAL ANALYSIS:
Summary statistics for continuous variables were to include the number of subjects, mean, standard deviation, median, minimum, and maximum. Summary statistics for categorical variables were to include the number and percentage of subjects in each category.

RESULTS:
All but one subject completed the study dosing and follow-up periods. Subject No. (b) (6) in the placebo group (Cohort 2) prematurely withdrew from the study during the dosing period; the reason for discontinuation was reported as subject's decision. The mean (SD) demographics for Cohort 1 (10 mg/kg), Cohort 2 (12 mg/kg), and Cohort 3 (6 and 8 mg/kg) are shown in Table 1.

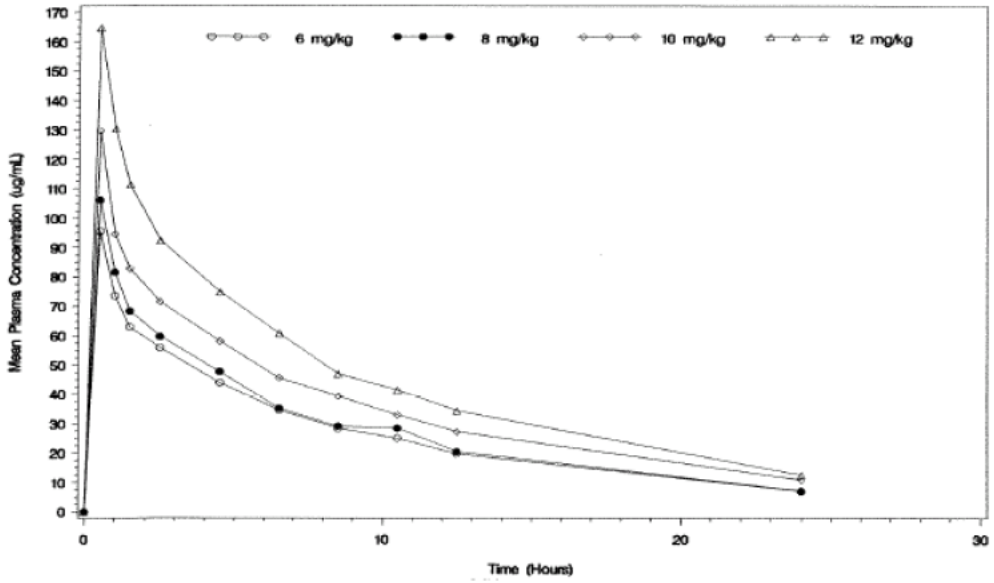
Table 1. Mean (SD) demographic parameters by treatment group

Demographic	Cohort 1		Cohort 2		Cohort 3	
	10 mg/kg	Control	12 mg/kg	Control	6 mg/kg	8 mg/kg
N	9	3	9	3	6	6
Sex (M/F)	5/4	2/1	5/4	2/1	2/4	3/3
Age (yrs)	34.8 (7.7)	30.7 (12.1)	35.1 (7.0)	36.3 (8.6)	31.8 (7.6)	31.3 (7.4)
Weight (kg)	62.9 (11.8)	80.5 (17.5)	72.4 (6.4)	77.8 (9.1)	68.7 (14.3)	68.6 (10.9)
Height (cm)	161 (6.5)	169 (12.0)	164 (8.5)	168 (12.3)	163 (7.6)	165 (11.0)

Single dose pharmacokinetics

The mean plasma concentration-time profiles following administration of daptomycin IV 6 mg/kg q24h, 8 mg/kg q24h, 10 mg/kg q24h, and 12 mg/kg q24h on day 1 are shown in Figure 1.

Figure 1. Mean daptomycin plasma concentration-time profiles following administration of daptomycin IV 6 mg/kg q24h, 8 mg/kg q24h, 10 mg/kg q24h, and 12 mg/kg q24h on day 1



The mean pharmacokinetic parameters following administration of daptomycin IV 6 mg/kg q24h, 8 mg/kg q24h, 10 mg/kg q24h, and 12 mg/kg q24h on day 1 are shown in Table 2. In general, the mean C_{max}, AUC_{0-24}, and $AUC_{0-\infty}$ increased nearly proportional to dose. The mean CL_T, V_{SS}, and $t_{1/2}$ remained unchanged with increasing dose. The mean CL_R and Fe % were higher with the 8 mg/kg, 10 mg/kg, and 12 mg/kg doses compared to the 6 mg/kg dose. The unbound fraction of daptomycin was 9%, 10%, 7%, and 10% with the 6 mg/kg, 8 mg/kg, 10 mg/kg, and 12 mg/kg dose, respectively and was relatively unchanged over the dosing range.

Table 2. Mean (CV%) pharmacokinetic parameters following administration of daptomycin IV 6 mg/kg q24h, 8 mg/kg q24h, 10 mg/kg q24h, and 12 mg/kg q24h on day 1

Dose (mg/kg)	C_{max} (µg/mL)	AUC_{0-24} (µg*hr/mL)	$AUC_{0-\infty}$ (µg*hr/mL)	Vss (L/kg)	CL_T (mL/hr/kg)	CL_R (mL/hr/kg)	$t_{1/2}$ (hrs)	Fe (%)
6	95.7 (32%)	653.5 (31%)	729.8 (32%)	97.0 (13%)	9.89 (12%)	3.97 (27%)	7.5 (11%)	36.9 (37%)
8	106.2 (20%)	694.9 (19%)	773.3 (20%)	94.0 (10%)	10.11 (24%)	5.65 (48%)	7.3 (18%)	49.0 (34%)
10	129.7 (11%)	880.1 (14%)	1013.5 (16%)	106.6 (12%)	9.92 (21%)	5.12 (40%)	8.3 (12%)	47.4 (50%)
12	164.8 (7%)	1122.5 (20%)	1269.2 (22%)	98.9 (11%)	10.04 (24%)	5.55 (30%)	7.8 (12%)	50.3 (30%)

NOTE: The mean C_{max}, AUC_{0-24}, and $AUC_{0-\infty}$ on day 1 in the 6 mg/kg dose group is greater than expected as a result of Subject #001-0312. This subject had a C_{max} value of 155 µg/mL (range 67.3 to 128 µg/mL excluding this subject), AUC_{0-24} value of 1056 µg*hr/mL (range 503 to 890 µg*hr/mL excluding this subject), and $AUC_{0-\infty}$ value of 1193 µg*hr/mL (range 535 to 988 µg*hr/mL excluding this subject). The

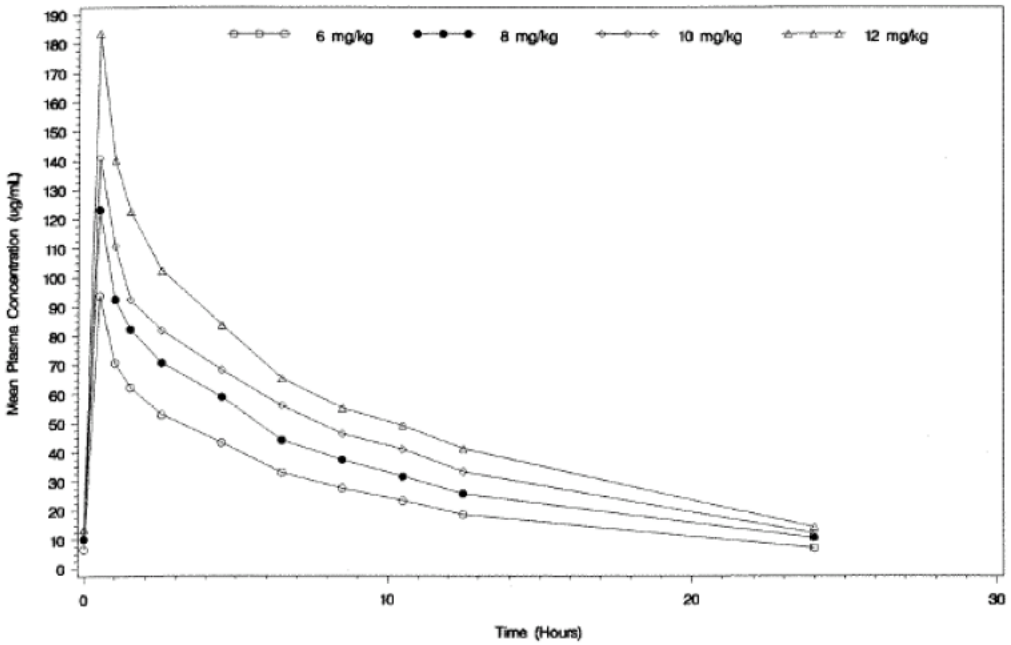
less-than dose proportional increase in C_{max} on day 1 and lack of accumulation for the 6 mg/kg group compared to the 4 mg/kg group was reduced if this subject was excluded. Although this subject was in the 6 mg/kg group, the actual dose of daptomycin administered was 10.86 mg/kg on day 1 and 6.62 mg/kg on day 4.

Multiple dose pharmacokinetics

The mean plasma concentration-time profiles of daptomycin IV 6 mg/kg q24h, 8 mg/kg q24h, 10 mg/kg a24h, and 12 mg/kg q24h on day 4 are shown in Figure 2.

The mean pharmacokinetic parameters of daptomycin on day 4 are shown in Table 3 for all four dose groups. The mean pharmacokinetic parameters on days 7 and 14 are shown in Table 4 for the 10 mg/kg and 12 mg/kg dose groups.

Figure 2. Mean daptomycin plasma concentration-time profiles following administration of daptomycin IV 6 mg/kg q24h, 8 mg/kg q24h, 10 mg/kg q24h, and 12 mg/kg q24h on day 4



On day 4, the daptomycin mean C_{max} and $AUC_{0-\tau}$ increased proportional to dose. No accumulation of daptomycin was observed with the 6 mg/kg dose following four days of administration based on C_{max} or AUC. The accumulation index of daptomycin for the other three doses ranged from 1.14 to 1.24 based on AUC and 1.09 to 1.16 based on C_{max}. The theoretical accumulation index of daptomycin is 1.14 (based on a 8 hr half-life and 24 hr dosing interval). Thus, the observed accumulation of daptomycin was similar to the predicted accumulation. The mean CL_T (L/hr/kg) decreased modestly on day 4 compared to day 1. The mean $t_{1/2}$ was unchanged between day 1 and day 4.

Table 3. Mean (CV%) pharmacokinetic parameters following administration of daptomycin IV 6 mg/kg q24h, 8 mg/kg q24h, 10 mg/kg q24h, and 12 mg/kg q24h on day 4

Dose (mg/kg)	C_{max} (μg/mL)	$AUC_{0-\tau}$ (μg*hr/mL)	CL_T (mL/hr/kg)	$t_{1/2}$ (hrs)
6	93.9 (6%)	631.8 (12%)	9.07 (17%)	7.9 (13%)
8	123.3 (13%)	858.2 (25%)	9.03 (33%)	8.3 (26%)
10	141.1 (17%)	1038.8 (17%)	8.76 (25%)	7.9 (8%)
12	183.7 (14%)	1277.4 (20%)	9.03 (30%)	7.7 (13%)

The mean pharmacokinetic parameters of daptomycin IV 10 mg/kg q24h and 12 mg/kg q24h on days 7 and 14 are shown in Table 4. The daptomycin mean C_{max} and $AUC_{0-\tau}$ values on days 7 and 14 were similar to day 4. The mean CL_T (L/hr/kg) was approximately 10% lower on day 7 compared to day 1 for both groups and 24% lower on day 14 compared to day 1 for the 10 mg/kg group and 11% for the 12 mg/kg group.

Table 4. Mean (CV%) pharmacokinetic parameters following administration of daptomycin IV 10 mg/kg q24h and 12 mg/kg q24h on days 7 and 14

Dose (mg/kg)	C_{max} (μg/mL)	$AUC_{0-\tau}$ (μg*hr/mL)	CL_T (mL/hr/kg)	CL_R (mL/hr/kg)	$t_{1/2}$ (hrs)	Fe (%)
Day 7						
10	138.9 (9%)	1015.9 (18%)	8.83 (25%)	5.89 (73%)	8.0 (9%)	56.1 (47%)
12	184.2 (12%)	1311.6 (19%)	8.75 (28%)	6.79 (46%)	7.9 (12%)	67.5 (34%)
Day 14						
10	139.3 (15%)	1082.1 (15%)	7.52 (19%)	5.53 (35%)	7.94 (6%)	64.4 (25%)
12	181.7 (13%)	1290.5 (22%)	8.96 (32%)	6.98 (45%)	7.91 (14%)	68.2 (33%)

Since a previous Phase 1 study (Study DAP-00-02) indicated that 8 mg/kg administered daily for 14 days exhibited a modest nonlinear PK relationship compared to 4 mg/kg, the reviewer compared the 6 mg/kg and 8 mg/kg plasma concentration-time profiles from study DAP-ADT-04-02 with the 6 mg/kg and 8 mg/kg regimens from study DAP-00-02 (submitted with original NDA). A comparison of the plasma concentration-time profiles following administration of 6 mg/kg q24h is shown in Figure 3 and 8 mg/kg q24h is shown in Figure 4.

The mean plasma concentration-time profiles demonstrated a higher degree of accumulation in study DAP-00-02 following administration of 6 mg/kg and higher mean plasma concentrations in study DAP-00-02 following administration of 8 mg/kg on day 1 and at steady-state (day 4 or day 7).

Figure 3. Mean daptomycin plasma concentration-time profiles following administration of daptomycin IV 6 mg/kg q24h on days 1 and 4 from study DAP-ADT-04-02 and daptomycin IV 6 mg/kg q24h on days 1 and 7 from study DAP-00-02

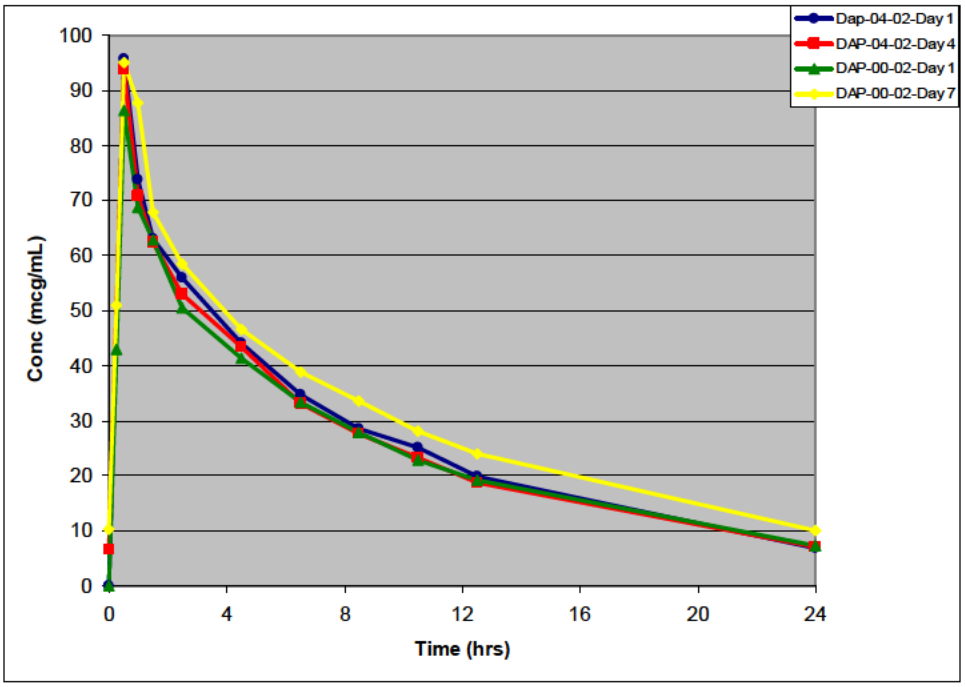
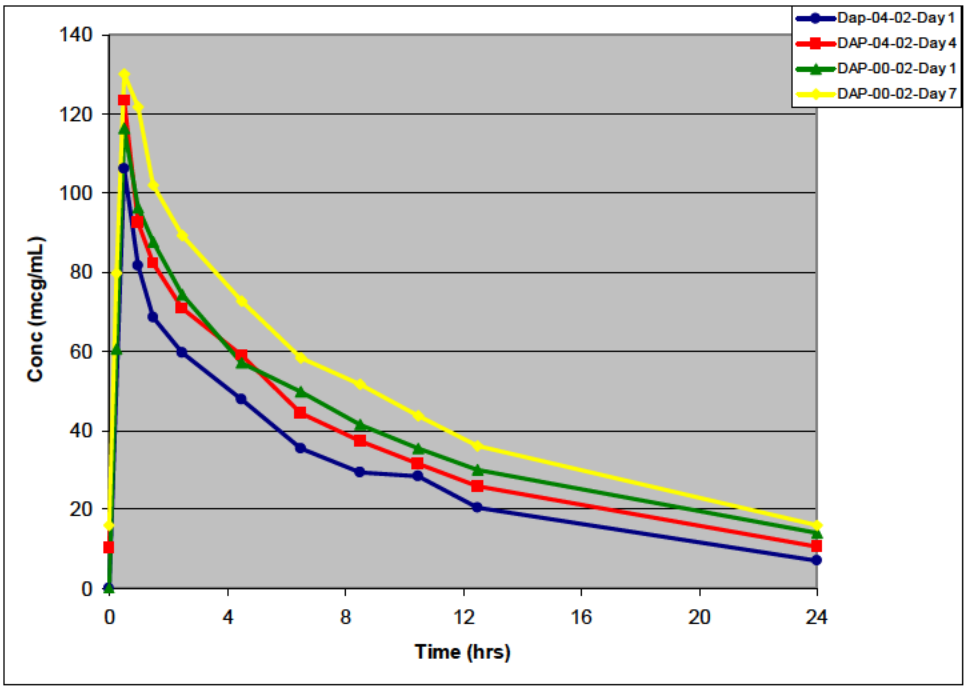


Figure 4. Mean daptomycin plasma concentration-time profiles following administration of daptomycin IV 8 mg/kg q24h on days 1 and 4 from study DAP-ADT-04-02 and daptomycin IV 8 mg/kg q24h on days 1 and 7 from study DAP-00-02



Protein binding
The mean unbound fraction of daptomycin on study day 1 was 9%, 10%, 7%, and 10% for the 6 mg/kg, 8 mg/kg, 10 mg/kg, and 12 mg/kg dosage regimens, respectively. The protein binding of daptomycin is independent of concentration over the dosing range of 6 mg/kg to 12 mg/kg.

