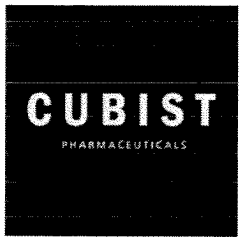

NDA 21-572 / Supplement 008
Cubicin® (daptomycin for injection)

Sponsor's Background Package

for the

Anti-Infective Drugs Advisory Committee Meeting Scheduled for March 6, 2006

January 31, 2006

Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
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EXECUTIVE SUMMARY

Introduction

Infections due to *Staphylococcus aureus,* particularly those due to methicillin-resistant *S. aureus* (MRSA), constitute a growing public health threat because of the increasing incidence of these infections in hospitals and in the community, and the increase in associated morbidity and mortality. Infective endocarditis (IE) is the most serious manifestation of *S. aureus* infection and may occur in patients with structurally normal heart valves after a clinically inapparent bacteremia. Recently reported mortality rates associated with *S. aureus* bacteremia and endocarditis are between 11% and 43% in patients receiving conventional therapy, and no decrease in mortality rates has been seen for more than 15 years. The problem is compounded by the emergence of community-acquired MRSA (CA-MRSA) infections, particularly because these can occur in patients not suspected of having MRSA. Recent cases of patients presenting with rapid-onset sepsis, purpura fulminans, toxic shock, and death have been reported.

Currently, limited options are available for patients with *S. aureus* bacteremia, who often require a prolonged course of intravenous (i.v.) therapy. Standard of care consists of empiric therapy with vancomycin, with switch to antistaphylococcal semisynthetic penicillin (SSP) for methicillin-susceptible *S. aureus* (MSSA) infections. Vancomycin requires twice-daily dosing and plasma concentration monitoring, while SSPs require dosing up to 6 times a day. For both of these agents, there is a risk of missed doses leading to a potential for decreased therapeutic effect, and there are challenges for outpatient therapy. Tolerability issues include a history of penicillin allergy in up to 20% of patients, sodium load associated with i.v. antistaphylococcal penicillins, and infusion-related hypersensitivity reactions with vancomycin. Both agents are potentially nephrotoxic, as is gentamicin, which is recommended at low dose as part of initial combination therapy for *S. aureus* bacteremia.

Because of the increasing prevalence of MRSA and the limitations of the currently available therapeutic options, patients are often treated with vancomycin, an agent that is, at best, weakly bactericidal and often bacteriostatic, particularly against stationary phase bacteria, characteristic of those in biofilm-associated vegetations. The properties of the ideal agent for the treatment of *S. aureus* bacteremia include bactericidal activity in both exponentially growing and stationary phase bacteria, potency against both MRSA and MSSA, proven efficacy in *S. aureus* infections, tolerability for long-term therapy, and suitability for outpatient administration.

There is no current Food and Drug Administration (FDA) guidance document that defines the requirements for a registration study to support an indication of *S. aureus* bacteremia or endocarditis. The last-approved drug for endocarditis was imipenem in 1985 and was based on the experience of 11 patients with endocarditis in 3 studies.

Cubicin® (daptomycin for injection) was approved in the United States in September 2003, in Israel in July 2004, in Argentina in July 2005, and in the European Union in January 2006 for the treatment of complicated skin infections, including infections caused by methicillin-susceptible and methicillin-resistant *S. aureus*. The approved dose is 4 mg/kg administered intravenously once daily.

Daptomycin has many characteristics of the ideal agent for the treatment of systemic *S. aureus* infections, including rapid bactericidal activity; *in vitro* potency against both MRSA and MSSA; proven efficacy in complicated skin infections, including those caused by MRSA; efficacy demonstrated in animal models of *S. aureus* endocarditis at exposures similar to the human 6 mg/kg daily dose; and once-daily dosing. In 2002, Cubist Pharmaceuticals, Inc., in collaboration with experts in *S. aureus* infections and with ongoing dialogue with the FDA, embarked on a landmark study to demonstrate the efficacy and safety of daptomycin in this seriously ill and growing patient population that urgently needs additional therapeutic options.

This Briefing Package summarizes data provided by Cubist to the FDA in a supplemental New Drug Application (sNDA) submitted on September 26, 2005, for the following proposed supplemental indication supported by data from the pivotal Study DAP-IE-01-02.

Proposed Supplemental Indication and Dose

- Daptomycin is indicated for the treatment of patients with *S. aureus* bacteremia, including those with known or suspected endocarditis, caused by methicillin-susceptible and methicillin-resistant strains.
- The proposed daptomycin dose is 6 mg/kg administered as a 30-minute i.v. infusion once per day for a minimum duration of 2 to 6 weeks, depending on the clinical condition.

Major Findings

The pivotal Study DAP-IE-01-02 was designed as an open-label, randomized (1:1), prospective, non-inferiority trial to evaluate monotherapy with daptomycin i.v. (6 mg/kg once daily) compared with conventional combination i.v. therapy (SSP 2 g q4h [nafcillin, oxacillin, cloxacillin, or flucloxacillin] or vancomycin 1 g q12h, both with initial low-dose gentamicin).

- A total of 236 patients were treated in the study, the largest randomized trial conducted to date in patients with bacteremia, with or without endocarditis, due to *S. aureus*.
- The baseline characteristics of the patient population and underlying risk factors were similar to those in several large recently reported epidemiologic studies in patients with *S. aureus* endocarditis. The population was hospitalized and severely ill (75% with systemic inflammatory response syndrome [SIRS]); 38% had infections caused by MRSA. Approximately one-quarter of the patients were 65 years of age or older.

The study met its primary endpoint, success documented 6 weeks following the end of therapy (test-of-cure [TOC] evaluation) determined by an independent Adjudication

Committee expert in the evaluation of *S. aureus* infections who were blinded to study drug therapy.