These results are consistent with previous findings in which the unbound fraction of daptomycin was determined to be 8% in healthy adults following the administration of 4 mg/kg or 6 mg/kg and was not altered as a function of daptomycin concentration.

SAFETY:
In Cohorts 1 and 2, all 9 (100%) subjects in the daptomycin 10 mg/kg group experienced at least one adverse event compared with 7 (78%) of 9 subjects in the daptomycin 12 mg/kg group and 5 (83%) of 6 subjects in the control group. In Cohort 3, at least one adverse event was reported by 4 (67%) of 6 subjects in the daptomycin 6 mg/kg group and 1 (17%) of 6 subjects in the daptomycin 8 mg/kg group. No adverse event was reported by more than 1 subject in Cohort 3.

CPK
A review of the CPK laboratory data by-subject revealed that no subject in any of the dosing groups had an elevated CPK value >500 U/L during the study. Furthermore, no subject had a post-Baseline CPK value that was above the upper limit of the normal range (204 U/L).

QT
There were no trends over time or clinically meaningful differences among dosing groups with regard to the changes from baseline in QTc interval for Cohorts 1 and 2. Median QTc values at screening (within two weeks of study drug administration), baseline, and day 14 were 400, 396, and 402 msec, respectively, for the 10 mg/kg dose group; 396, 394, and 400 msec, respectively for the 12 mg/kg dose group; and 401, 403, and 413 msec, respectively, for the control group.

No subject in Cohorts 1 or 2 (daptomycin 10 or 12 mg/kg) or control groups had a prolonged QTc interval (>450 msec for males and >470 msec for females) at any timepoint during the study.

Table 5. Median baseline QTc interval and median changes in QTc interval from baseline over time

	Cohorts 1 and 2		
	Daptomycin		
QTc Interval	10 mg/kg (N = 9)	12 mg/kg (N = 9)	Control (N = 6)
Baseline (Day 1 pre-dose)	396.0	394.0	403.0
Median change from Baseline to Day 7			
Pre-dose	4.0	8.0	-0.5
Post-dose	5.0	-2.0	-7.0
Median change from Baseline to Day 10			
Pre-dose	8.0	14.0	9.0
Post-dose	12.0	5.0	-10.0
Median change from Baseline to Day 14L (pre-dose)	7.0	4.0	10.0

Electrophysiology
There were no statistically significant differences among dosing groups in Cohorts 1 and 2 with regard to the change from baseline in F-wave latency, CMAP, or DML parameters from the electrophysiologic testing and there was no indication of apparent trend across time or treatment. For each of these parameters, changes from baseline to day 14 and to the post-treatment assessment were small in both the

active groups and the control group. The mean value for the DML, CMAP and the F-wave latency and the associated standard deviations were within normal limits for each group at each time point.

CONCLUSIONS:
The mean C_{max} and AUC increased less-than proportional to dose when compared to the 6 mg/kg dose on day 1. The mean C_{max} and AUC increased proportional to dose when compared to the 6 mg/kg dose on day 4 for all doses. The less-than proportional increase in dose is likely due to an excessive dose administered to a single subject (10.86 mg/kg rather than 6 mg/kg).

The mean CL_T, V_{SS}, and $t_{1/2}$ were unchanged with increasing dose from 8 mg/kg to 12 mg/kg.

Daptomycin was excreted in the urine with 37-68% of the administered dose being excreted in 24 hrs as unchanged drug.

No elevations in serum CPK values above 500 U/L were observed at any dose level.

The results of electrophysiologic testing showed no evidence of changes in muscle or nerve electrophysiology associated with daptomycin at the doses and of 10 and 12 mg/kg when given once daily for 14 days.

COMMENTS:
1. Although the sponsor has not provided details on the correction method used to correct the QT interval for changes in heart, it has previously been shown that daptomycin does not to effect heart rate when dosed up to 8 mg/kg.

4.2.3 Pharmacokinetics and drug metabolism report No. PKR-05-006

Study number DM-05-034: Examination of human urine and plasma samples for metabolites of daptomycin by LC/MS/MS

Dates: April 4, 2005 to May 24, 2005
Analytical sites: (b) (4)

OBJECTIVES:
The primary objective of this study was to assess the metabolism of daptomycin *in vivo* using human urine and plasma samples from an ongoing phase 1 human healthy subject study (Study DAP-ADT-04-02).

FORMULATION:
Daptomycin 500 mg vial (lot No. 010853A)

STUDY DESIGN:
Study DAP-ADT-04-02 is a single center, randomized, double-blinded, placebo controlled, multiple dose, safety, tolerability and pharmacokinetic study of ascending doses of daptomycin in healthy volunteers. Subjects were assigned to three dosing cohorts according to the table below.

Dosing Cohort	Daily Dose (mg/kg/day)	Total Subjects (n)	Daptomycin subjects	Control Subjects	Maximum # of Dosing Days
1	10	12	9	3	14
2	12	12	9	3	14
3	6 or 8	12	12	0	4

In Cohort 3, 12 subjects with a creatinine clearance ≥80 mL/min were to be randomized 1:1 to receive daptomycin IV 6 or 8 mg/kg infused over 30 min to establish a pharmacokinetic baseline for comparison with cohorts 1 and 2. Metabolism data were obtained from the analysis of plasma and urine samples at select time points on day 1 and only from subjects that received daptomycin 6 mg/kg. Plasma and urine samples from the 6 mg/kg dose were selected for the current study because it is closest to 4 mg/kg approved dose of daptomycin.

Plasma samples for daptomycin concentration determination were collected and analyzed at predose, end of infusion (0), 4, 8, and 24 hrs relative to the end of infusion for the first dose.

Urine samples for pharmacokinetic analysis were to be pooled for 0-12 hrs and 12-24 hrs from the start of study drug administration on day 1. A pre-dose sample also was to be obtained on day 1.

RESULTS:
Plasma
No metabolite was observed in any plasma sample at any timepoint (0, 4, 8 or 24 hrs relative to the end of infusion).

Urine

Four metabolites were detected in the urine samples collected at 12-24 hr interval. The metabolites were not observed in the predose urine samples. The sponsor reported the results from the 12-24 hr post-treatment urine samples since they contained higher metabolite concentrations than the 0-12 hr post-treatment samples. The results from the 0-12 hr post-treatment samples were not reported. The QC urine samples showed only trace amounts of metabolite 3.

Metabolite 1 was eluted at 16.6 min with a $[M+H]^+$ signal at m/z 1637.1. This metabolite was 16 amu above daptomycin, probably indicating a Phase I oxidative metabolite.

Metabolite 2 was eluted at 16.7 min with a $[M+H]^+$ signal at m/z 1637.1. This metabolite was also 16 amu above daptomycin, probably indicating a Phase I oxidative metabolite.

Metabolite 3 was eluted at 23.1 min with a $[M+H]^+$ signal at m/z 1638.8. A trace amount of this component could be detected in the QC sample spiked with daptomycin, (b) (4) (b) (4) The urine samples did show an increase in signal intensity of this component compared to the QC sample.

Metabolite 4 was a trace metabolite eluted at 24.6 min with a $[M+H]^+$ signal at m/z 1109.8.

These four metabolites were present at low concentrations with each of them contributing to <5% of daptomycin based on the daptomycin UV response. A summary of the analytical findings for daptomycin and the four metabolites are shown in Table 1. Metabolites 1, 2, and 4 were observed in the urine from all subjects. Metabolite 3 was observed in the urine from 4/6 subjects.

Table 1. Summary of human urine metabolites

	Retention Time (min)	$[MH]^+$	Fragment ions
Daptomycin	23.2	1620.8	(b) (4)
M1	16.6	1637.1	
M2	16.7	1637.1	
M3	23.1	1638.8	
M4	24.6	1109.7	

Table 2. Summary of urine metabolites observed per subject

	Subject	Subject	Subject	Subject	Subject	Subject
	[redacted] (b) (6)					
M1	√	√	√	√	√	√
M2	√	√	√	√	√	√
M3	√	x	√	√	√	x
M4	√	√	√	√	√	√

CONCLUSIONS:
Four minor metabolites were observed in the human urine samples, of which three are likely oxidative metabolites. No molecular structure was assigned for the fourth metabolite.

No metabolite of daptomycin was observed in plasma samples collected at 0, 4, 8 and 24 hrs post infusion.

[redacted]
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ON ORIGINAL

4.2.4 Evaluation of the tolerability and pharmacokinetic profile of multiple-dose daptomycin as compared with placebo in subjects with end stage renal disease (ESRD) on hemodialysis with high-flux dialysis membranes and low-flux dialysis membranes (DAP-REN-02-03)

Dates: April 8, 2003 to August 20, 2003
Clinical sites: DaVita Clinical Research, Minneapolis, MN 55404 and New Orleans Center for Clinical Research, New Orleans, LA 70119
Analytical sites: (b) (4)

OBJECTIVES:
The primary objective of this study was to evaluate the tolerability of IV daptomycin as compared to placebo administration following every dialysis for 3 weeks in subjects with end-stage renal disease (ESRD) undergoing hemodialysis three times weekly using one of two different dialysis membranes (high-flux and low-flux). Secondary objectives were to obtain the pharmacokinetic (PK) profile and to evaluate the possible effects on safety parameters of IV daptomycin administration following every dialysis for 3 weeks in subjects with ESRD undergoing hemodialysis three times weekly using one of two different dialysis membranes (high-flux and low-flux).

FORMULATION:
Daptomycin 500 mg vial (lot No. 701703A)

STUDY DESIGN:
This study was a two center, randomized, double-blind study to evaluate the tolerability and pharmacokinetics following multiple dose IV administration of daptomycin in subjects with end-stage renal disease (ESRD) receiving hemodialysis with low-flux and high-flux dialysis membranes. Subjects were to be stable on hemodialysis for a period of at least 3 months and were to receive their hemodialysis according to their normal schedule during the study. Study medication administration was to occur immediately following each dialysis with the initial dose administered after the first dialysis session of the week, on a Monday or Tuesday. All subjects were to receive a total of 9 doses of study medication during the course of this study. Dosing was to occur after hemodialysis three times weekly for three weeks.

A minimum of 24 subjects in Cohort 1 followed by a minimum of 12 subjects in Cohort 2 were to be enrolled. Subjects in Cohort 1 were to be randomized to one of four membrane-study medication group combinations: high-flux or low-flux dialysis membranes and to multiple doses of daptomycin IV or normal saline (1:1:1:1 ratio). Subjects randomized to daptomycin were to receive a single loading dose of 8 mg/kg on study day 1 (Monday or Tuesday) followed by 8 additional doses of IV daptomycin 6 mg/kg, given after every dialysis on Study Days 3, 5, 8, 10, 12, 15, 17, and 19 for a total of 9 doses over 21 days. Subjects randomized to placebo were to receive normal saline on the same dosing schedule as that of daptomycin.

Subjects in Cohort 2 were to be dosed only if subjects in Cohort 1 that were randomized to high-flux dialysis membranes had no safety concerns and a median C_{max} value of ≤78 µg/mL on study day 19 (<80% of the median C_{max} at steady state in normal subjects at 6 mg/kg). Additionally, progression to Cohort 2 was to be considered if, upon review of the data from Cohort 1, there were no safety concerns but the median C_{max} value was >78 µg/mL. Subjects in Cohort 2 were to receive hemodialysis with high-flux dialysis membranes and were to be randomized in a 1:1 ratio to IV daptomycin or normal saline. Subjects randomized to daptomycin were to receive 8 mg/kg on study day 1 (Monday or Tuesday), followed by 8 additional doses of IV daptomycin 8 mg/kg, given after every dialysis session on study days 3, 5, 8, 10, 12, 15, 17, and 19 for a total of 9 doses over 21 days. Subjects randomized to placebo were to receive normal saline on the same dosing schedule as that of daptomycin.

Plasma Samples:
Plasma samples for daptomycin concentration determination were to be collected on days 1, 2, 3, 5, 8, 9, 10, 12, 15, 17, 18, and 19. On study days 1, 8, and 17, blood samples were to be drawn pre-dialysis (within 1 hr before start of dialysis), post-dialysis (within 1 hr after end of dialysis and before dosing), within 5 min after the end of the study medication infusion, and 2, 4, 6, 8, 12, and 24 hrs after the initiation of the study medication infusion. On study days 3, 5, 10, 12, 15, and 19, blood samples were to be drawn pre-dialysis (within 1 hr before start of dialysis), post-dialysis (within 1 hr after end of dialysis), and within 5 min after the end of the study medication infusion. On study days 2, 9, and 18, blood samples for pharmacokinetic analysis were to be collected 24 hrs after the initiation of the study drug infusion from the previous day.

Urine Samples:
Urine was collected for 24 hrs on study days 1, 8, and 17 in subjects who made urine.

DAPTOMYCIN ASSAY METHODOLOGY:
High Performance Liquid Chromatography with ultraviolet detection (HPLC/UV)

Criterion	Plasma	Urine	Comments
Concentration range	3.00 to 500 μg/mL	3.00 to 500 μg/mL	Satisfactory
LLOQ	3.00 μg/mL	3.00 μg/mL	Satisfactory
Linearity	$R^2 \geq 0.9987$	$R^2 \geq 0.9991$	Satisfactory
Accuracy	94.79% to 101.59%	96.57% to 99.65%	Satisfactory
Precision	3.61% to 5.46%	1.67% to 10.54%	Satisfactory
Specificity	Satisfactory	Satisfactory	Satisfactory
Stability	Stability in matrix at 4°C, extracted samples at 4°C, long-term stability in matrix at -20°C, freeze-thaw for 3 cycles	stability in matrix at RT, freeze-thaw for 3 cycles	Satisfactory

Each standard curve was calculated using a linear weighted ($1/concentration^2$) least-squares regression algorithm.

DATA ANALYSIS:
Plasma daptomycin concentration data were analyzed by non-compartmental methods. The following parameters were estimated: maximum plasma concentration (C_{max}); time at which the C_{max} occurred (T_{max}); trough concentration prior to dosing on days (C_{min}); area under the plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$); AUC from zero to tau ($AUC_{0-\tau}$); AUC from zero to last quantifiable concentration (AUC_{0-t}); plasma clearance (CL_T); renal clearance (CL_R); percent of daptomycin dose excreted unchanged in urine over the dosing interval (Fe %); terminal volume of distribution (Vd); volume of distribution at steady-state (V_{SS}); mean residence time (MRT); and terminal elimination half-life ($t_{1/2}$).

STATISTICAL ANALYSIS:
Pharmacokinetic parameters were analyzed using descriptive statistics.

RESULTS:
Twenty-six subjects were enrolled in Cohort 1. The study was terminated after the planned review of safety and pharmacokinetic data following the completion of Cohort 1. No subjects were enrolled in Cohort 2. Of the 26 subjects randomized to Cohort 1, 14 were randomized to high-flux dialysis membranes and 12 were randomized to low-flux dialysis membranes. Of those randomized to high-flux dialysis membranes, six were randomized to normal saline and eight were randomized to daptomycin. However, one subject randomized to daptomycin withdrew from the study after randomization and did

not receive any study medication. Of those subjects randomized to low-flux dialysis membranes, six were randomized to normal saline and 6 were randomized to daptomycin; all of these subjects received at least one dose of study medication.

Table 1. Mean (SD) demographic parameters by treatment group

Demographic	Low-Flux Membrane		High-Flux Membrane	
	Normal saline	Daptomycin	Normal saline	Daptomycin
N	6	6	6	7*
Sex (M/F)	5/1	4/2	4/2	5/2
Age (yrs)	43.7 (8.2)	49.8 (14.5)	55.5 (6.6)	54.3 (10.7)
Weight (kg)	98.7 (29.1)	69.2 (19.3)	81.9 (6.7)	80.5 (16.6)
Height (cm)	178.7 (6.9)	167.5 (12.1)	173.6 (10.7)	169.2 (8.6)

*One subject randomized to daptomycin withdrew from the study and did not receive study medication

Pharmacokinetic analyses were based on data from a maximum of 13 daptomycin subjects, 6 in the low-flux membrane group and 7 in the high-flux membrane group. Study day 1 (dose 1) analyses included data from a maximum of 13 subjects, study day 8 (dose 4) analyses included data from a maximum of 11 subjects and study day 17 (dose 8) analyses included data from a maximum of 7 subjects.

Three (50%) of 6 subjects in the low-flux daptomycin group and 3 (43%) of 7 subjects in the high-flux daptomycin group received all 9 doses of study medication. In the low-flux daptomycin group, Subject (b) (6) received 3 doses of study medication, Subject (b) (6) received 5 doses of study medication, and Subject (b) (6) received 8 doses of study medication before early discontinuation from the study due to adverse events (upset stomach/gastroparesis, intracranial bleed, and elevation of CPK). In the high-flux daptomycin group, Subjects (b) (6) and (b) (6) each received 5 doses of study medication before withdrawing consent to continue, and Subjects (b) (6) and (b) (6) received 2 and 5 doses of study medication, respectively, before early discontinuation due to adverse events (elevation of CPK). All but one subject in each of the normal saline groups received all 9 doses of study medication. Subject (b) (6) (low-flux normal saline) received 6 doses of study medication and Subject (b) (6) (high-flux normal saline) received 3 doses of study medication before early discontinuation due to adverse events.

The mean plasma concentration-time profiles following administration of daptomycin IV 8 mg/kg on day 1, then 6 mg/kg following hemodialysis with low-flux and high-flux dialyzers are shown in Figures 1 (day 1) and 2 (days 8 and 17).

Figure 1. Mean daptomycin plasma concentration-time profiles following administration of daptomycin IV 8 mg/kg after hemodialysis with low-flux and high-flux dialyzers on day 1

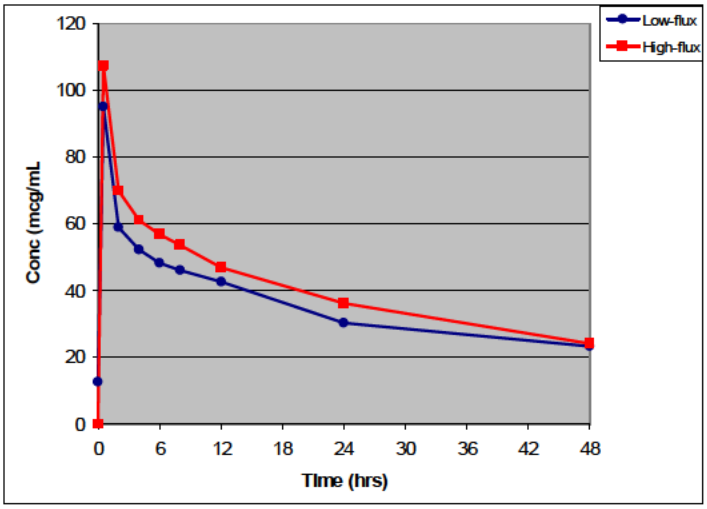
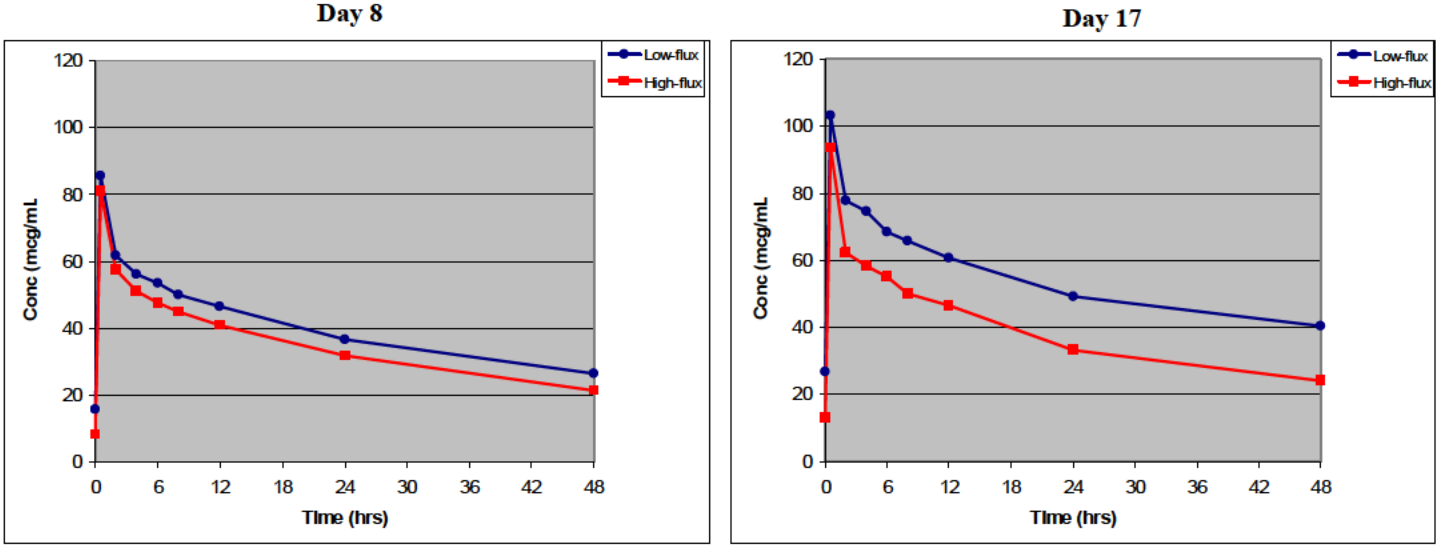


Figure 2. Mean daptomycin plasma concentration-time profiles following administration of daptomycin IV 8 mg/kg, then 6 mg/kg after hemodialysis with low-flux and high-flux dialyzers on days 8 and 17



On day 1, the mean plasma concentrations of daptomycin were greater among subjects in the high-flux group compared to the low-flux group even though the mean V_{SS} (L/kg) was the same for both groups. On days 8 and 17, the mean plasma concentrations of daptomycin were greater among subjects in the low-flux group compare to the high-flux group.

The mean pharmacokinetic parameters following administration of daptomycin 8 mg/kg on day 1, then 6 mg/kg following hemodialysis three times weekly are shown in Table 2 with the low-flux dialyzer and Table 3 with the high-flux dialyzer. In general, the C_{max} ranged from 81 to 107 µg/mL across all subjects and the mean half-life of daptomycin ranged from 36 to 56 hours with a trend toward increasing half-life with prolonged dosing. The mean half-life increased after multiple dosing to a greater extent in the low-flux dialyzer group compared to the high-flux dialyzer group. The mean V_{SS} ranged from 0.14–0.27 L/kg, consistent with high protein binding in plasma. Although urine data were available for only seven

subjects, the mean fraction of dose excreted from urine ranged from 0.45–7.2%, indicating that renal clearance was not a major pathway in the removal of intact daptomycin from the body of subjects with ESRD.

Table 2. Mean (CV%) pharmacokinetic parameters on days 1, 8, and 17 following administration of daptomycin 8 mg/kg IV (day 1), then 6 mg/kg IV after hemodialysis (low-flux) for 21 days

Parameter	N	Day 1	N	Day 8	N	Day 17
Actual dose (mg/kg)	5	7.6 (31%)	5	5.5 (16%)	4	5.3 (12%)
C_{max} (μg/mL)	6	91.0 (31%)	5	85.6 (33%)	4	103.1 (26%)
$AUC_{0-\tau}$ (μg*hr/mL)	6	1697 (33%)	5	1917 (45%)	4	2586 (35%)
$AUC_{0-\infty}$ (μg*hr/mL)	6	3067 (43%)	5	3704 (55%)	4	6263 (54%)
V_{SS} (L)	5	10.0 (30%)	5	12.7 (20%)	4	11.92 (36%)
V_{SS} (L/kg)	5	0.14 (18%)	5	0.19 (29%)	4	0.16 (20%)
CL_T (mL/hr/kg)	5	2.83 (40%)	5	3.49 (55%)	4	2.24 (34%)
CL_R (mL/hr/kg)	4	0.18 (166%)	4	0.15 (144%)	2	0.01 (141%)
$t_{1/2}$ (hrs)	6	38.5 (21%)	5	42.3 (27%)	4	55.9 (36%)
Xe (mg)	4	10.94 (130%)	4	9.81 (90%)	2	1.20 (141%)

Table 3. Mean (CV%) pharmacokinetic parameters on days 1. 8, and 17 following administration of daptomycin 8 mg/kg IV (day 1), then 6 mg/kg IV after hemodialysis (high-flux) for 21 days

Parameter	N	Day 1	N	Day 8	N	Day 17
Actual dose (mg/kg)	7	8.0 (41%)	6	5.3 (13%)	3	5.7 (14%)
C_{max} (μg/mL)	7	107.4 (39%)	6	81.1 (38%)	3	93.6 (17%)
$AUC_{0-\tau}$ (μg*hr/mL)	7	1945 (34%)	6	1672 (36%)	3	1716 (27%)
$AUC_{0-\infty}$ (μg*hr/mL)	7	3185 (33%)	6	2877 (40%)	3	3246 (9%)
V_{SS} (L)	7	11.49 (68%)	6	15.27 (47%)	3	20.91 (71%)
V_{SS} (L/kg)	7	0.14 (545)	6	0.19 (55%)	3	0.27 (85%)
CL_T (mL/hr/kg)	7	2.76 (51%)	6	3.72 (50%)	3	3.63 (44%)
CL_R (mL/hr/kg)	3	0.18 (54%)	2	0.16 (96%)	2	0.19 (8%)
$t_{1/2}$ (hrs)	7	35.7 (11%)	6	38.1 (17%)	3	45.3 (38%)
Xe (mg)	3	17.28 (70%)	2	19.33 (116%)	2	15.76 (585%)

The dose normalized C_{max} and $AUC_{0-\tau}$ were statistically significantly higher on study day 17 than study day 1 for the low-flux and high-flux groups. The dose normalized $AUC_{0-\tau}$ values for subjects in both groups increased from day 1 to day 17, although the dose normalized $AUC_{0-\tau}$ increased to a greater extent among subjects in the low-flux group. The dose normalized C_{max} values increased from day 1 to day 17 for subjects in both the low-flux and high-flux groups to a similar extent.

NOTE: The changes from day 1 to day 17 in the dose normalized $AUC_{0-\tau}$ values and C_{max} values for subjects in the high-flux group should be interpreted with caution since data for only 3/7 subjects in the high-flux group and 4/6 subjects in the low-flux group were available on day 17.

There was no statistical difference between the dose normalized $AUC_{0-\tau}$ values and C_{max} values on day 8 and day 1 as daptomycin may not have reached steady state by day 8.

The mean (SD) daptomycin plasma concentrations pre- and post-dialysis for study days 1, 8 and 17 are shown in Table 4 by dialysis membrane. No statistically significant differences were seen for subjects on low-flux membrane dialysis between pre- and post-dialysis concentrations. Subjects on high-flux dialysis membranes had a markedly greater reduction in daptomycin concentrations pre- to post-dialysis compared to those on low-flux dialysis membranes. The mean pre-dialysis plasma concentration was reduced

41.4% on day 8 and 40.6% on day 17 with a high-flux dialyzer. In comparison, the mean pre-dialysis plasma concentration was reduced 4.5% on day 8 and 7.4% on day 17 with a low-flux dialyzer.

Table 4. Mean (SD) daptomycin plasma concentrations (μg/mL) pre- and post-dialysis by study day and dialysis membrane

Dialysis Membrane	Study Day 1		Study Day 8		Study Day 17	
	Pre-dialysis	Post-dialysis	Pre-dialysis	Post-dialysis	Pre-dialysis	Post-dialysis
Low-flux[a]	0.79 (1.93)	12.65 (28.38)	16.53 (8.81)	15.78 (8.39)	28.93 (11.43)	26.80 (9.85)
High-flux	0.00 (0.00)	0.00 (0.00)	13.91 (5.61)	8.15 (3.38)	21.87 (2.82)	13.00 (2.48)

[a] The pre- and post-dialysis concentrations on Study Day 1 should theoretically be 0. See the text for details.

NOTE: The presence of daptomycin pre- and post-dialysis on day 1 (prior to dosing) was not anticipated. One subject (Subject (b) (6)) had very low concentrations, near the limit of quantitation. The post-dialysis sample for Subject (b) (6) (70.40 μg/mL), which was also the subject's C_{max}, may have been switched inadvertently with the end of infusion sample (0 μg/mL). The data had no effect on C_{max} mean values and reduced the mean T_{max} value slightly.

The sponsor previously evaluated the pharmacokinetics of a single dose of daptomycin IV 4 mg/kg in six subjects with end-stage renal disease (ESRD) on and off hemodialysis (Study DAP-00-01 submitted with original NDA - refer to the daptomycin review dated September 12, 2003). The mean C_{max} and $AUC_{0-\infty}$ while not receiving hemodialysis (hemodialysis occurred 24 hrs after the start of the infusion) were 41.1 μg/mL and 1138 μg*hr/mL, respectively. The mean C_{max} and $AUC_{0-\infty}$ while receiving hemodialysis (hemodialysis occurred 4 hrs after the start of the infusion) were 40.1 μg/mL and 994 μg*hr/mL, respectively. Compared to control subjects with normal renal function (CL_{CR} >80 mL/min), the mean $AUC_{0-\infty}$ was 1.20-fold higher in ESRD subjects receiving hemodialysis at 24 hrs after the start of the infusion.

In Study DAP-REN-02-03, the mean $AUC_{0-\tau}$ values on day 17 from ESRD subjects receiving hemodialysis three times weekly were 2586 and 1716 μg*hr/mL for low-flux and high-flux membranes, respectively. Since the sponsor did not enroll a control group, the mean $AUC_{0-\infty}$ from healthy subjects with normal renal function who received a single 6 mg/kg dose of daptomycin IV (Study DAP-ADT-04-02) was 730 μg*hr/mL. Thus, the mean AUC was 2.54-fold higher and 1.35-fold higher in the low-flux and high-flux hemodialysis groups, respectively. The results from the high-flux group in Study DAP-REN-02-03 are consistent with the findings previously reported in Study DAP-00-01. Based on the dosage recommendations in the DOSAGE AND ADMINISTRATION section of the label, it is estimated that the AUC of patients with ESRD receiving hemodialysis with high-flux membranes will be approximately 1.12 times the AUC of patients with normal renal function.

SAFETY:

The overall incidence of adverse events was similar between the daptomycin and normal saline groups, regardless of dialysis membrane and the majority of events were mild to moderate in severity. The reported incidence of elevated blood CPK, with or without a concurrent reported increase in myoglobin level, was highest in the high-flux daptomycin group compared to all other groups. A higher proportion of subjects in the daptomycin groups discontinued from the study due to adverse events, primarily reports of elevated CPK levels, compared to subjects in the normal saline group.

Select treatment-emergent adverse events are shown in Table 5. The most commonly reported adverse events among the 13 subjects in the daptomycin groups included in the safety population were elevated blood CPK (4 subjects, 31%) (concurrent with increased myoglobin in 3 subjects, 23%), and nausea,

headache, and hypotension (2 subjects each, 15%). In the normal saline groups, the most commonly reported events were nausea (4 subjects, 33%), and vomiting and rash (2 subjects each, 17%). All other events were reported in only one subject in each membrane-study medication group.

Table 5. Select treatment-emergent adverse events - safety population

Adverse Event	Low-flux membrane		High-flux membrane	
	Normal saline (n=6)	Daptomycin (n=6)	Normal saline (n=6)	Daptomycin (n=7)
Subjects with at least one treatment emergent AE	4 (67%)	5 (83%)	4 (67%)	5 (71%)
Nausea	2 (33%)	1 (17%)	2 (33%)	1 (14%)
Vomiting	1 (17%)	0	1 (17%)	1 (14%)
Headache	0	0	0	2 (29%)
Blood CPK increased: • CPK >ULN at screening • CPK >ULN any time during study • CPK elevated (>50% increase from CPK values on day 1 and a CPK >500 U/L)	 3 (50%) 2 (33%) 0	 1 (17%) 3 (50%) 1 (17%)	 0 3 (50%) 1 (17%)	 4 (57%) 6 (86%) 3 (43%)
Blood myoglobin increased	0	1 (17%)	0	2 (29%)

CPK normal range is 38 to 174 U/L

The AUC and C_{max} values for the three subjects in the high-flux group and one subject in the low-flux group with elevated blood CPK (CPK >500 U/L) is shown in Table 6. In the high-flux group, only one subject (Subject (b) (6)) had an AUC and C_{max} values that were elevated compared to the group mean whereas the sole subject in the low-flux group (Subject (b) (6)) had AUC and C_{max} values that were elevated compared to the group mean.

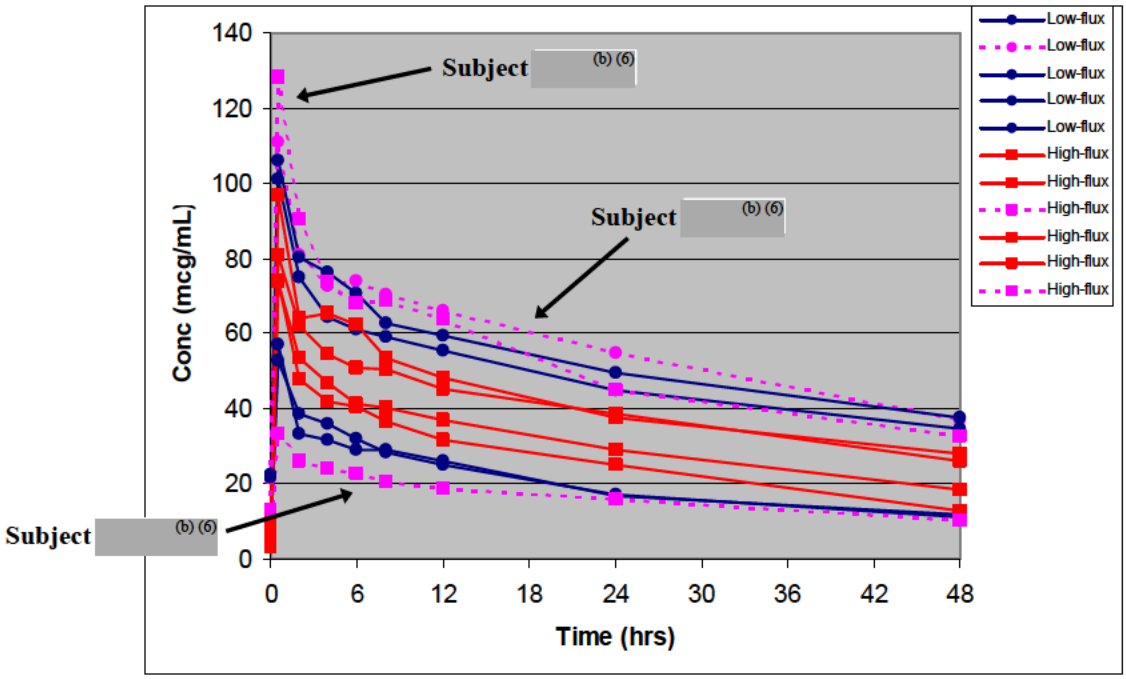
The daptomycin plasma concentration-time profiles for subjects with data available on day 8 are shown in Figure 7. Subjects with elevated blood CPK are represented by broken lines. Two subjects with blood CPK elevation (Subjects (b) (6) [low-flux] and (b) (6) [high-flux]) were associated with the highest daptomycin plasma concentrations whereas one subject (Subject (b) (6) [high-flux]) was associated with the lowest. Plasma concentration-time data were not available on day 8 for subject (b) (6) (b) (6) The sponsor did not report previous use of HMG-CoA reductases inhibitors to assess the relationship between use of HMG-CoA reductases inhibitors and CPK elevation.