- Results were robust, meeting the primary efficacy endpoint in the co-primary intent-to-treat (ITT) and per protocol (PP) populations.
  - In the ITT population, 44.2% of daptomycin-treated patients had a successful outcome 6 weeks post-treatment compared with 41.7% of comparator-treated patients.
  - In the PP population, 54.4% of daptomycin-treated patients had a successful outcome 6 weeks post-treatment compared with 53.3% of comparator-treated patients.
- The greatest difference in success rates was observed in patients in the ITT population with infections caused by MRSA, with 44.4% and 31.8% of patients in the daptomycin and comparator groups, respectively, experiencing success 6 weeks post-treatment. Success rates were similar between the treatment groups for patients with infections caused by MSSA (44.6% and 48.6% in the daptomycin and comparator groups, respectively).
- Daptomycin efficacy was demonstrated across pre-specified diagnostic strata:
  - In patients with known or suspected *S. aureus* IE at baseline (Definite or Possible IE according to the Modified Duke Criteria), who accounted for 77% of the population, success rates at 6 weeks post-treatment were 45.6% and 40.7% in the daptomycin and comparator groups, respectively; and
  - In patients retrospectively categorized with *S. aureus* complicated bacteremia or right-sided IE (RIE), who accounted for 66% of the population, success rates at 6 weeks post-treatment were 43.0% and 39.0% in the daptomycin and comparator groups, respectively.

Each study Investigator also determined response to treatment. Investigator-assessed success rates at the 6-week post-treatment time point were similar between the treatment groups:

- In the ITT population, 53.3% of daptomycin-treated patients had a successful outcome 6 weeks post-treatment compared with 50.4% of comparator-treated patients.
- In the PP population, 63.3% of daptomycin-treated patients had a successful outcome 6 weeks post-treatment compared with 58.3% of comparator-treated patients.

Overall success rates were higher at the end-of-therapy (EOT) visit relative to those reported at TOC and were comparable between the treatment groups. The overall lower success rates at TOC were related to reasons other than relapse of *S. aureus* infection, and included receipt of potentially effective non-study antibiotics and lack of documented blood cultures.

- Adjudication Committee-reported success rates at EOT were 61.7% and 60.9% in the daptomycin and comparator groups, respectively.
- Investigator-reported success rates at EOT were 64.2% and 64.3% in the daptomycin and comparator groups, respectively.

- These EOT results were consistent with response rates reported in recent *S. aureus* bacteremia and endocarditis studies (>60%).

The secondary efficacy endpoint of the study, time to clearance of *S. aureus* bacteremia in the ITT population, was not significantly different between the treatment groups.

- Median times to clearance of *S. aureus* bacteremia were 5 and 4 days in the daptomycin and comparator groups, respectively. For patients with infections caused by MSSA, median times to clearance were 4 and 3 days, respectively, and for patients with infections caused by MRSA, 8 and 9 days, respectively.

Patients in the daptomycin group were more likely to be reported by the Adjudication Committee as failures due to persisting/relapsing *S. aureus* infection and/or clinical failure (19.2% in the daptomycin group and 13.0% in the comparator group), and 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).

- Most patients who failed treatment with daptomycin, vancomycin, or SSPs due to persisting or relapsing *S. aureus* infections had deep-seated infections and did not or could not receive necessary surgical intervention, including, for example, valve replacement surgery for left-sided IE (LIE), drainage of abscesses, removal of prosthetic devices, and debridement of septic arthritis.
- No association was found between plasma daptomycin or vancomycin levels and microbiologic failure.
- Six daptomycin patients with persisting or relapsing *S. aureus* had treatment-emergent decreases in susceptibility of *S. aureus* to daptomycin (daptomycin minimum inhibitory concentration [MIC] increase to 2 µg/mL [5 patients] or 4 µg/mL [1 patient]).
- One vancomycin patient with persisting or relapsing *S. aureus* had a treatment-emergent *S. aureus* with a rise in vancomycin MIC to 2 µg/mL isolated on study.
- The most common treatment-limiting adverse events reported as the reason for failure were rash (2 patients), increased creatine phosphokinase (CPK) (2 patients), and gastrointestinal events (2 patients) in the daptomycin group and hypersensitivity-type events (6 patients) and renal toxicities (5 patients) in the comparator group.

There was no difference in overall survival between the treatment groups (p=0.976; log-rank statistic). As of last follow-up, 85% of daptomycin-treated patients and 84% of comparator-treated patients were alive.

Treatment with daptomycin was well tolerated in a seriously ill patient population with *S. aureus* bacteremia and endocarditis, and the safety profile was similar to the known safety profile of daptomycin at 4 mg/kg.

- Similar overall rates of adverse events and serious adverse events were reported in daptomycin and comparator patients.
  - The most commonly reported events in the daptomycin group were gastrointestinal in nature. The incidence of these events was similar or higher in the comparator group.

- Elevations in CPK were observed more often in the daptomycin group, with 3 daptomycin patients discontinuing for elevated CPK.
- More renal toxicity adverse events and abnormal laboratory findings were observed in the comparator group, irrespective of comparator agent, with 5 comparator patients discontinuing for renal toxicity.