Table 6. AUC* and C_{max} values for subjects with CPK events compared to group mean values

Day	Parameter	High-flux membrane				Low-flux membrane	
		Subject (b) (6)	Subject (b) (6)	Subject (b) (6)	Group Mean (SD)	Subject (b) (6)	Group Mean (SD)
1	AUC (μg*hr/mL) C_{max} (μg/mL)	3082 109	2641 70	5309 187	3185 (1050) 107 (42) (n=7)	5092 133	3067 (1325) 91 (29) (n=6)
8	AUC (μg*hr/mL) C_{max} (μg/mL)	---	797 33	2491 128	1672 (600) 81 (38) (n=6)	2721 111	1916 (860) 86 (33) (n=5)
17	AUC (μg*hr/mL) C_{max} (μg/mL)	---	---	---	1716 (466) 94 (16) (n=3)	3481 132	2586 (912) 103 (27) (n=4)

*$AUC_{0-\infty}$ on day 1 and $AUC_{0-\tau}$ on days 8 and 17

Figure 7. Individual daptomycin plasma concentration-time profiles for subjects with available data <u>on day 8</u>



CONCLUSIONS:

There were no statistically significant differences in daptomycin pharmacokinetics between the low-flux and high-flux dialysis membranes. However, subjects dialyzed with high-flux dialysis membranes exhibited a markedly greater reduction in daptomycin concentrations pre- to post-dialysis compared to those on low-flux dialysis membranes.

In subjects with normal renal function, the mean C_{max} on day 7 was 98.6 µg/mL following doses of 6 mg/kg and was similar to that in the present study. In contrast, the mean AUC on study day 17 in the current study in both high-flux (1716 µg*hr/mL) and low-flux (2586 µg*hr/mL) groups was markedly increased compared to subjects on the same dose (6 mg/kg) at steady-state with normal renal function (747 µg*hr/mL).

Review of pharmacokinetic parameters in subjects with and without CPK elevations revealed that there was a lack of a consistent relationship between exposure (as assessed by AUC or trough) and increased CPK levels. Although, as expected, subjects dialyzed with a high-flux membrane had lower post-dialysis trough levels (mean range 8-15 µg/mL) than subjects dialyzed with low-flux membranes (mean range 16-30 µg/mL), they did not appear to be at lower risk of CPK events.

COMMENTS:

1. The sponsor did not collect dialysate fluid from subjects under hemodialysis with either the low-flux or high-flux membranes. Thus, the amount of unchanged daptomycin removed during dialysis could not be calculated.

4.3. Pharmacometrics Review

PHARMACOMETRICS REVIEW

NDA	21-572
Product	6 mg/kg IV infusion
Brand name	Cubicin®
Generic name	Daptomycin
Sponsor:	Cubist Pharmaceuticals
Type of submission	Supplemental NDA
Pharmacometrics Reviewer	Dakshina Chilukuri, Ph.D.
Secondary Pharmacometrics Reviewer	Rajanikanth Madabushi, Ph.D.
Pharmacometrics Team Leader	Jogarao Gobburu, Ph.D.
Submission Date	09/22/05
Review Date	03/15/06
PDUFA Date	03/22/06

Data Filenames of EDR: ALL2.xpt, IEACOC.xpt, MIC_DVD.xpt,

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EXECUTIVE SUMMARY

Daptomycin is recommended by the sponsor to be administered for the treatment of *Staphylococcus aureus* Bacteremia including those with known or suspected endocarditis caused by Methicillin-Susceptible and Methicillin-Resistant Strains. The proposed dosage regimen is 6 mg/kg to be administered over a 30-minute period by IV infusion once every 24 hours.

The key findings of pharmacometrics analysis are:

1. The proportion of patients with higher exposure do not show increased success measured by the composite endpoint (IEAC Success).
2. The proportion of patients with clinical and microbiological failures in bacteremia and infective endocarditis decreases as the trough concentration to MIC ratio (C_{min}/MIC) increases. However, the decrease is not statistically significant.
3. The proportion of patients with elevations in creatine phosphokinase (CPK) levels increase with increasing $C_{min.}$ This increase is seen both with elevations of CPK ≥500 IU/L and ≥1000 IU/L. The difference was statistically significant, with p=0.007 for ≥ 500 IU/L and p=0.012 for ≥ 1000 IU/L.

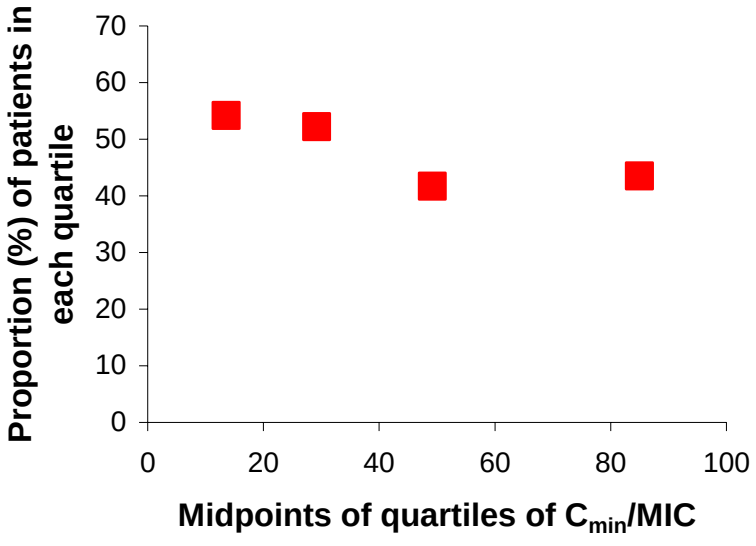
QUESTION BASED REVIEW FOR PHARMACOMETRICS

1. Do the patients with bacteremia and endocarditis and higher exposure have a higher proportion of IEAC Success?

No. The proportion of patients with higher exposure do not show increased success measured by the composite endpoint (IEAC Success).

- As seen below in Figure 1, there is no clear trend for increased IEAC success with increasing C_{min}/MIC.

Figure 1. Higher exposure does not result in higher proportion of IEAC Success (N=94)



- In view of the lack of a relationship with this composite endpoint, an attempt was made to look at individual components of the composite endpoint, namely,

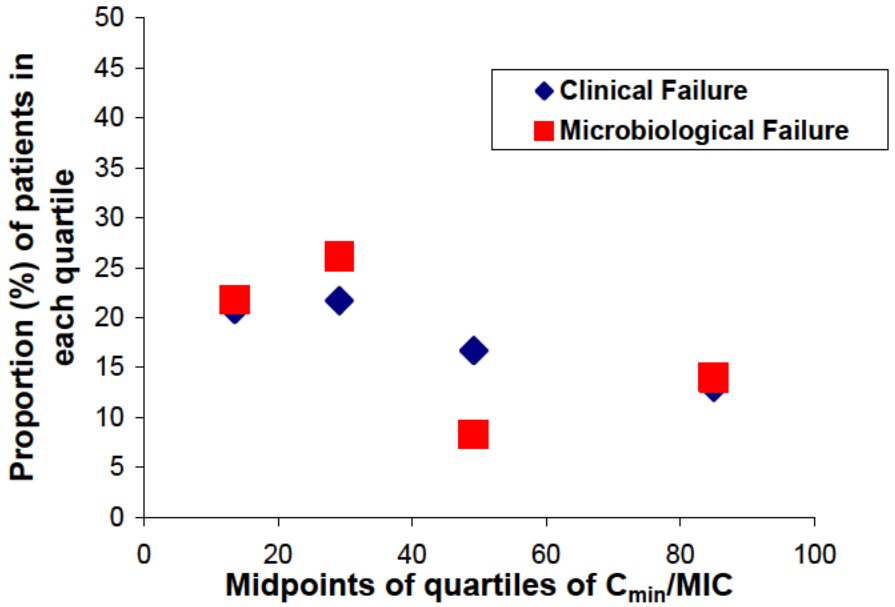
clinical success and microbiological success. The data submitted by the sponsor included clinical and microbiological failures and thus the relationship between clinical and microbiological failures and exposure (C_{min}/MIC) were explored.

2. ***Do the patients with bacteremia and endocarditis and higher exposure have a lower proportion of clinical/microbiological failures?***

Yes. The proportion of patients with higher exposure tends to have lower clinical and microbiological failures.

- Trough concentration (C_{min}) to baseline MIC ratio was used as the exposure metric. Clinical failures and microbiological failures were the measures of effectiveness. There were a total of 21 clinical failures and 19 microbiological failures.
- The proportion of patients with clinical and microbiological failures decreased with higher C_{min}/MIC, as shown in Figure 2. The clinical failure rates were about 20% at the first C_{min}/MIC quartile (median 15) and were about 14% at the fourth C_{min}/MIC quartile (median 80). The microbiological failure rates were about 20% at the first C_{min}/MIC quartile (median 15) and were 13% at the fourth C_{min}/MIC quartile (median 80). The difference was not statistically significant.

Figure 2. Higher exposure results in reduced proportion of clinical and microbiological failures (N=94)

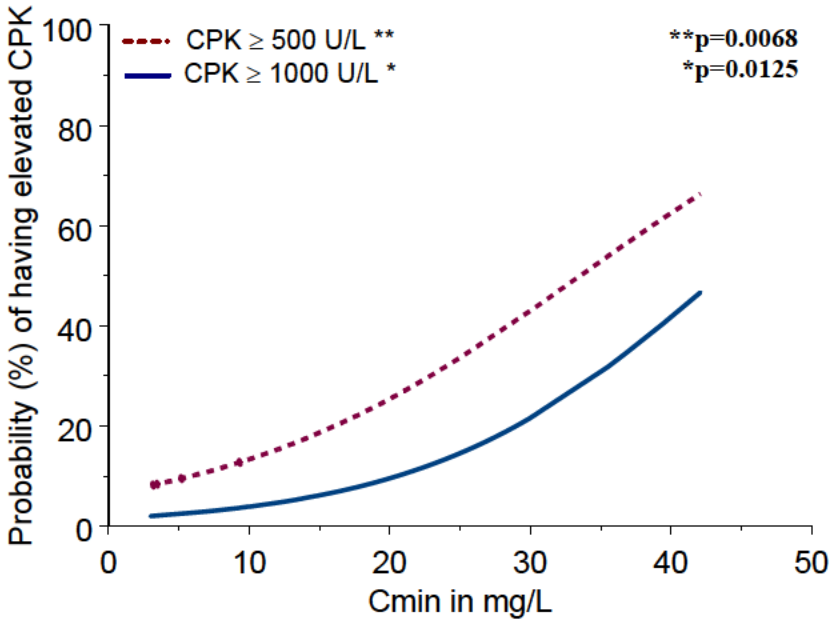


3. ***Do the patients with higher C_{min}/MIC have a higher likelihood of elevated CPK levels?***

- The probability of patients with elevated CPK levels increase with C_{min} indicating a relationship between C_{min} and CPK elevations of $\geq$ 500 IU/L and $\geq$ 1000 IU/L, as shown in Figure 3.

- When the C_{min} increases from 5.2 mg/L (5th percentile) to 30 mg/L (95th percentile), the probability of having CPK ≥ 500 IU/L increases from 10% to 43%
- Similarly, the probability of having CPK elevations ≥ 1000 IU/L increases from 3% to 22%. The difference was statistically significant, with p=0.0068 for ≥ 500 IU/L and p=0.0125 for ≥ 1000 IU/L.

Figure 3. Higher exposure results in higher probability of patients with elevated CPK levels (N=96). Logistic regression was performed using C_{min} as continuous variable and the events as binary variables (yes or no). The lines represent regression fit.



METHODS:
Sponsors Analysis
A. Population Pharmacokinetics and Pharmacodynamics (Elevated CPK)
Data
A total of 418 subjects from ten Phase 1 and eight Phase 2/3 clinical trials contributed 4350 observation records (daptomycin concentrations) for the final population PK database, and 1686 observation records (CPK measurements) for the final population PD database.

Methodology:
Pharmacokinetic Analysis:
The model structure was based on the model defined in the previous population PK analysis. Modeling was conducted using a two–compartment model parameterized in terms of CL, V1, Q, V2, and D1 (ADVAN3 TRANS4), with interindividual random effects on CL, V1, Q, and V2. Assessment of model adequacy and decisions about increasing model complexity were driven by the data and guided by goodness–of–fit criteria, including: (i) visual inspection of diagnostic scatter plots (observed vs. predicted concentration, residual/weighted residual vs. predicted concentration or time, and histograms of individual random effects, for example), (ii) successful convergence of the minimization routine with at least 2 significant digits in parameter estimates, (iii) plausibility of parameter estimates, (iv) precision of parameter estimates, (v) correlation between model parameter estimation errors < 0.95, and (vi) the AIC, given the minimum objective function value and number of estimated parameters. All parameter estimates were reported with a measure of estimation uncertainty, such as the standard error of the estimates (obtained from the NONMEM $COVARIANCE step), or non-parametric bootstrap 95% confidence intervals (as described in the model evaluation methods).

An exploratory investigation of covariate-parameter relationships was also undertaken as part of the population PK analysis. A covariate modeling approach emphasizing parameter estimation rather than step– wise hypothesis testing was implemented for this population PK analysis. The final population PK structural and statistical model from the previous population PK analysis was the initial model for this analysis. The covariates to be added to the model in this analysis were pre-defined, and a full model was constructed based on exploratory graphics, scientific interest, and mechanistic plausibility of prior knowledge. The full model was constructed with care to avoid correlation or collinearity in predictors. Population parameters, including fixed effects parameters (covariate coefficients and structural model parameters), and random effects parameters were estimated. An exploratory assessment of any remaining trends was conducted by graphical inspection of all covariate effects (plots of MAP Bayes estimates of individual random effects and/or weighted residuals from the full model vs. covariates). Inferences about clinical relevance of parameters were based on the resulting parameter estimates of the full model and measures of estimation precision (asymptotic standard errors or bootstrap 95% confidence intervals). No hypothesis testing was conducted. This approach enabled the direct assessment of clinical relevance of covariate effects and also provided

some explanation for the apparent absence of a covariate effect (true lack of an effect vs. lack of information about that effect).

Pharmacodynamic Analysis:
An exposure-response relationship between CPK and measures of daptomycin exposure was investigated using the data in the pivotal study and the final population PK model. CPK measurements coinciding with measures of daptomycin exposure were merged to create matched pairs. For C_{max} and/or trough measurements that were not present, the final population PK model was used to predict the daptomycin concentration using subject–specific pharmacokinetic parameter estimates. For single dose studies, crossover designs, and the first dose of a multiple dose regimen, a coincident CPK measurement was defined as that CPK measurement that was closest in time to the measure of exposure and that was collected up to 4 h prior (trough only) to the exposure measurement, and up to 24 h following (all exposure measures) the exposure measurement (-4 h, 24 h), or up to the time of the next dose, whichever duration was less. For the last daptomycin dose of a multiple dose regimen, a coincident CPK measurement was defined as that CPK measurement that was closest in time to the measure of exposure and that was collected in the time interval (-24 h, 24 h), relative to the measure of exposure.

The measures of daptomycin exposure used in this analysis were area under the daptomycin plasma concentration-time curve at steady–state (AUC_{ss}), maximum daptomycin plasma concentration at steady– state (C_{max},ss), minimum daptomycin plasma concentration at steady-state (C_{min},ss), and daptomycin plasma CL. All subjects supplied one daptomycin CL value and one AUC_{ss}. A subject-specific CL value was generated by the final population PK model. This CL value was used with the subjects' daptomycin dose to calculate an AUCss. For C_{max},ss and C_{min},ss, each subject supplied one value for each measure, where possible. Subjects who received only a single dose or who were not at steady–state at the time of PK or CPK sampling did not supply a value for C_{max},ss or C_{min},ss. For CPK measures, each subject could supply as many as were available in the database, with the limitation described above regarding CPK and exposure matching. However, any baseline CPK values were removed from the dataset prior to the graphical evaluation and linear regression analysis.

The graphical evaluation and linear regression analysis were performed using the dataset containing the measures of daptomycin exposure and corresponding CPK values for each subject. Due to the lack of multiple exposures measures within a subject for daptomycin, a naïve pooled approach was used for the pharmacodynamic analysis.

B. Pharmacokinetic/Pharmacodynamic (Efficacy) analysis

Data
Of the 120 patients treated with daptomycin, 108 (90.0%) patients had PK blood sampling performed. Two patients, (b) (6) and (b) (6) were not at steady-state on the day of PK sampling. Two patients (b) (6) and (b) (6) did not have their baseline *S. aureus* isolates sent to the Central Lab; and are excluded from analyses that require a daptomycin MIC or MBC value.

Methods
Pharmacokinetic (PK) sampling was to be performed only for patients randomized to daptomycin. A 10 mL blood sample was to be collected for PK analysis within the 24 hours prior to first dose of study medication and on Day 5 (steady-state) within 30 minutes before the start of the study medication infusion and 15 to 30 minutes, 60 to 90 minutes, 3 to 5 hours, and 9 to 12 hours following the end-of-infusion.

Individual steady-state (SS) PK parameters were analyzed as provided from the population PK model. No consideration was given to excluding statistical outliers. For the purposes of analysis, serum trough concentrations (C_{min} values), reported as "< 3" µg/mL were set to zero. Daptomycin MIC and MBC values were determined for the baseline infecting *S. aureus* for all daptomycin-treated patients except four. The primary analyses involved the use of C_{max}/MIC and AUC_{0-24}/MIC ratios as exposure metrics and IEAC success as the efficacy metric.

RESULTS

A. Population Pharmacokinetics and Pharmacodynamics (Elevated CPK)

Pharmacokinetic Analysis
The final model from the previous population PK analysis was chosen as the base model for this analysis. The model was parameterized in terms of CLdialysis, CLnon-dialysis, V1, Q, V2, and D1. Interindividual random effect distributions were modeled using exponential variance models on the parameters CL, V1, Q, and V2, while residual random effects were described with an additive model. Covariate effects on the prior final model included creatinine clearance, sex, and temperature on CLnon-dialysis; temperature and sex on CLdialysis; weight on Q; and weight and the presence of a Gram–positive infection on V2. This model was implemented using the PREDPP subroutine ADVAN3 TRANS4, which accounts for multiple dosing or steady–state conditions using recursive superposition. The final population PK model is given below:

$$CL_{DIALYSIS_i} = \theta 1 \cdot \left(\frac{TEMP(°C)}{37(°C)}\right)^{\theta 9} \cdot \theta 8^{SEX[Female]} \cdot \theta 13^{DIAM[LowFlux]} \cdot \theta 14^{DIAM[HighFlux]} \cdot \exp^{\eta_{CL_i}}$$

$$V1_i = \theta 2 \cdot \exp^{\eta_{V1_i}}$$

$$Q_i = \theta 3 \cdot \left(\frac{WT(kg)}{70(kg)}\right)^{\theta 10} \cdot \exp^{\eta_{Q_i}}$$

$$V2_i = \theta 4 \cdot \left(\frac{WT(kg)}{70(kg)}\right)^{\theta 11} \cdot \theta 12^{INFN[INFN1]} \cdot \exp^{\eta_{V2_i}}$$

$$D1 = \theta 5$$

$$CL_{NON-DIALYSIS_i} = \theta 6 \cdot \left(\frac{CLC0(mL/min)}{80(mL/min)}\right)^{\theta 7} \cdot \left(\frac{TEMP(°C)}{37(°C)}\right)^{\theta 9} \cdot \theta 8^{SEX[Female]} \cdot \theta 15^{IEAC[IEAC1]} \cdot \theta 16^{IEAC[IEAC2]} \cdot \theta 17^{IEAC[IEAC3]} \cdot \theta 18^{IEAC[IEAC4]} \cdot \theta 19^{IEAC[IEAC5]} \cdot \exp^{\eta_{CL_i}}$$

$$CP_i = \frac{A1_i}{V1_i}$$

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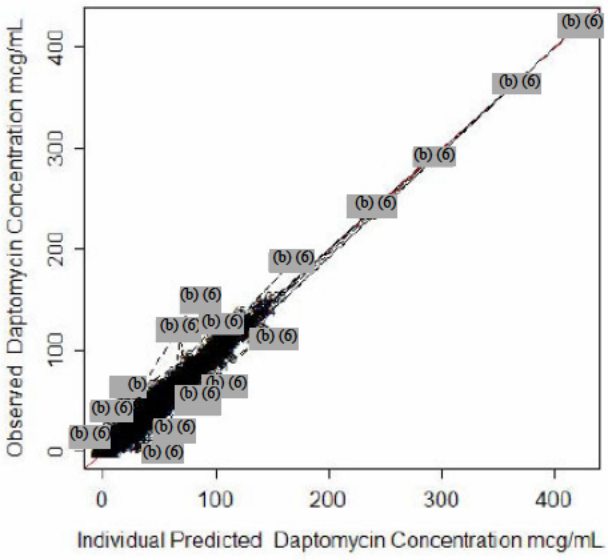
Table 1: Sponsor's Final Model Population PK parameters

Parameter	Fixed Effect Parameter	Bootstrap 95% CI
$CL_{DIALYSIS}$ (L/hr)= θ1	0.238 (6%)	0.215, 0.265
*(TEMP/37)$^{\theta 9}$	2.95 (50%)	0.310, 5.46
*θ8$^{SEX\,[Female]}$	0.871 (3%)	0.824, 0.929
*θ13$^{DIAM\,[LowFlux]}$	0.879 (14%)	0.686, 1.15
*θ14$^{DIAM\,[HighFlux]}$	1.28 (12%)	1.01, 1.60
V1 (L) = θ2	4.71 (5%)	4.29, 5.13
Q (L/hr) = θ3	3.68 (7%)	3.18, 4.23
*(WT/70)$^{\theta 10}$	0.996 (25%)	0.386, 1.49
V2 (L) = θ4	3.16 (3%)	2.98, 3.33
*(WT/70)$^{\theta 11}$	0.821 (13%)	0.626, 1.04
*θ12$^{INFN\,[INFN]}$	1.76 (6%)	1.56, 1.97
D1 (hr) = θ5	0.4 (24%)	0.0584, 0.551
$CL_{NON\text{-}DIALYSIS}$ (L/hr) = θ6	0.747 (3%)	0.707, 0.784
*(CLC0/80)$^{\theta 7}$	0.549 (7%)	0.477, 0.617
*(TEMP/37)$^{\theta 9}$	2.95 (50%)	0.310, 5.46
*θ8$^{SEX\,[Female]}$	0.871 (3%)	0.824, 0.929
*θ15$^{IEAC\,[LIE]}$	1.16 (12%)	0.971, 1.48
*θ16$^{IEAC\,[Complicated\,RIE]}$	1.3 (9%)	1.19, 1.48
*θ17$^{IEAC\,[Uncomplicated\,RIE]}$	1.3 (9%)	1.14, 1.48
*θ18$^{IEAC\,[Complicated\,Bacteremia]}$	1.11 (4%)	1.02, 1.19
*θ19$^{IEAC\,[Uncomplicated\,Bacteremia]}$	1.14 (5%)	1.04, 1.24
Interindividual Variance %SE		
ω^2_{CL}	0.0903 (10%) CV%=30%	0.0720, 0.107
COV_{CL-V1}	(23%) r=0.53	0.0696, 0.164
ω^2_{V1}	0.489 (20%) CV%=70%	0.317, 0.692
ω^2_{Q}	0.504 (25%) CV%=71%	0.277, 0.740
ω^2_{V2}	0.0747 (22%) CV%=27%	0.0461, 0.117
Residual Variance %SE		
$\sigma^2_{prop[ADDY1]}$	4.28 (23%) SD=2	2.60, 6.32
$\sigma^2_{prop[ADDY0]}$	24.4 (15%) SD=5	18.4, 31.8

CL = clearance
TEMP = temperature
DIAM = dialysis membrane
V1 = central compartment volume of distribution
Q = intercompartmental clearance
WT = weight
INFN = presence of Gram-positive infection
D1 = duration of infusion
CLC0 = creatinine clearance at baseline
IEAC = IEAC Final Diagnosis
COV = covariance
add = additive
%SE = percent standard error
CV% = percent coefficient of variation
SD = standard deviation
CI = confidence interval

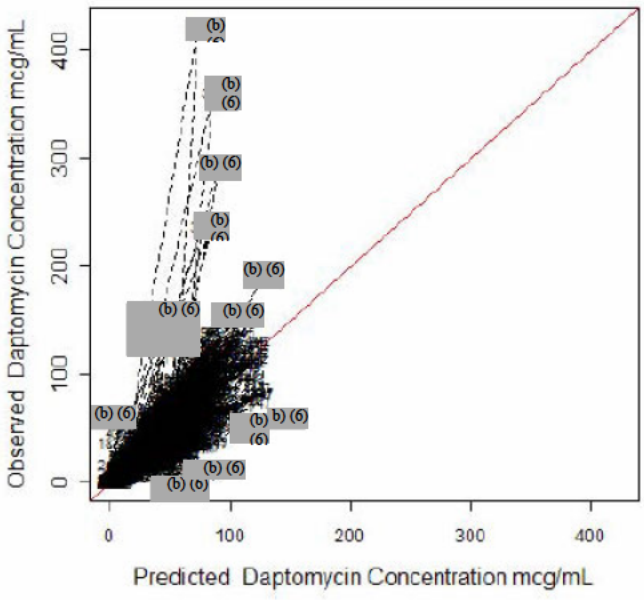
In Figure 4 the relationship between individual predicted concentrations and observed concentrations is plotted. The degree of scatter of the individual data about the line of identity indicates that the final model predicts the individual concentration profiles well.

Figure 4. Observed Daptomycin concentration values (mcg/mL) are plotted versus individual predictions. Values are indicated by individual ID numbers with a dotted line connecting individual data points. The line of identity (solid red) is included as a reference.



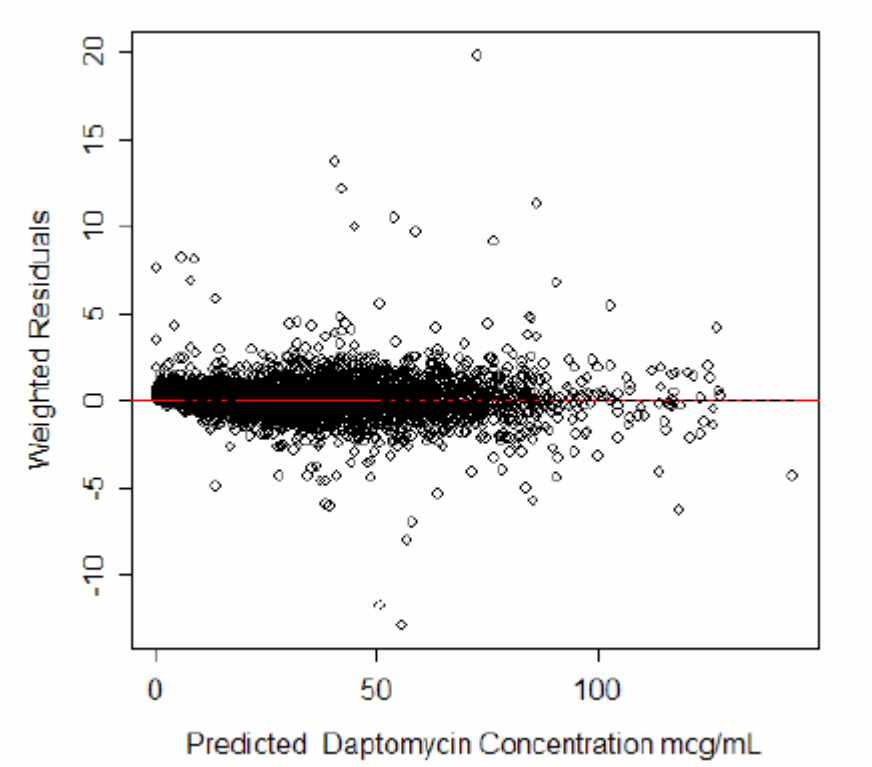
In Figure 5 the relationship between the populations predicted concentrations and the observed concentrations are shown.

Figure 5.Observed Daptomycin concentration values (mcg/mL) are plotted versus population predictions. Values are indicated by individual ID numbers with a dotted line connecting individual data points. The line of identity (solid red) is included as a reference.



In Figure 6 the relationship between the populations predicted concentrations and the observed concentrations are shown.

Figure 6. Weighted residuals are plotted versus population predicted Daptomycin concentration (mcg/mL). Values are indicated by open circles with a dashed black lowess (local regression smoother) trend line through the data. A solid red line at y = 0 is included as a reference.



Pharmacodynamics:
The measures of daptomycin exposure are plotted against the observed CPK values in Figures 7 and 8. All plots are presented as linear–linear, log–linear, and log–log. A review of these figures indicates that a trend is present in the CPK~AUCss and CPK~$C_{min,ss}$ plots. In both plots, it is evident that higher CPK values are associated with higher values of AUC_{ss} and $C_{min,ss}$.

Figure 7. Observed CPK is plotted vs. Daptomycin. Values are indicated by open circles and a red lowess (local regression smoother) trend line. Top Left: CPK vs. Area Under the Concentration-Time Curve at Steady–state (mcg*hr/mL); Top Right: CPK vs. Area Under the Concentration-Time Curve at Steady–state (mcg*hr/mL), CPK axis is log; Bottom: CPK vs. Area Under the Concentration-Time Curve at Steady–state (mcg*hr/mL), CPK and AUCss axes are log.

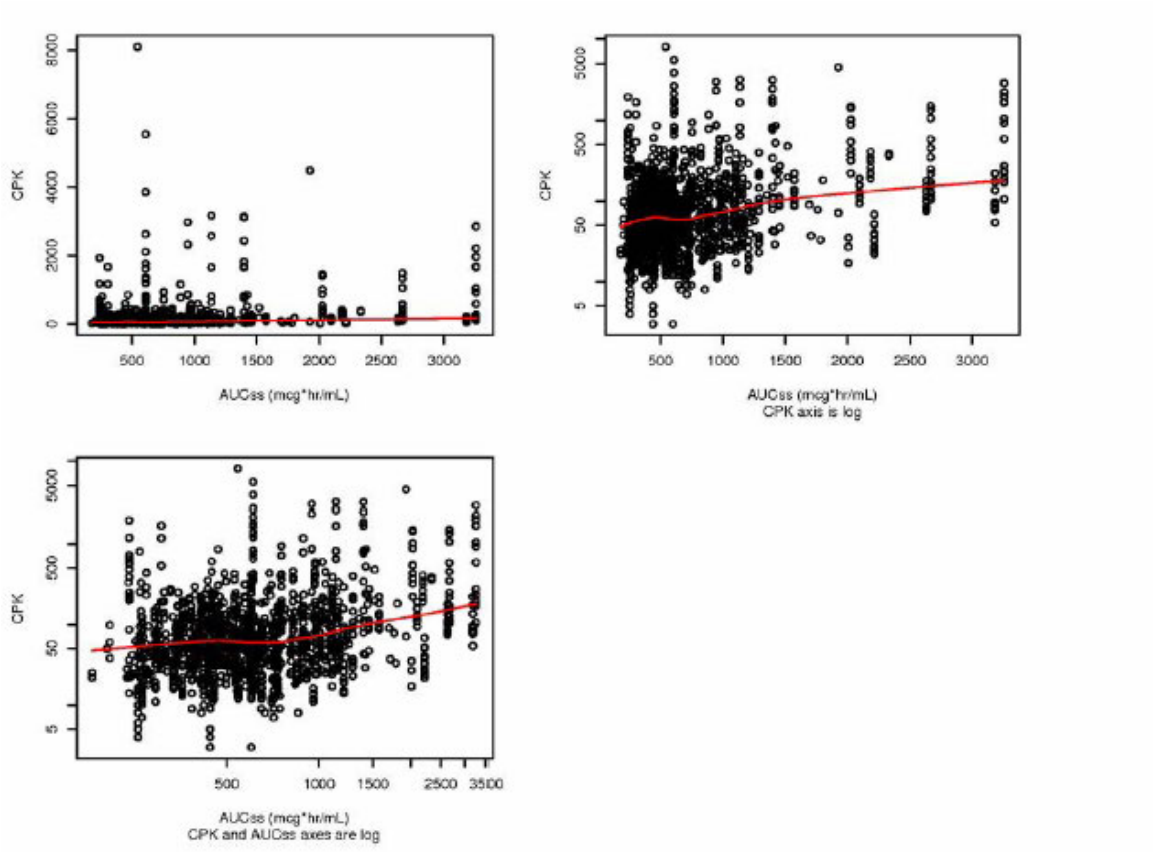
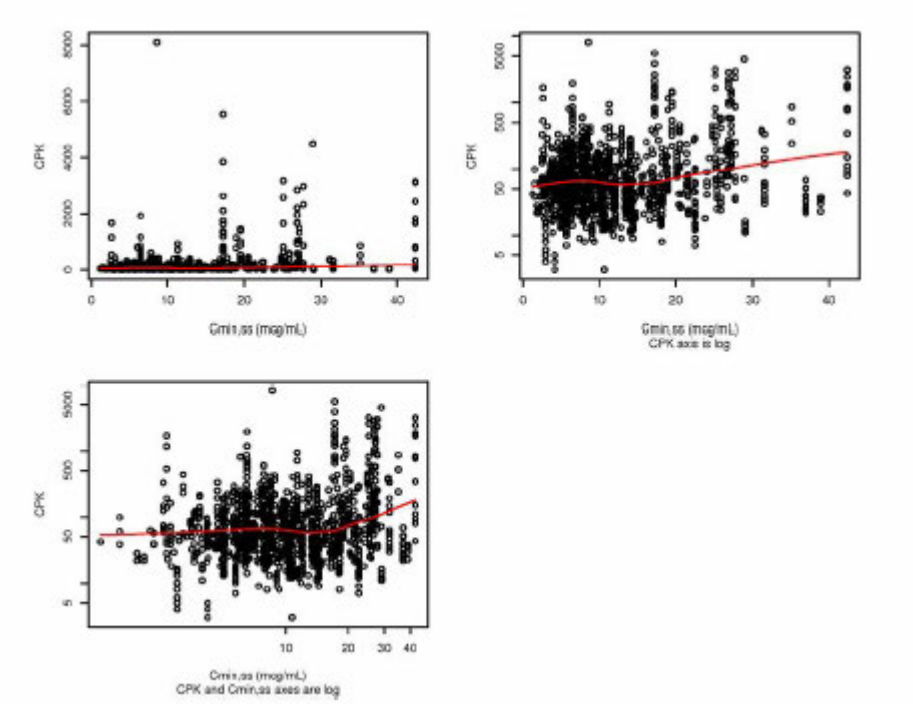


Figure 8. Observed CPK is plotted vs. C_{min},ss (mcg/mL). Values are indicated by open circles and a red lowess (local regression smoother) trend line. Top Left: CPK vs. C_{min},ss (mcg/mL); Top Right: CPK vs. C_{min},ss (mcg/mL), CPK axis is log; Bottom: CPK vs. C_{min},ss (mcg/mL), CPK and C_{min},ss axes are log.