Conclusions

Daptomycin administered i.v. at 6 mg/kg once daily is an effective alternative to standard of care in the treatment of patients with *S. aureus* bacteremia with known or suspected endocarditis and has several advantages over current therapy, including:

- rapid bactericidal activity
- activity in stationary phase bacteria, typical of biofilm-associated vegetations
- proven efficacy in *S. aureus* bacteremia with known or suspected endocarditis, including infections caused by MRSA and MSSA
- demonstrated tolerability for long-term therapy
- convenient once-daily administration, allowing for outpatient therapy

In an era of limited therapeutic options and in the face of an emerging public health threat, daptomycin 6 mg/kg once daily provides a much-needed treatment option for patients with *S. aureus* bacteremia with known or suspected endocarditis.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
µg	microgram(s)
µmol	micromole(s)
AE	adverse event
AICD	automatic implantable cardioverter defibrillator
AIDAC	Anti-Infective Drugs Advisory Committee
ANCOVA	analysis of covariance
AUC	area under the concentration x time curve
AUC_{0-24}	AUC from 0 to 24 hours
$AUC_{0-24,ss}$	AUC from 0 to 24 hours at steady-state
AUC_{ss}	AUC at steady state
BAP	bronchial alveolar pneumonia
BMI	body mass index
C	Celsius
$C_{24,ss}$	concentration 24 hours post-dose at steady-state (trough)
CA-MRSA	community-acquired methicillin-resistant *Staphylococcus aureus*
cBAC	complicated bacteremia
CFU	colony-forming units
CI	confidence interval
CL	clearance
CL_{cr}	creatinine clearance
C_{max}	maximum concentration
$C_{max,ss}$	maximum concentration at steady-state
$C_{min,ss}$	minimum concentration at steady-state
CPK	creatine phosphokinase
CRBSI	catheter-related bloodstream infection
cRIE	complicated right-sided infective endocarditis
cSSSI	complicated skin and skin structure infection
CV	coefficient of variation
DBP	diastolic blood pressure
DC	discontinued
dL	deciliter(s)
DNA	deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EOT	end-of-therapy
FDA	Food and Drug Administration

Abbreviation	Definition
g	gram(s)
GISA	glycopeptide-intermediate-susceptible *Staphylococcus aureus*
h	hour(s)
HIV	human immunodeficiency virus
HLT	high level term
HR	heart rate
IDSA	Infectious Disease Society of America
IE	infective endocarditis
IND	Investigational New Drug
ITT	intent-to-treat
i.v.	intravenous
IVDU	intravenous drug user
kg	kilogram(s)
L	liter(s)
LFT	liver function test
LIE	left-sided infective endocarditis
m	meter(s)
MBC	minimum bacteriocidal concentration
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram(s)
MIC	minimum inhibitory concentration
MIC_{50}	minimum inhibitory concentration of daptomycin against 50% of isolates
MIC_{90}	minimum inhibitory concentration of daptomycin against 90% of isolates
MIC_{99}	minimum inhibitory concentration of daptomycin against 99% of isolates
min	minute(s)
mL	milliliter(s)
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-susceptible *Staphylococcus aureus*
n.d.	not done
NEC	not elsewhere classified
NOS	not otherwise specified
PBSA	primary bacteremia due to *Staphylococcus aureus*
PD	pharmacodynamic
PENS	potentially effective non-study (antibiotics)
PK	pharmacokinetic
PP	per protocol
PRSA	persisting/relapsing *Staphylococcus aureus*

Abbreviation	Definition
PS	post-study
Pts	patients
Q	intercompartmental clearance
q8h	every 8 hours
q12h	every 12 hours
q24h	every 24 hours (once daily)
q4h	every 4 hours
RIE	right-sided infective endocarditis
RNA	ribonucleic acid
RR	respiratory rate
SAE	serious adverse event
SBP	systolic blood pressure
s.c.	subcutaneous
SD	standard deviation
SEV	simulated endocardial vegetations
SIRS	systemic inflammatory response syndrome
sNDA	supplemental New Drug Application
SOC	System Organ Class
SSP	antistaphylococcal semisynthetic penicillin
$T_{1/2}$	plasma half-life (terminal)
TEAE	treatment-emergent adverse event
TEE	transesophageal echocardiography
TOC	test-of-cure
U	units
uBAC	uncomplicated bacteremia
ULN	upper limit of normal
uRIE	uncomplicated right-sided infective endocarditis
US	United States
V_1	volume of the central compartment
V_2	volume of the peripheral compartment
VRSA	vancomycin-resistant *Staphylococcus aureus*
V_{ss}	volume of distribution at steady-state

1. INTRODUCTION

1.1 Overview of Daptomycin

Daptomycin is a cyclic lipopeptide that represents the first in a new class of antibiotics derived from the fermentation of a strain of *Streptomyces roseosporus*. It is a concentration-dependent, rapidly bactericidal antibiotic that targets Gram-positive organisms.

The development of daptomycin began with Eli Lilly and Co. (Lilly) in the early 1980s. Lilly discovered the compound in a soil-screening program and began clinical development in the United States (US) in 1985. Lilly conducted several Phase 1 and 2 studies prior to terminating the development of daptomycin after 2 subjects experienced myopathic events (i.e., elevated creatine phosphokinase [CPK] enzymes together with muscle pain and/or weakness) during a Phase 1 trial. At that time, there was less pressing need for new antibiotics effective against resistant organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), and less was known about drug-induced myopathies, including their frequency with other classes of drugs, their reversibility, and the ability of other events to induce CPK elevation, such as surgical procedures and exercise. As antimicrobial resistance increased and other antibacterials became less effective, Cubist re-evaluated the daptomycin non-clinical and clinical data. Cubist licensed daptomycin from Lilly in 1997, re-established the manufacturing process, filed a new Investigational New Drug (IND) application in 1998, and continued the non-clinical and clinical development of daptomycin.

In non-clinical studies and clinical trials, Cubist refined the dose and regimen such that microbicidal efficacy was enhanced and potential toxicity was minimized by once-a-day dosing. In addition, pharmacokinetic/pharmacodynamic modeling predicted that daptomycin should be effective when given once daily. This provided a positive risk/benefit ratio that permitted further clinical development of daptomycin for the treatment of Gram-positive infections, particularly with the rapid emergence of MRSA and its documented role in causing hospital-acquired infections.

Cubist initiated a Phase 3 program to evaluate daptomycin at a dose of 4 mg/kg once daily to treat complicated skin and skin structure infections (cSSSIs) and community-acquired pneumonia. In two pivotal Phase 3 studies, daptomycin demonstrated efficacy similar to standard of care in treating cSSSI. However, in the community-acquired pneumonia studies daptomycin did not meet the protocol-specified non-inferiority criteria against the comparator. It was subsequently shown that daptomycin is inactivated by pulmonary surfactant *in vitro,* thus providing an explanation for the outcome in these studies.(1) Safety data from the Phase 3 studies of daptomycin at 4 mg/kg demonstrated that skeletal muscle signs and symptoms rarely emerged, were fully reversible, and could be monitored effectively by CPK.(2)

Cubicin® (daptomycin for injection) 4 mg/kg once daily was approved in the US in September 2003, in Israel in July 2004, in Argentina in July 2005, and in the European Union in January 2006 for the treatment of complicated skin infections caused by susceptible strains

of Gram-positive organisms, including methicillin-susceptible and methicillin-resistant *S. aureus*.

1.2 Unmet Medical Need in *Staphylococcus aureus* Bacteremia and Endocarditis

Infections due to *S. aureus*, particularly those due to MRSA, comprise a growing public health threat because of the increasing incidence of these infections in hospitals and in the community, and due to an increase in the associated morbidity and mortality.(3-14) As a consequence of improved medical and surgical therapies for common diseases such as coronary artery disease and the aging of the "baby boom" generation, the population at risk for *S. aureus* also is growing.(15) Both nosocomial and community-acquired MRSA (CA-MRSA) infections are increasing in incidence.(3-5, 16) Kuehnert *et al.* estimated that a total of 125,969 hospitalizations for MRSA infection occurred from 1999 to 2000.(17) Moreover, many CA-MRSA strains appear to be of clonal origin and are of particularly high infectivity and virulence (7), demonstrating the convergence of resistance and virulence in *S. aureus*.(8)

Clinically, *S. aureus* bacteremia and endocarditis result in unusually high morbidity and mortality.(9, 10, 13, 18-23) Along with bacteremia and endocarditis due to *S. aureus*, recent cases of CA-MRSA presenting with rapid onset sepsis, purpura fulminans, toxic shock, and death have been reported, as have severe soft tissue infections requiring aggressive debridement and antibiotic therapy.(24-27)

S. aureus is the most clinically significant pathogen causing bacteremia in the US. In contrast to coagulase negative staphylococci, a single positive blood culture for *S. aureus* is considered a true pathogen that requires aggressive medical and surgical therapy.(28) Mortality rates between 11% and 43% have been recently reported, and no decrease in mortality has been seen for more than 15 years.(19, 29, 30)

Current antimicrobial therapeutic options for *S. aureus* bacteremia and endocarditis are limited. Clinicians must initiate early appropriate therapy in order to avoid complications and poor outcomes (18, 29, 31-33) and must make empiric decisions based on the local prevalence of MRSA. In addition, the allergy history of each patient, the need for long-term intravenous therapy, and the need to receive some of this therapy in the outpatient setting further limit current choices. Therapy with standard antistaphylococcal antibiotics carries with it the need for frequent dosing and the associated risk of missed doses with antistaphylococcal semisynthetic penicillins (SSPs), the tolerability issues associated with the sodium load of SSPs, and the need to follow plasma vancomycin levels, which also leads to a risk of delayed or missed doses.

Because of the growing problem with methicillin resistance, the choices for initial therapy have been essentially limited to linezolid, dalfopristin-quinupristin, and vancomycin. Linezolid, because of its lack of bactericidal activity and its bone marrow toxicity with long-term administration, is not viewed as suitable for *S. aureus* bacteremia, particularly if there is a possibility of associated endocarditis.(34) Likewise, dalfopristin-quinupristin, which has been FDA-approved for methicillin-susceptible *S. aureus* (MSSA) cSSSI but not MRSA cSSSI, requires central venous catheter administration and can be associated with severe

arthralgias and myalgias, leading to drug discontinuation, as well as significant interference with the cytochrome P-450 3A4 enzyme system. For these reasons, many clinicians use vancomycin, with or without other antibiotics, as the preferred initial therapy for serious infections suspected or proven to be due to *S. aureus*. Unfortunately, vancomycin often is bacteriostatic (and, at best, weakly bactericidal) and has been associated with suboptimal outcomes when used to treat *S. aureus* bacteremia or endocarditis (29, 31, 32) and has been recently associated with intermediate (35) and high-level resistance (36), as well as tolerance to its activity.(37)

Early and aggressive adjunctive non-medical therapy in many patients also is vital to success in the treatment of *S. aureus* infections. Failure of therapy occurs with delayed surgery, inadequate debridement, and/or failure to remove foreign bodies.

These data emphasize the clinical need for new, effective agents for the treatment of *S. aureus* bacteremia and infective endocarditis (IE). Indeed, following approval for serious skin infections, clinicians have used daptomycin "off-label" to treat *S. aureus* bacteremia. Recent review of treatment use registry data from Cubist Medical Affairs shows that approximately 25% of daptomycin use is for bacteremia with or without IE, of which approximately 50% is at the 4 mg/kg daily dose rather than the 6 mg/kg daily dose used in the pivotal *S. aureus* bacteremia and IE study.(38) This demonstrates physician need for additional treatment options in patients with *S. aureus* bacteremia and IE and underscores the importance of providing appropriate treatment guidelines for use in these patients.