A naïve pool linear regression model was fit to the data using log(CPK) as the response, and AUC_{ss} or C_{min},ss as the predictor. The results of the linear regression are displayed in Figures 9 and 10 and Tables 1 and 2. The use of AUC_{ss} as a predictor resulted in a model with a statistically significant ($p<0.001$) positive slope. This result supported the trend of increasing CPK with increasing AUC_{ss} demonstrated in the graphical evaluation. The results for the use of C_{min},ss as a predictor were similar. The results from the linear regression analysis supported the trend demonstrated in the graphical evaluation. The dotted red lines on each plot represent the 95% confidence interval for the fitted line, which is the average predicted response.

Predicted CPK values for a given AUCss or C_{min},ss based on the linear regression models are shown in Tables 2 and 3. The values in the table for AUCss and C_{min},ss represent the range of observed values in the study for the 2.5th to the 97.5th percentile. Based on the results in this table, mean CPK values that would be expected from some of the higher AUCss and C_{min},ss are less than 2–3x the ULN for CPK. These results are consistent with the previous exploratory exposure–response analysis of daptomycin C_{min} and CPK. However, as can be seen by the regression plots, there is a significant amount of variability both within and between subjects that is not being accounted for by these models.

Figure 9. Log(CPK) is plotted against AUCss. Values are indicated by open circles. The solid black line is the best fit linear regression line and the dotted red lines are the 95% confidence interval for the linear regression line.

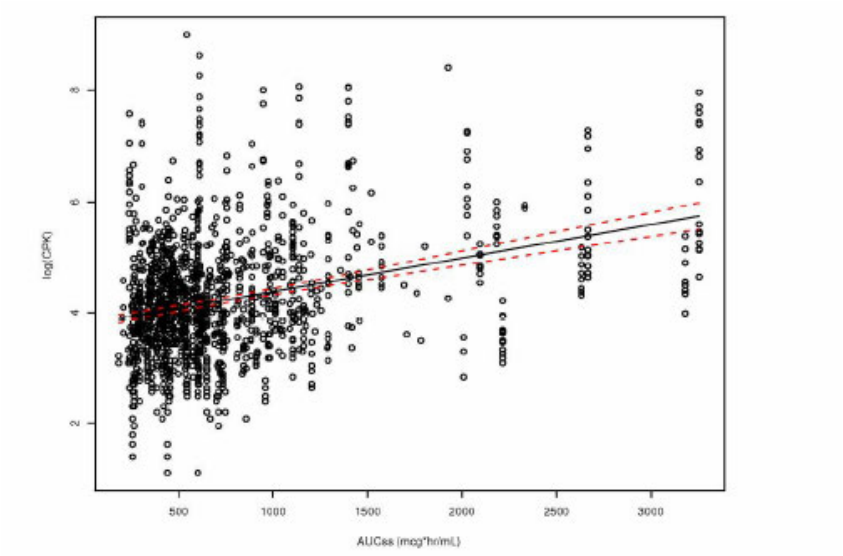
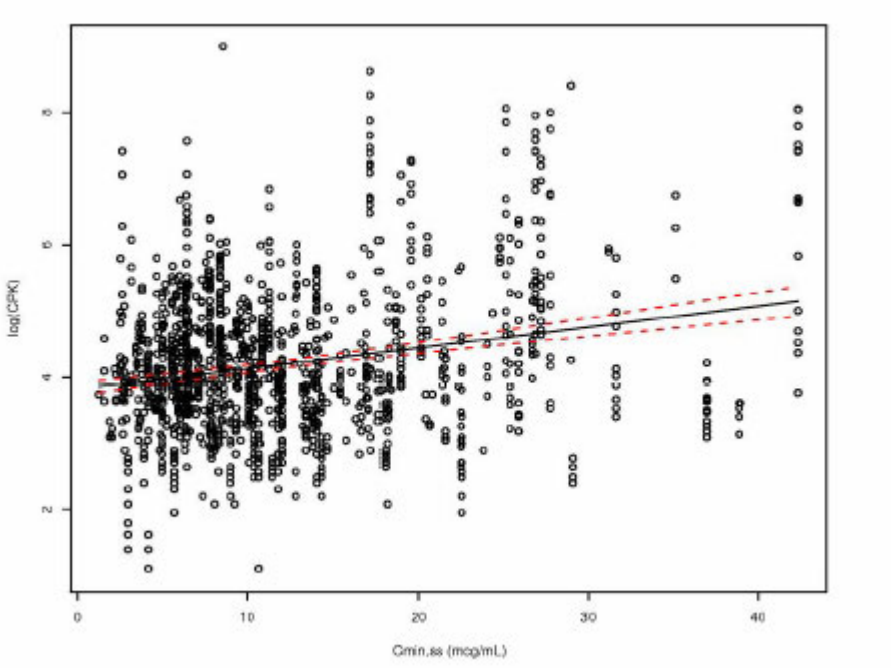


Figure 10. Log(CPK) is plotted against $C_{min,ss}$. Values are indicated by open circles. The solid black line is the best fit linear regression line and the dotted red lines are the 95% confidence interval for the linear regression line.



Note: In the above plots, the Y-axis is labeled as log(CPK). However, it is to be noted that the correct notation should be Ln(CPK), i.e., logarithm to the base e.

Table 2. Linear Regression Results for log(CPK) vs. AUCss. Results for naïve pool linear regression model fit of log(CPK) vs. AUCss.

	Estimate	SE	t-value	Pr(>|t|)
Intercept	3.78	0.04338	87.12	<2e-16
Slope	6.06E-04	4.709E-05	12.87	<2e-16

Residual standard error: 1.024 on 1519 degrees of freedom
Multiple R-Squared: 0.09834
F-statistic: 165.7 on 1 and 1519 DF, p-value: < 2.2e-16

Table 3. Linear Regression Results for log(CPK) vs. $C_{min,ss}$
Results for naïve pool linear regression model fit of log(CPK) vs. $C_{min,ss}$

	Estimate	SE	t-value	Pr(>|t|)
Intercept	3.82	0.0529	72.1	<2e-16
Slope	0.0314	0.00362	8.68	<2e-16

Residual standard error: 1.087 on 1373 degrees of freedom
Multiple R-Squared: 0.05206
F-statistic: 75.4 on 1 and 1373 DF, p-value: < 2.2e-16

B. Pharmacokinetic/Pharmacodynamic (Efficacy) analysis

1. Several efficacy variables were assessed for a relationship with daptomycin PK/PD parameters. Tables 3 and 4 summarize the results for the ITT population for IEAC outcome at EOT and pathogen eradication at EOT, respectively. The EOT time point is preferred for these analyses, as it is less confounded by patients deemed IEAC failures at TOC for reasons not related to daptomycin (e.g., lost to follow-up, received other antibiotics). As shown in Tables 4 and 5, there was no statistical significance between any PK/PD parameter and efficacy

Table 4: Summary of daptomycin PK/PD parameters by IEAC outcome at EOT indicating a lack of statistically significant relationship between PK/PD parameters.

PK/PD Parameter	Success (Mean ± SD)	Failure (Mean ± SD)	P-value[a]
N	73	33	
C_{min} (µg/mL)	9.8 ± 6.57	11.2 ± 7.89	0.340
C_{max} (µg/mL)	108.1 ± 140.38	84.1 ± 41.00	0.337
AUC_{0-24} (µg·hr/mL)	592.6 ± 249.84	616.9 ± 261.12	0.648
C_{max} / Baseline MIC value[b]	375.8 ± 391.70	306.9 ± 160.41	0.334
AUC_{0-24} / Baseline MIC value (hr)[b]	2168.0 ± 1025.33	2229.2 ± 930.49	0.771

a. P-values determined by a t-test.
b. Two patients (b) (6) and (b) (6) did not have their baseline *S. aureus* isolates sent to the Central Lab, and are excluded from this analysis. Daptomycin MIC values were generated by the Central Lab.

Table 5. Summary of daptomycin PK/PD parameters by pathogen eradication at EOT indicating a lack of statistically significant relationship between PK/PD parameters.

PK / PD Parameter	Eradicated (Mean ± SD)	Persisted (Mean ± SD)	P-value[a]
N	88	18	
C_{min} (µg/mL)	10.1 ± 6.39	10.7 ± 9.65	0.730
C_{max} (µg/mL)	103.9 ± 128.22	84.6 ± 54.20	0.532
AUC_{0-24} (µg·hr/mL)	603.8 ± 236.05	582.1 ± 328.54	0.741
C_{max} / Baseline MIC value[b]	364.7 ± 357.97	302.5 ± 205.96	0.479
AUC_{0-24} / Baseline MIC value (hr)[b]	2216.5 ± 980.51	2048.3 ± 1063.90	0.516

a. P-values determined by a t-test.
b. Two patients (b) (6) and (b) (6) did not have their baseline *S. aureus* isolates sent to the Central Lab, and are excluded from this analysis. Daptomycin MIC values were generated by the Central Lab.

2. As shown in Figures 11 and 12, the daptomycin C_{max}/MIC and C_{min}/MIC ratios do not appear to be different between the population of patients with IEAC success and failure.

Figure 11. C_{max}/MIC does not appear to be different between the population with IEAC success and failure.

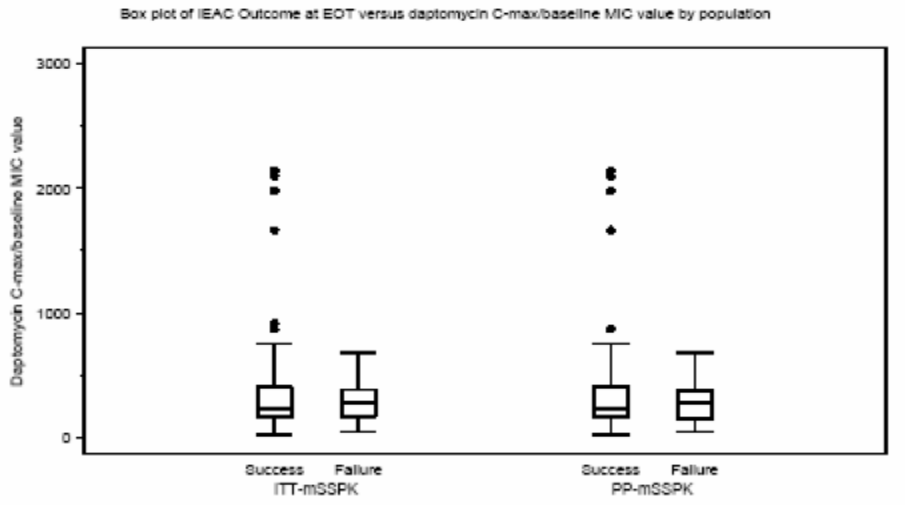
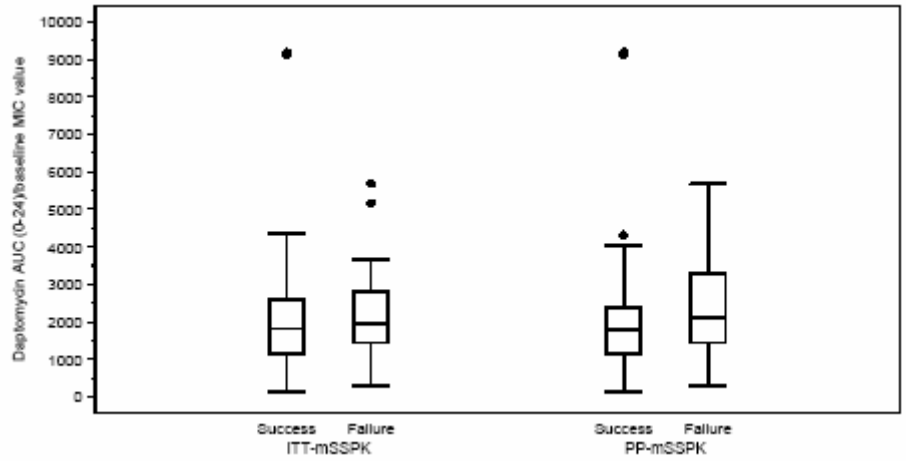


Figure 12. AUC/MIC does not appear to be different between the population with IEAC success and failure.



3. Overall, no correlation was observed between any PK/PD parameter examined and the efficacy variables of IEAC outcome at EOT and pathogen eradication status at EOT.

Reviewer's Comments:

1. The population PK model appears to identify a number of covariates such as body temperature, gender, presence of gram-positive infection, final diagnosis of the patients, etc. However, the proposed package insert provided by the sponsor does not contain any dosage adjustments based on the final model. Thus, it appears that the sponsor has chosen to develop a population PK model merely based on statistical significance and not on physiological plausibility or significance.
2. The sponsor did not evaluate the relationship between the exposure parameters such as C_{max}/MIC, AUC/MIC and C_{min}/MIC and the components of the composite endpoint, namely, clinical success and microbiological success due to the lack of the clinical and microbiological success data. The sponsor concluded a lack of PK/PD relationship for daptomycin based on the comparison of the exposure parameters for the composite endpoint (IEAC success). Please see Reviewer's Analysis for an evaluation of the individual components of the composite endpoint.
3. The sponsor's exposure-toxicity analysis indicated that to establish a relationship between exposure and CPK levels, by including all the CPK levels, the ability to detect the signals of concern (clinically significant elevations of CPK) are lost. It is essential to analyze the data by using cutoffs for CPK levels (> 500 IU/L and >1000 IU/L etc.) and then attempt to establish a relationship between exposure and CPK levels.

Reviewer's analysis

Exposure-effectiveness analysis:

Data

In the overall dataset for daptomycin (N=120), there were 53 patients with clinical success (derived from the IEAC Success data) and 21 clinical failures. Similarly, there were 53 microbiological successes (derived from the IEAC Success data) and 19 microbiological failures (these were true microbiological failures who showed positive culture for *S. aureus* at TOC).There were 108 out of 120 patients in the pivotal study DAP-IE-01-02 who received daptomycin and who participated in the pharmacokinetic assessments. There were 104 out of 120 patients in the pivotal study DAP-IE-01-02 who participated in the pharmacokinetic assessments as well who had baseline MIC values. A total of 94 patients with steady state C_{min}(s) and baseline MIC values were used in the exposure-effectiveness analysis.

Methods

Using the plasma concentrations obtained in these patients, a relationship between C_{min} and effectiveness endpoints such as clinical failure and microbiological failure.

In the exploratory analysis, a trend of increasing effectiveness was seen most predominantly for C_{min}/MIC. Moreover, a potential issue with using C_{max} as the exposure metric was detected. In the pivotal study, blood samples to determine the PK of daptomycin were drawn at six time points (baseline, then on Day 5 within the following sampling windows: pre-dose, 15 - 30 minutes after the end of infusion (EOI), 60 - 90 minutes following EOI, 3 – 5 hours following EOI, and 9 - 12 hours following EOI). The blood sampling schedule in the pivotal study included a sample with a window of 15-30 minutes following the end of infusion. However, with a low distribution half-life of daptomycin (5 minutes), the estimation of C_{max} is prone to large variability. Hence, a decision to use the trough concentrations (C_{min}) was taken and thus, the relationship between the C_{min}/MIC and the effectiveness endpoints was further studied.

For the purpose of studying the exposure-effectiveness relationship, quartiles of C_{min}/MIC were calculated and the relationship between the quartiles of C_{min}/MIC and the effectiveness metrics were studied. Also, a logistic regression in treating C_{min}/MIC as a continuous variable was conducted for each endpoint.

Software

Exposure-effectiveness and exposure-toxicity analyses were performed using SAS System for Windows (Release 8.02 TS Level 02MO) on a Windows XP operating system.

Exposure-toxicity analysis:

Data

In the pivotal study, CPK measurements were made for 120 patients at baseline and at the following time-points: Days 1, 4 and 7, and every other day during treatment to EOT (minimum 3 days/week). CPK values exceeding 4 x ULN while the patient was receiving

study medication were to be monitored daily until the CPK results returned to within the laboratory's normal range or the patient's baseline level and <2 x ULN. PK measurements were made in a total of 108 patients. The combined PK/PD dataset had a total of 94 patients, with steady-state C_{min} and CPK levels.

Methods

Using C_{min} as the exposure metric and CPK as the toxicity metric, the relationship between exposure and toxicity was explored. Specifically, proportion of patients with elevations of CPK ≥500 IU/L and 1000 IU/L were determined for each of the quartiles of C_{min}. Also, the time course of CPK elevations in patients with CPK elevations of ≥1000 IU/L was obtained to see the nature of the CPK elevations and whether the elevations are reversible or not. Also, a logistic regression in treating C_{min} as a continuous variable was conducted for CPK levels ≥ 500 and 1000 IU/L.