There is, thus, a great clinical need for new, effective agents for the treatment of serious systemic infections caused by *S. aureus*.

1.3 Scientific Rationale for the Use of Daptomycin in the Treatment of Endocarditis

The mechanism of action of daptomycin is unique. Daptomycin binds preferentially to Gram-positive bacterial membranes; in the presence of physiological calcium, daptomycin inserts into the membrane and causes a rapid depolarization of membrane potential, which results in inhibition of protein, DNA, and RNA synthesis, and, consequently, bacterial cell death. *In vitro,* daptomycin is rapidly bactericidal and its activity is concentration-dependent.(39-41)

1.3.1 In Vitro Potency

Daptomycin is active *in vitro* against most clinically relevant Gram-positive bacteria, including antibiotic-resistant pathogens for which there are very limited therapeutic alternatives, e.g., methicillin-resistant staphylococci, vancomycin-resistant *S. aureus* (VRSA), and most glycopeptide-intermediate-susceptible *S. aureus* (GISA).

In surveys of large numbers of clinical isolates, the minimum inhibitory concentration of daptomycin against 90% of isolates (MIC_{90}) is 0.5 µg/mL for staphylococci and most streptococci.(39) The results from 2002, 2003, and 2004 surveillance studies of greater than 11,000 *S. aureus* isolates from more than 270 sites in North America and Europe support previous surveillance studies and demonstrate daptomycin activity *in vitro* against oxacillin-

susceptible and oxacillin-resistant *S. aureus* (Table 1). Daptomycin was active against 99.9% of isolates, with minimum inhibitory concentration (MIC) values of ≤1 µg/mL and a normal distribution range up to 2 µg/mL. The activity of daptomycin against *S. aureus* was similar in North America and Europe. Additionally, daptomycin potency was demonstrated against multidrug-resistant *S. aureus* strains and genetically characterized CA-MRSA, with a daptomycin MIC_{90} ≤0.5 µg/mL.(40)

Table 1: Daptomycin MIC Value Distribution against *Staphylococcus aureus*

Study Group Study Year	N	MIC Range (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
Development studies[a]				
1998-2003	5,248	≤ 0.12 – 2	0.12 – 1.0	0.25 – 1
Multisite surveillance[b]				
1999	547	≤ 0.12 – 2	0.25	0.5
2000-2001	2,240	≤ 0.12 – 1	0.25	0.25 – 0.5
2002	2,623	≤ 0.12 – 2	0.25	0.5
2003	4,898	≤ 0.12 – 2	0.25 – 0.5	0.25 – 0.5
2004	5,260	≤ 0.12 – 2	0.25 – 0.5	0.5
Total	20,816	≤ 0.12 – 2	0.12 – 1.0	0.25 – 1

Note: MIC_{50} and MIC_{90} = minimum inhibitory concentration of daptomycin against 50% and 90% of isolates, respectively.

a Data from multiple studies (>128 sites) in North America and Europe.

b Multisite surveillance studies include 10 separate studies representing 287 study sites in North America, Europe, and Latin America.

Daptomycin exhibits a concentration-dependent post-antibiotic effect of up to 6 hours for Gram-positive cocci.(41)

1.3.2 Resistance Potential

The most productive method of selecting bacteria less susceptible to daptomycin is by serial passage under conditions of sub-inhibitory concentrations of antibiotic.(42) Under such circumstances, 4-fold to 8-fold increases in MIC occur as readily with vancomycin as with daptomycin and require 25 to 30 serial passages. This is in contrast to some other antibiotics, such as rifampin, which can select for high-level resistance by a single mutation at high frequency (1×10^{-7}) after single exposures.(43)

1.3.3 Daptomycin Efficacy in Animal Models of Bacteremia and Endocarditis and Cardiac Valve Vegetations

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.(44)

Daptomycin has been shown to be effective against clinical isolates in several animal models of bacteremia and endocarditis. Before Study DAP-IE-01-02 was initiated, 4 published reports examined the effect of daptomycin in animal models of *S. aureus* endocarditis.(45-48) In each of these studies, daptomycin was at least comparable to standard therapy (i.e.,

SSPs or vancomycin) and, in some instances, superior in reducing vegetation density and increasing survival. The efficacy of daptomycin was also demonstrated in several *in vivo* experimental models of endocarditis with other Gram-positive pathogens.(49-54)

A rat model of endocarditis demonstrated that daptomycin at a dose that produced exposures (maximum concentration [C_{max}] and area under the concentration x time curve [AUC]) consistent with ≤6 mg/kg/day in humans produced significant bactericidal activity against *S. aureus*.(47) After Study DAP-IE-01-02 was initiated, 2 additional models of *S. aureus* endocarditis in rabbits also demonstrated a high degree of efficacy, with daptomycin exposures consistent with that produced by a daily dose of ≤6 mg/kg/day in humans (Table 2). Moreover, the serum concentrations produced by the 6 mg/kg human equivalent dose were consistently greater than the minimum inhibitory concentration of daptomycin against 99% of isolates (MIC_{99}) of *S. aureus,* including MRSA.

Table 2: Efficacy of Daptomycin and Vancomycin in the Treatment of MRSA and GISA Endocarditis in Rabbits Dosed Using Infusion Pumps to Simulate Clinical Dosages

Group	No. Surviving at Day 3/total	No. Sterile Vegetations/Total	Log_{10} Mean ± SD CFU/g Vegetation
GISA			
Saline	-/-	0/17 (0%)	9.1 ± 0.9
Vancomycin	20/23 (87%)	4/20 (20%)	6.0 ± 2.4
Daptomycin	19/19 (100%)	12/19 (63%)[a]	4.8 ± 3.5
MRSA			
Saline	-/-	0/20 (0%)	8.9 ± 0.6
Vancomycin	20/20 (100%)	7/20 (35%)	4.4 ± 2.6
Daptomycin	18/19 (95%)	13/18 (72%)[a]	3.3 ± 2.3

Reference: Garcia de la Maria 2005 (55).

a Daptomycin was significantly more effective than vancomycin in sterilizing vegetations.

Additional studies were undertaken to assess the efficacy of daptomycin in larger vegetations, similar to those seen in human endocarditis. The efficacy of daptomycin was studied in an *S. aureus* fibrin clot model simulating endocarditis vegetations in rats.(56) 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 3 to 6 days, and the clots were harvested, homogenized, and evaluated for colony-forming units (CFU).

Daptomycin dosed at 33 mg/kg twice daily (66 mg/kg/day) for 6 days resulted in a significant reduction (5 log_{10}) of bacterial counts.(57) Vancomycin dosed at 100 mg/kg twice daily (200 mg/kg/day) for 6 days produced a 2 log_{10} reduction in MRSA counts. This model demonstrates penetration and bactericidal activity of daptomycin against *S. aureus* in fibrin clots *in vivo* (Table 3).

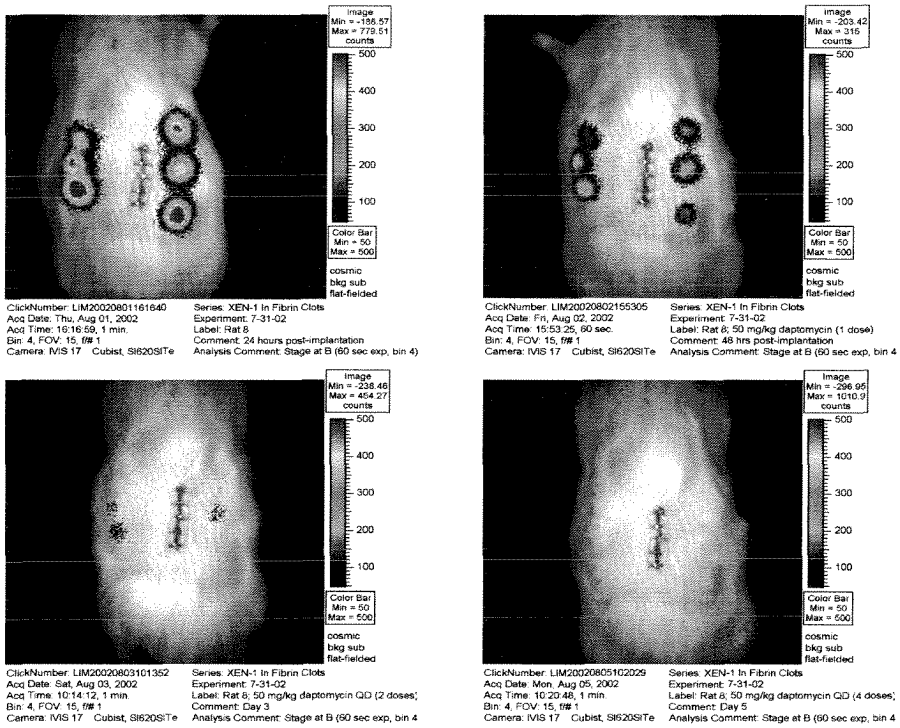
Table 3: Efficacy of Daptomycin in a Rat Model of *S. aureus* Infection of Fibrin Clots

Treatment Group Dose	Log_{10} CFU of MRSA
Saline	
Negative control	8.73
Daptomycin	
10 mg/kg q12h	7.42
22 mg/kg q12h	4.41
33 mg/kg q12h	3.81
Vancomycin	
100 mg/kg q12h	6.74

Reference: Mortin 2005 (57)

Figure 1 depicts the rapid bactericidal activity of daptomycin when bioluminescent MRSA bacteria are used in the subcutaneously 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 5 days of dosing no bioluminescence is apparent (panel D).

Figure 1: Daptomycin Efficacy Against Bioluminescent Bacteria in Implanted MRSA-Containing Fibrin Clots



Reference: Mortin 2003 (58)

Note: (A) [top left] 24 h post infection, pre-daptomycin dose; (B) [top right] 48 h post infection, 1 daptomycin dose of 50 mg/kg s.c.; (C) [bottom left] 72 h post infection, 2 daptomycin doses of 50 mg/kg s.c.; (D) [bottom right] 120 h post infection, 4 daptomycin doses of 50 mg/kg s.c.

Daptomycin has demonstrated efficacy in *in vitro* pharmacodynamic models of endocarditis that utilized infusion pumps to simulate clinical pharmacokinetic parameters against simulated endocardial vegetations (SEV) in biochambers. In this model, daptomycin demonstrated efficacy against a variety of drug-resistant *S. aureus* strains, including MRSA, GISA, and VRSA (Table 4).(59-64) 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 24 hours. In addition, under these simulated conditions throughout the 72-hour time course no daptomycin resistance developed. Daptomycin was the only antibacterial to produce bactericidal activity against stationary phase *S. aureus* in high-inoculum (1 x 10^9) SEV models (63), whereas gentamicin, linezolid, and vancomycin failed.