RESULTS

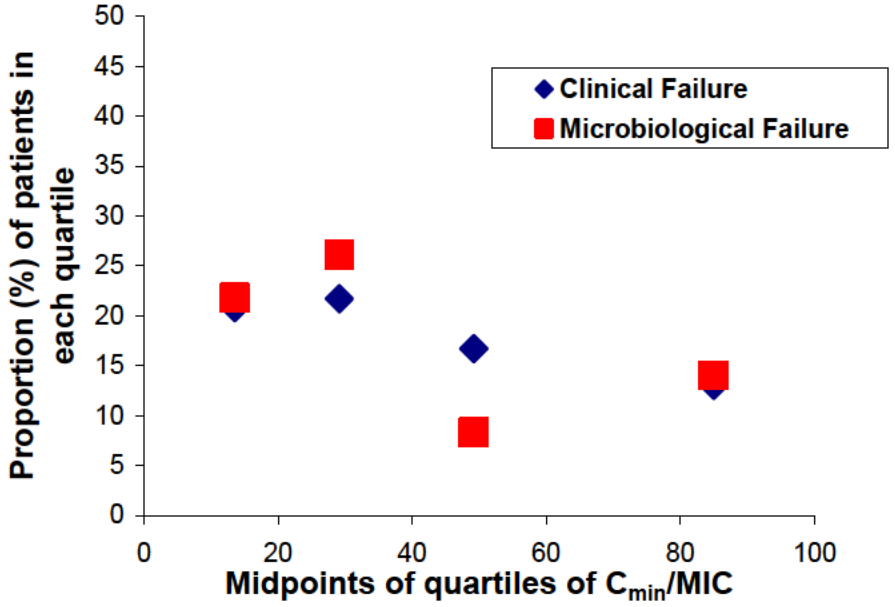
Exposure-effectiveness:

1. The primary effectiveness endpoint was success based on the IEAC outcome at Test-of-Cure (TOC) in the Intent-to-treat (ITT) and Per Protocol (PP) populations pooled across diagnostic strata, and was a composite endpoint based on clinical as well as microbiologic success. Clinical success was evaluated by measures of fever as well as clinical signs and symptoms of infection. Microbiological success was measured by achieving bacterial eradication via negative blood cultures. All exploratory analyses to characterize the exposure-effectiveness relationships were performed using the composite endpoint and its individual components, namely, clinical and microbiological failures.

2. Initially, exploratory analysis was performed to study the relationship between exposure parameters such as C_{max}, AUC and C_{min}, C_{max}/MIC, C_{min}/MIC and AUC/MIC and the effectiveness endpoints such as clinical failures, microbiological failures, persistence of infection and IEAC success. Based on the results of these exploratory analyses, the exposure parameter of C_{min}/MIC was chosen to further characterize the exposure-response relationship.

3. The relationship between C_{min}/MIC and clinical and microbiological failures is shown in Figure 13. As indicated in Figure 13 the proportion of patients with clinical and microbiological failures decreased with higher C_{min}/MIC. The clinical failure rates were about 20% at the first C_{min}/MIC quartile (median 15) and were about 11% at the fourth C_{min}/MIC quartile (median 80). However, the difference was not statistically significant.

Figure 13. Higher exposure results in reduced proportion of clinical and microbiological failures (N=94).



Exposure -toxicity:

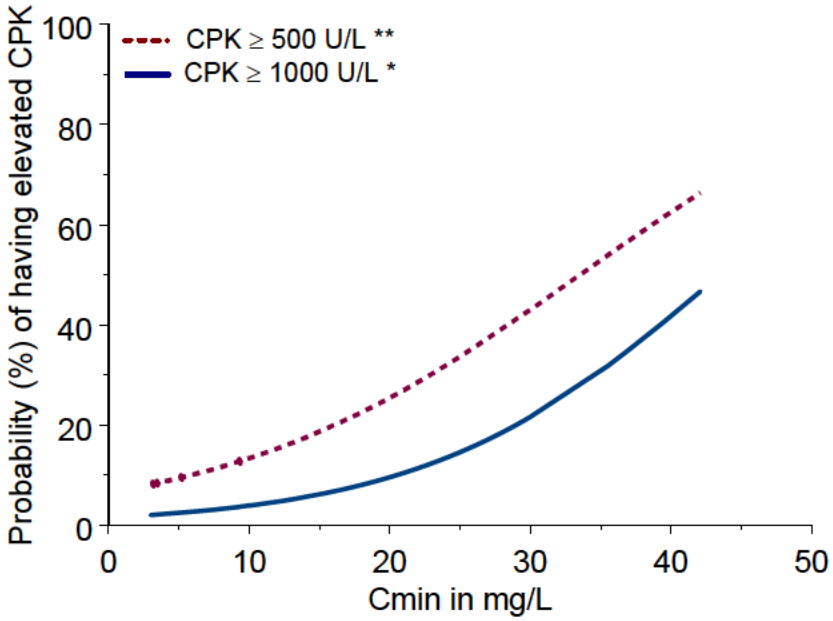
Do the patients with higher C_{min}/MIC have a higher likelihood of elevated CPK levels?

For the purpose of evaluating the relationship between exposure and elevations in CPK levels, quartiles of C_{min} were constructed for patients with CPK levels ≥ 500 IU/L and ≥ 1000 IU/L. In Figure 14, the relationship between the exposure and proportion of patients with elevated CPK levels is shown. As seen in Figure 14, When the C_{min} increases from 5.2 mg/L (5th percentile) to 30 mg/L (95th percentile), the probability of having CPK ≥ 500 IU/L increases from 10% to 43%. Similarly, the probability of having CPK elevations ≥ 1000 IU/L increases from 3% to 22%. The difference was statistically significant, with p=0.0068 for ≥ 500 IU/L and p=0.0125 for ≥ 1000 IU/L.

There was 1 patient in the pivotal study with CPK levels >5000 IU/L. This patient (ID (b) (6) had baseline CPK level of 771 IU/L and reached a maximum of 5548 IU/L during the course of the study on day 10 and daptomycin was discontinued due to the elevation in CPK. The investigator assessed the event as possibly related to daptomycin. This patient was receiving a number of concomitant mediacations including lisinopril, diltiazem, theophylline, albuterol, salmeterol, zafirlukast, fluticasone, prednisone, dexamethasone, insulin, heparin, warfarin, metoclopramide, lansoprazole, potassium, calcium, tramadol, codeine, Vicodin (hydrocodone/acetaminophen), morphine, hydromorphone, fentanyl, midazolam, diphenhydramine, amitriptyline, and acyclovir. Previous antibiotic therapy includes vancomycin, gentamicin, nafcillin, and Zosyn (piperacillin/tazobactam).

There were no patients with >10,000 IU/L CPK elevation in the pivotal study.

Figure 14. Higher exposure results in higher proportion of patients with elevated CPK levels (N=98). Logistic regression was performed using C_{min} as continuous variable and the events as binary variables (yes or no). The lines represent regression fit.



The CPK elevations seen in the patients in the pivotal trial along with this relationship of exposure-CPK elevations indicate that doses higher than 6 mg/kg for the treatment of bacteremia and endocarditis may lead to increased incidence of CPK elevations.

What is the time course of the elevations in CPK in patients with CPK ≥ 1000 IU/L. In Figure 15, the relationship between time after dosing and CPK levels is plotted for the individual patients. In Figure 16, the relationship between time after dosing and CPK levels is plotted for the individual patient with CPK elevations ≥ 1000 IU/L. As seen from the plots, the CPK elevations occur at various time points following administration of daptomycin.

Figure 15. Individual CPK time-course plots for all patients. The red color line indicates the cutoff for CPK elevations >1000 IU/L and the blue color line indicates the cutoff for CPK elevations >500 IU/L. (N=120)

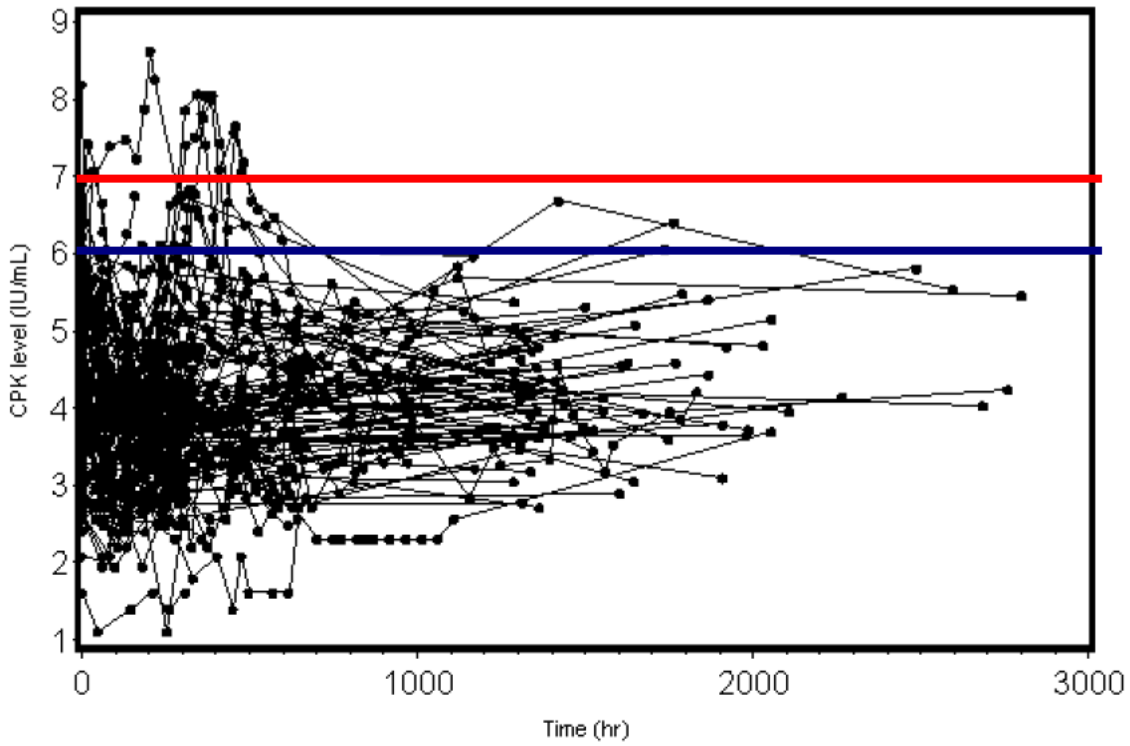
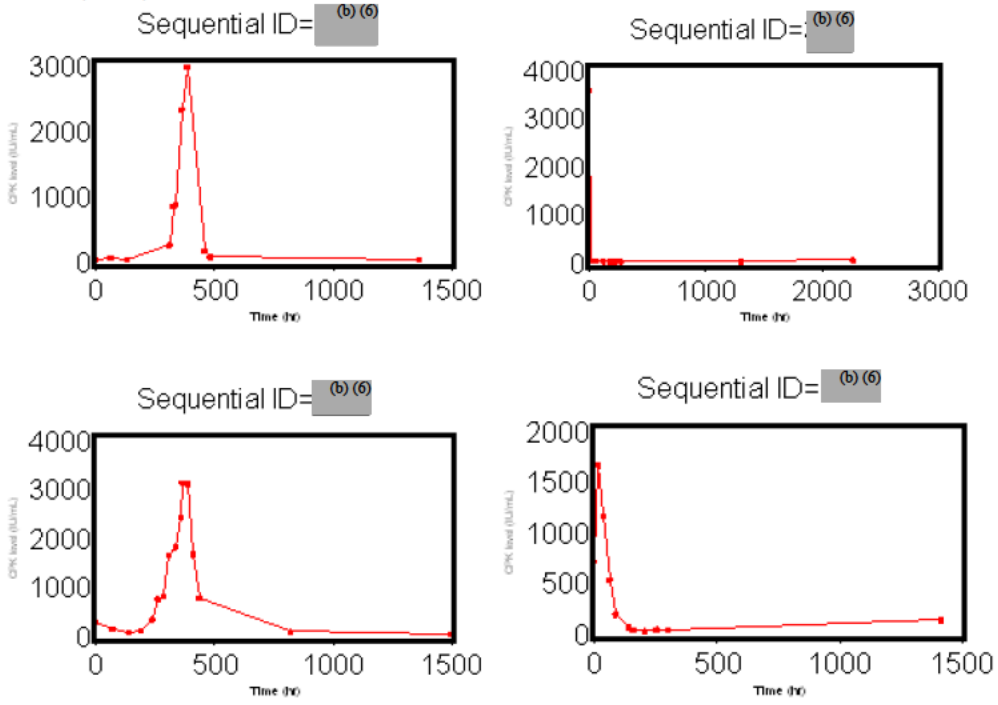


Figure 16. Individual time-course plots for patients with CPK elevations ≥ 1000 IU/L (N=8)



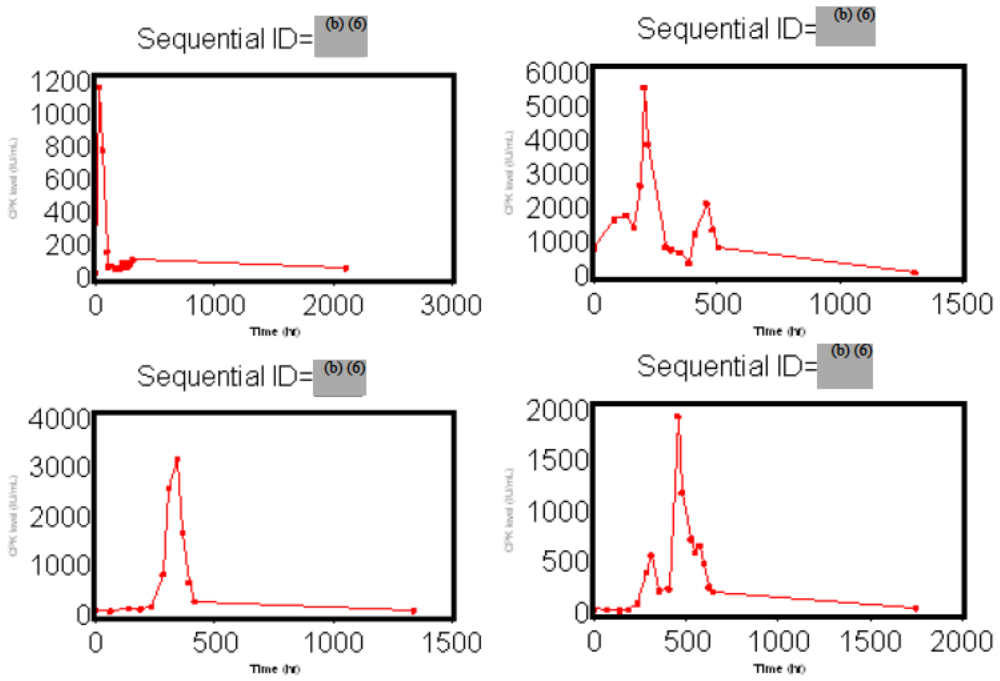
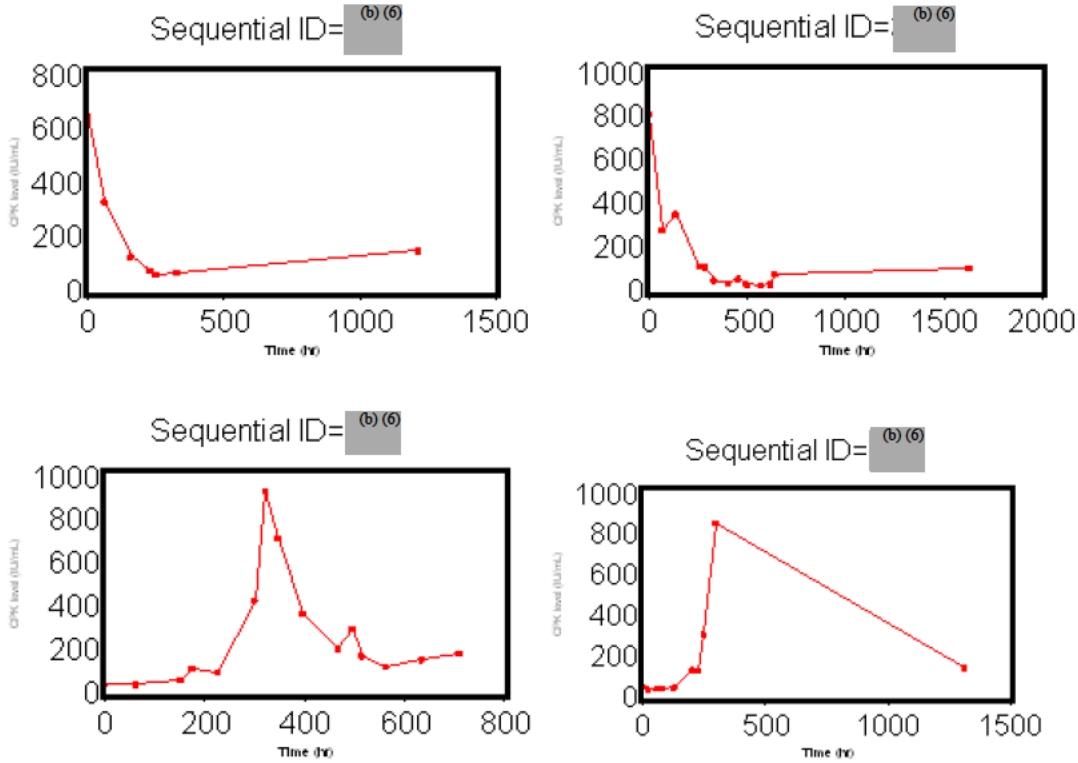
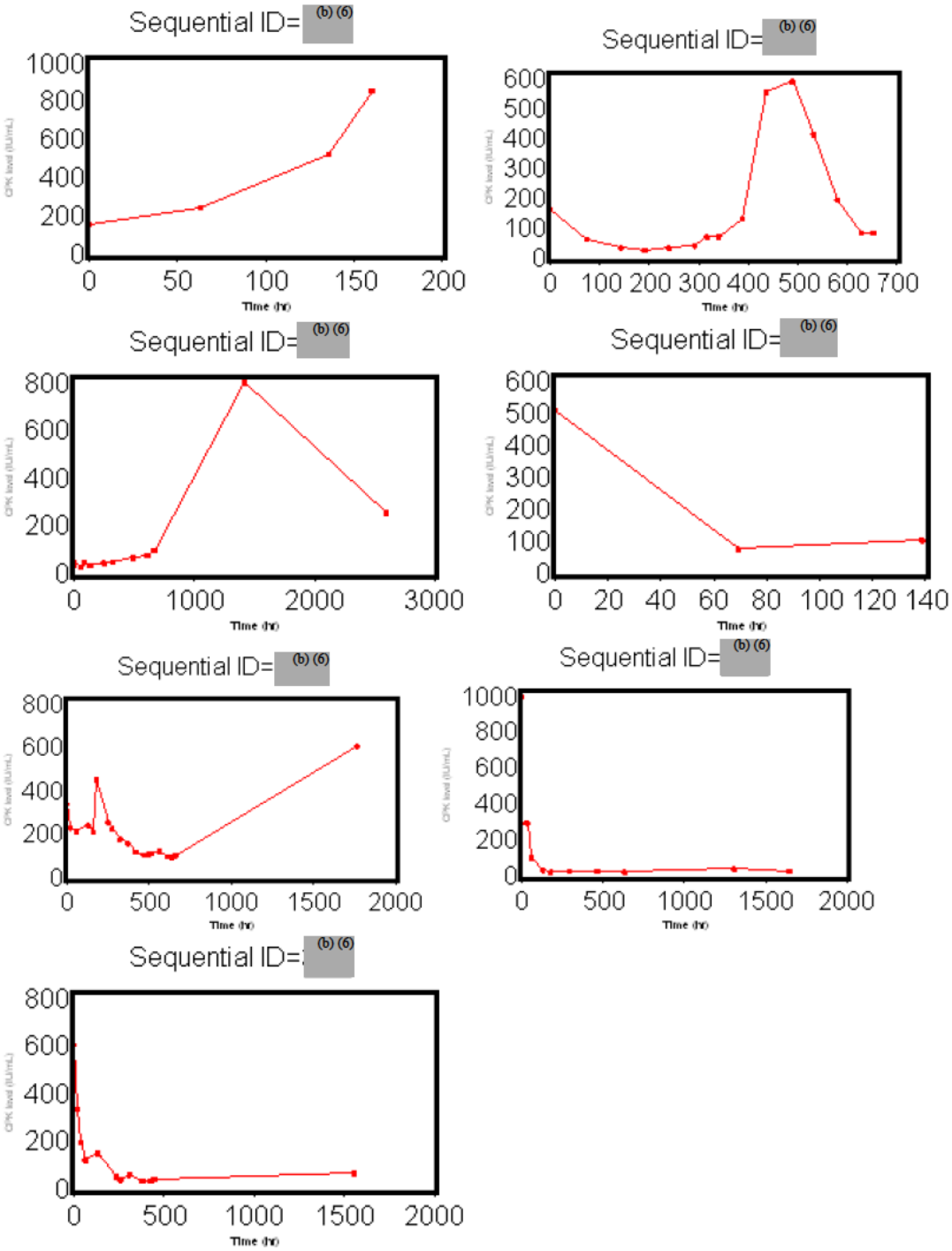