Table 4: Summary of Bactericidal Activity of Daptomycin against a Variety of *S. aureus* Isolates in Simulated Endocarditis Vegetations

Strains	MIC Value (µg/mL)	MBC Value (µg/mL)	Simulated Human Dosing	Log_{10} CFU/g reduction at 72 h	Reference
MRSA	0.25	0.25	6 mg/kg/day	6.73	(60)
MRSA	0.12	0.25	6 mg/kg/day	>6	(61)
MRSA	0.25	0.25	10 mg/kg/day	8.14	(60)
GISA	0.5	1	6 mg/kg/day	8.05	(60)
GISA	0.5	1	10 mg/kg/day	8.57	(60)
VRSA	0.25	0.5	6 mg/kg/day	>6	(61)

The results from this SEV model demonstrate that daptomycin can penetrate into vegetations and retain its bactericidal activity, suggesting the potential for effective treatment of endocarditis. Along with the *in vivo* efficacy in animal models of endocarditis, these data provided support for pursuing clinical studies of endocarditis with 6 mg/kg daily daptomycin.

1.3.4 Efficacy in Other Animal Models Relevant to Endocarditis

Both hematogenous pneumonia and meningitis have been reported as complications of serious bloodstream infections with *S. aureus*.

Hematogenous pneumonia was of potential concern because daptomycin did not meet the protocol-specified non-inferiority criteria against ceftriaxone for the treatment of hospitalized community-acquired pneumonia.(1, 65) It was subsequently shown that daptomycin is inactivated by pulmonary surfactant *in vitro*. Because of these findings, Cubist evaluated the ability of daptomycin to treat hematogenous pneumonia in an animal model. Mice or rats were inoculated intravenously with 2 to 5 x 10^7 *S. aureus* cells microencapsulated in agarose beads (50 µm in diameter). The beads lodged into the lung capillaries, causing a hematogenous embolic pulmonary infection with significant lung pathology. Daptomycin, at doses providing exposure similar to that seen in humans treated with 6 mg/kg daily, was effective in promoting survival, in clearing bacteremia, and in lowering the bacterial burden in the lungs of animals challenged with either MRSA or MSSA.

Cottagnoud and colleagues evaluated the efficacy of daptomycin against experimental *S. aureus* meningitis using a rabbit model and found that daptomycin was superior to vancomycin in the treatment of MSSA meningitis.(66)

1.4 Overview of Regulatory Guidance

1.4.1 Available Guidance for the Development of Antibiotics for the Treatment of Endocarditis

The only FDA guidance that addresses the requirements for endocarditis labeling is the 1992 FDA "Guidance for Industry: Clinical Development and Labeling of Anti-Infective Drug Products" (also called the "Points to Consider" document).(67) This document outlines the requirements for the study of IE. It suggests 1 open-label trial of 50 patients to establish a predetermined overall clinical and microbiologic success rate, and suggests that patients must be both clinically and microbiologically evaluable. The guidance also suggests that the trial should include at least 2 investigators from different geographic areas. In addition, adequate human and/or animal pharmacokinetic/pharmacodynamic (PK/PD) data should be available to support the efficacy.

Following publication of the 1992 Guidance document, questions regarding the appropriateness of "bacteremia" indications as they related to infections at specific body sites were raised. This topic was further discussed at subsequent Anti-Infective Drugs Advisory Committee (AIDAC) meetings in 1993 and 1998.(68, 69)

At the AIDAC meeting of October 16, 1998, members concluded that "bacteremia" secondary to an identified site of infection should not be considered as a separate indication, but should be retained within the context of site-specific indications (pages 157, 160, 182 of the transcript).(69) Primary bacteremia due to *S. aureus* (PBSA), including catheter-related bloodstream infections (CRBSI), was identified as a potential area of interest for future study (pages 189, 193, 236 from transcript), and the Committee stated that a single positive blood culture for *S. aureus* was sufficient for the diagnosis of PBSA (page 247). This led to the development in 1999 of a preliminary guidance document for antimicrobial drug development for the treatment of CRBSI.(70)

At a joint Infectious Disease Society of America (IDSA)-FDA-Industry Workshop on April 15-16, 2004, academic investigators, FDA representatives, and drug sponsor representatives discussed the challenges of studying CRBSI and PBSA.(71, 72) The merits of studying the indication of PBSA were contrasted with those of studying CRBSI.

Further discussion of PBSA as an indication occurred at the AIDAC meeting of October 14, 2004.(73) The consensus of the panel was that PBSA is an important condition to study, particularly due to its associated morbidity and mortality, and because of growing antibiotic resistance coupled with the declining efficacy of present therapeutic options. The imperative to initiate antimicrobial therapy on an emergent basis in patients with *S. aureus* bacteremia (a condition that untreated would generate mortality rates of ≥80%), combined with the difficulty of determining the exact diagnosis on presentation (e.g., complicated infection and/or IE, presence of MRSA), was recognized as a clear challenge to optimization of study

design. Irrespective of these issues, it was considered that a trial including "all-comers" presenting with *S. aureus* bacteremia (with the exception of the cases presenting with obvious left-sided IE [LIE], which represents a much sicker subgroup) could support an indication for PBSA provided that a sufficient patient population with IE and complicated bacteremia were studied (pages 304-321 of the transcript).(73)

Due to the lack of specific guidance documents on the evaluation of patients with *S. aureus* bacteremia with known or suspected IE, Cubist sought guidance from the FDA during both the development phase and the conduct phase of the pivotal study.

1.4.2 Regulatory Guidance on Study Design

Study DAP-IE-01-02 was the largest randomized trial conducted to date designed to evaluate the treatment of patients with known or suspected endocarditis caused by methicillin-susceptible and methicillin-resistant *S. aureus*. The clinical data in support of the proposed expanded indication are derived primarily from this pivotal Phase 3 study that was conducted in 236 patients with *S. aureus* bacteremia and endocarditis at the proposed daptomycin dose of 6 mg/kg q24h.