Figure 17. Individual time-course plots for patients with CPK elevations ≥ 500 IU/L but less than 1000 IU/L (N=11)





Are the CPK elevations seen in patients reversible?

As seen in Figures 16 and 17, the CPK elevations in patients appear to return to near baseline for all of the patients. Moreover, there were 5 patients with abnormally high CPK values which subsequently normalized on therapy with daptomycin. There were 6 patients who had normal CPK levels at baseline and then increased during therapy. There were 2 patients who had abnormally high values at baseline and who worsened while receiving daptomycin and in these two patients, daptomycin was discontinued.

CONCLUSIONS:

1. The exposure-effectiveness analysis indicates that with increasing C_{min}/MIC, the proportion of patients with clinical and microbiological failures decreases. However this decrease is not statistically significant.
2. The exposure-toxicity analysis indicates that with increasing C_{min}, the proportion of patients with elevated CPK levels increases in a statistically significant manner.
3. In order to maximize the effectiveness of daptomycin, it may be necessary to increase the dose beyond 6 mg/kg. However, this is accompanied by a risk of increasing CPK levels.
4. Infective endocarditis is a fatal disease if untreated. Based on the discussions with the clinical review team, it is suggested that the risk of the disease (infective endocarditis) is greater than the risk of the adverse event of CPK elevation. The package insert for daptomycin indicates that for the treatment of skin and skin structure related infections, elevations in CPK may be of a greater concern. However, with due consideration to the endocarditis disease, the CPK elevations do not appear to be a major issue
5. Overall, it is essential to weigh the benefit-risk ratio in these patients with a high-mortality disease of endocarditis and the possibility to increase the dose should be explored.

_____ Date: _____
Dakshina Chilukuri, Ph.D.
Pharmacometrics Reviewer

_____ Date: _____
Jogarao Gobburu, Ph.D.
Pharmacometrics Team Leader

4.4. Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	NDA 21-572, SE1-008	**Brand Name**	Cidecin®
OCPB Division (I, II, III)	DPE III	**Generic Name**	Daptomycin
Medical Division	DAIOP, HFD-520	**Drug Class**	Lipopeptide anti-infective
OCPB Reviewer	Charles R. Bonapace, Pharm.D.	**Indication(s)**	*Staphylococcus aureus* bacteremia
OCPB Team Leader	Venkat R. Jarugula, Ph.D.	**Dosage Form**	Sterile lyophilized powder
		Dosing Regimen	6 mg/kg every 24 hrs
Date of Submission	September 22, 2005	**Route of Administration**	Intravenous
Estimated Due Date of OCPB Review	February 1, 2006	**Sponsor**	Cubist Pharmaceuticals, Inc.
PDUFA Due Date	March 24, 2006	**Priority Classification**	Priority review granted
Division Due Date	February 24, 2006		

1.2.1.1.1.1.1.1 Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:	**X**	**1**		DAP-ADT-04-02
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	**X**	**1**		DAP-REN-02-03 (HD only)
hepatic impairment:				
Obesity:				
Cardiac repolarization:				
Tissue penetration:				
PD:				
Phase 2:				
Phase 3:	**X**	**1**		DAP-IE-01-02

PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	**X**	**1**		DAP-IE-01-02-PKPD
Population Analyses -				
Data rich:				
Data sparse:	**X**	**1**		DAP-IE-01-02-POPPK
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Drug metabolism	**X**	**1**		PKR-05-006
Pediatric development plan				
Literature References	**X**	**85**		
Total Number of Studies		**5**		

Filability and QBR comments

	"X" if yes	***1.2.1.1.1.1.1.1 Comments***
Application filable ?	**X**	
Comments sent to firm ?		
QBR questions (key issues to be considered)	1) Do PK/PD data support the 6 mg/kg q24h dosing regimen for *S. aureus* bacteremia? 2) What is the relationship between measures of exposure (i.e., C_{min} and AUC) and CPK elevation? 3) What is the impact of renal impairment on the proposed dosage regimen for *S. aureus* bacteremia? 4) How do the pharmacokinetics of daptomycin in healthy subjects compare to patients with *S. aureus* bacteremia? 5) What is the impact of covariates on the pharmacokinetics of daptomycin?	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-572, HFD-520 (Davi), HFD-880 (Lazor, Selen, Jarugula, Bonapace), HFD-850 (Gobburu), CDR (B. Murphy)

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/s/

Charles Bonapace
3/24/2006 12:17:54 PM
BIOPHARMACEUTICS

Dakshina Chilukuri
3/24/2006 01:39:44 PM
BIOPHARMACEUTICS

Rajnikanth Madabushi
3/24/2006 01:44:42 PM
PHARMACOLOGIST

Jogarao Gobburu
3/24/2006 01:49:02 PM
BIOPHARMACEUTICS

Venkateswar Jarugula
3/24/2006 02:42:00 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021572Orig1s008

OTHER REVIEW(S)

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 8, 2006

TO: Janice Soreth, MD, Director
Division of Anti-Infective and Ophthalmology Products

THROUGH: Jonca Bull, MD, Acting Deputy Director
Office of Drug Safety, HFD-400

Rosemary Johann-Liang, MD, Deputy Director
Division of Drug Risk Evaluation

FROM: ODS Cubicin RMP Review Team

Ron Wassel, Pharm.D., Safety Evaluator, DDRE, Lead Author
Melissa Truffa, R.Ph., Safety Evaluator Team Leader, DDRE
Mary Dempsey, Project Management Officer, ODS-IO
Claudia Karwoski, Pharm.D., Scientific Coordinator, ODS-IO
Cherye Milburn, Regulatory Health Project Manager, OSD-IO

DRUG: Cubicin (daptomycin for injection)

NDA#: 21-572

SPONSOR: Cubist Pharmaceuticals

SUBJECT: Review of Risk Minimization Action Plan (RiskMAP) submitted January 19, 2006

PID #: D050634

EXECUTIVE SUMMARY

This consult follows a request from the Division of Anti-Infective and Ophthalmology Products (DAIOP) for the Office of Drug Safety (ODS) to review and comment on the proposed Risk Minimization Action Plan (RiskMAP for Cubicin (daptomycin for injection).

Cubicin is approved for the treatment of complicated skin and skin structure infections (cSSSI) caused by susceptible strains of Gram-positive microorganisms. Cubist Pharmaceuticals has identified an interaction between daptomycin for injection (Cubicin®) and a particular reagent kit (HemosIL™ RecombiPlasTin) used in some assays of prothrombin time (PT) and International Normalized Ratio (INR) resulting in a concentration–dependent prolongation of the PT and elevation of the INR results. Cubist has submitted a labeling supplement to incorporate this information in the product labeling and has designed a RiskMAP utilizing targeted outreach correspondence (letters) to minimize the potential risks to patients resulting from this drug–laboratory test interaction.

We agree with the sponsor's proposal, but recommend that DAIOP consult the Center for Devices and Radiological Health (CDRH) to coordinate the incorporation of this information in the specific reagent kits that are affected by this interaction and for other possible recommendations to manage this risk. It is important that this information clearly outlines the steps to be taken to evaluate an abnormally high PT/INR result in a patient being treated with daptomycin so as not to assume a falsely elevated laboratory value. Also, the Targeted Outreach Correspondence should include health–system pharmacists as this group often manages patients' drug therapy and monitors laboratory data.

BACKGROUND

Daptomycin for injection (Cubicin®) is a cyclic lipopeptide antibacterial agent with clinical utility in the treatment of infections caused by aerobic Gram–positive bacteria including multiple antibiotic–resistant and –susceptible strains. It was approved in the United States in September 2003 for the treatment of (cSSSI) caused by susceptible strains of Gram–positive microorganisms at a dose of 4 mg/kg per day

The Sponsor has identified an interference between daptomycin and a particular reagent kit (HemosIL™ RecombiPlasTin) used in some assays of PT and INR resulting in a concentration–dependent prolongation of the PT and elevation of the INR results. Cubist has submitted a labeling supplement to incorporate this information in the product labeling and has designed a RiskMAP to minimize the potential risks to patients resulting from this drug–laboratory test interaction.

Current Labeling (as of August 2004)

Under **CLINICAL PHARMACOLOGY, Drug-Drug Interactions**:

> **Warfarin**
> In 16 healthy subjects, concomitant administration of daptomycin 6 mg/kg once daily for 5 days followed by a single oral dose of warfarin (25 mg) had no significant effect on the pharmacokinetics of either drug and did not significantly

alter the INR (International Normalized Ratio). (see **PRECAUTIONS, Drug Interactions**).

Under **PRECAUTIONS, Drug Interactions**:

Warfarin
Concomitant administration of daptomycin (6 mg/kg once every 24 hours for 5 days) and warfarin (25 mg single oral dose) had no significant effect on the pharmacokinetics of either drug and the INR was not significantly altered. As experience with the concomitant administration of daptomycin and warfarin is limited to volunteer studies, anticoagulant activity in patients receiving daptomycin and warfarin should be monitored for the first several days after initiating therapy with Cubicin (see **CLINICAL PHARMACOLOGY, Drug-Drug Interactions**).

The current approved labeling states there are no reported drug-laboratory test interactions.

SAFETY CONCERNS

Cubist Pharmaceuticals has identified an interference between daptomycin for injection (Cubicin®) and a particular reagent kit (HemosIL™ RecombiPlasTin) used in some assays of prothrombin time (PT) and International Normalized Ratio (INR) resulting in a concentration–dependent prolongation of the PT and elevation of the INR results. This false elevation in INR could lead to unnecessarily delaying surgery, inappropriately adjusting anticoagulant therapy, and administering procoagulant treatment (e.g., vitamin K, fresh frozen plasma (FFP)).

AERS was searched on 11/15/2005 and a total of 17 unduplicated cases were retrieved. Of these 17 cases, 14 originated from the [redacted] (b) (6) (b) (6) Following the cluster of reported cases from two geographically distinct institutions, clinical investigation identified the presence of a circulating inhibitor resulting in an interference between daptomycin and a particular reagent kit used in assays of PT and INR.

Out of the 17 cases, only 5 patients were receiving warfarin at the time daptomycin was administered. There were eight transplant patients (two intestinal, four multi-visceral [digestive], one liver, and one either a liver or kidney) and one patient was being worked up for a liver transplant.

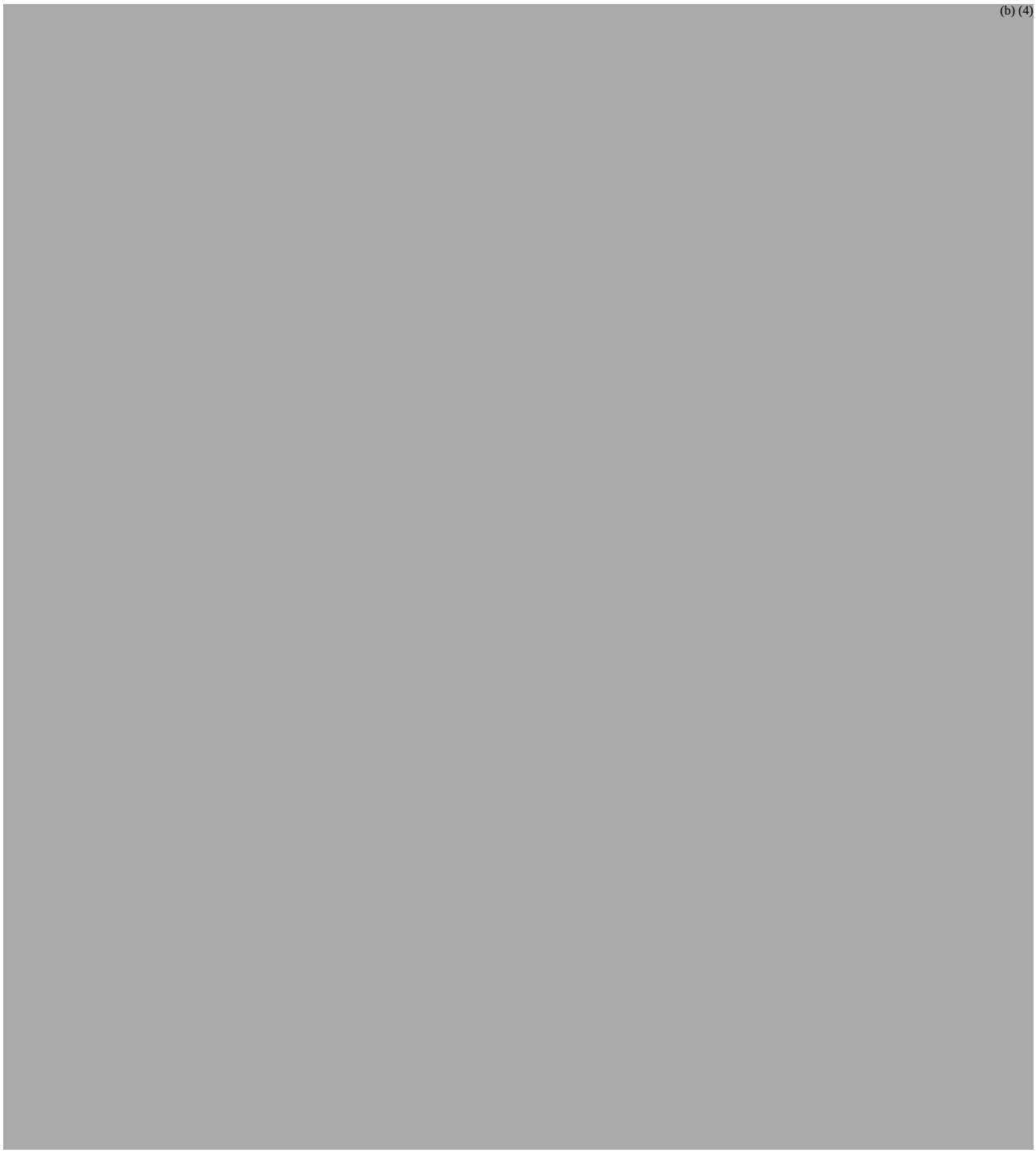
Typically, there was an approximate two–fold increase in the INR during treatment with daptomycin, ranging from 1.6 times to 4.8 times the baseline. There were no bleeding complications. Vitamin K was administered in 11 cases, generally showing no response. There was one case of a delayed surgery, one case of a delayed discharge, and 3 cases in which the patients received FFP. There were five positive dechallenges and five cases

showed a concentration–dependent effect, i.e., the INR was more elevated shortly after a dose of daptomycin was given than an INR taken shortly before a dose.

Following the cluster of reported cases from two geographically distinct institutions, clinical investigation identified the presence of a circulating inhibitor resulting in an interference between daptomycin and a particular reagent kit (HemosIL™ RecombiPlasTin) used in assays of PT and INR.

PROPOSED RISK MINIMIZATION ACTION PLAN

(b) (4)



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/s/

Cherye Milburn
2/8/2006 07:46:55 AM
CSO

Jonca Bull
2/14/2006 05:11:44 PM
MEDICAL OFFICER