The initial version of the DAP-IE-01-02 study protocol was submitted to FDA on November 9, 2001. Early discussions with FDA 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 Safety Monitoring Board (DSMB) to assure patient safety. FDA allowed the trial to proceed but required that data from the first 30 patients be reviewed by the DSMB to assure that patients would not be placed at undue risk if daptomycin failed to perform adequately (meeting date April 18, 2002). In addition, it was recommended that patients with a high likelihood of LIE be initially excluded from the trial until after the DSMB reviewed data from the first 30 patients. The DSMB was to perform a qualitative review of safety and efficacy data (as they related to safety); i.e., no interim statistical analyses of efficacy data were conducted. Following this review, FDA agreed that Cubist could expand the study to evaluate daptomycin in patients with LIE (meeting date February 19, 2004).

The protocol was amended to allow inclusion of patients suspected of having a high likelihood of LIE at presentation (Amendment 4A) in April 2004. In addition, an independent external Adjudication Committee was established to perform a blinded assessment of each individual patient's diagnosis and outcome.

Despite the approval of Amendment 4A and screening of over 1200 patients with *S. aureus* bacteremia between April and October 2004, few patients were enrolled who were suspected of having a high likelihood of LIE. Thus, Cubist determined that further attempts at enrolling LIE patients in this protocol would not yield a sufficient number for evaluation in a feasible time period. At a meeting between Cubist and FDA on November 3, 2004, it was determined that an indication for *S. aureus* bacteremia and right-sided IE (RIE) in the absence of data from LIE patients could be justified provided there were sufficient data, including an adequate experience in complicated *S. aureus* bacteremia.

2. REVIEW OF RESULTS FROM THE PIVOTAL STUDY DAP-IE-01-02

2.1 Study Design

2.1.1 Overview of Study Design

Study DAP-IE-01-02 was a Phase 3, international, multicenter, randomized (1:1), open-label, non-inferiority study comparing intravenous (i.v.) daptomycin monotherapy with conventional combination i.v. therapy (SSP [nafcillin, oxacillin, cloxacillin, or flucloxacillin] or vancomycin, both with initial low-dose gentamicin) in patients with bacteremia or IE caused by *S. aureus*. An independent external Adjudication Committee expert in the evaluation of *S. aureus* infections independently assessed outcomes blinded to study treatment. The use of an external Adjudication Committee is consistent with analysis of studies evaluating new anti-infective therapies. The primary efficacy endpoint was success at the test-of-cure (TOC) visit conducted 6 weeks after the end-of-therapy (EOT) visit. The study was conducted between August 2002 and February 2005.

2.1.1.1 Study Patients

Eligible patients were 18 years of age or older with 1 or more blood cultures positive for *S. aureus* within 2 calendar days prior to initiating study medication. Patients were randomized to either daptomycin or conventional therapy on a 1:1 basis. 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.

Patients were ineligible for entry into the study if they had intravascular foreign materials at the time of the positive blood culture, unless intended to be removed within 4 days after Day 1; had prosthetic heart valves; had cardiac decompensation and/or valve damage that would require valve replacement surgery within 3 days of randomization; were in a moribund clinical condition; or had shock, hypotension, oliguria, creatinine clearance <30 mL/min, polymicrobial blood infection, pneumonia, or osteomyelitis.

2.1.1.2 Diagnosis of Endocarditis

Even in the absence of endocarditis, one-third of *S. aureus* bacteremias are marked by clinically significant complications, including metastatic deep tissue infection such as abscesses and osteomyelitis, septic shock, acute respiratory distress syndrome, disseminated intravascular coagulation, and intravascular complications such as septic thrombophlebitis.(13, 74) A delay in the manifestation and recognition of the importance of often non-specific symptoms such as back pain, as well as the difficulty in obtaining often expensive diagnostic studies (e.g., computed tomography, magnetic resonance imaging, bone scans, and transesophageal echocardiography [TEE]), frequently results in a prolonged interval between presentation and final diagnosis.

The difficulty in diagnosing severely ill patients at presentation led to the use of the Modified Duke Criteria(75) in Study DAP-IE-01-02. These criteria attempt to categorize patients with bacteremia at presentation into those most likely to have endocarditis and include the categories of Definite IE, Possible IE, and Not IE. To determine the diagnosis, patients were required to meet specific major and minor criteria as detailed below:

Major Criteria	Minor Criteria

• Two blood cultures positive for *S. aureus*
• Evidence of endocardial involvement
  ♦ Echocardiogram positive for IE
  ♦ New valvular regurgitation[a]
	• Predisposing heart condition or IVDU
	• Temperature >38° C
	• Vascular phenomena
	• Immunologic phenomena
	• Only 1 positive blood culture for *S. aureus*

Note: IVDU=intravenous drug user.

a If valvular regurgitation was present, but new onset was uncertain, it was to be considered a "predisposing heart condition" under Minor Criteria.

The number and specific criteria met for an individual patient led to the entry diagnosis as follows:

Number of Criteria and Type Met							
No. of Major Criteria	0	0	0	1	1	1	2
No. of Minor Criteria	1 or 2	3 or 4	5	0	1 or 2	3 to 5	0 to 5
Interpretation							
Definite IE			X			X	X
Possible IE		X			X		
Not IE (bacteremia)	X			X			

However, it is known that applying the Modified Duke Criteria to patients with *S. aureus* bacteremia at the time of presentation often underestimates the severity of infection.(76) Therefore, in order to further define the patient population, the Adjudication Committee retrospectively assessed patients blinded to study treatment using all available clinical data from baseline and throughout the treatment course to determine a final diagnosis as follows:

- *S. aureus* LIE
  - Definite or Possible IE according to the Modified Duke Criteria; and
  - echocardiographic evidence of mitral or aortic valve involvement.
- Complicated *S. aureus* RIE
  - Definite or Possible IE according to the Modified Duke Criteria; and
  - echocardiographic evidence indicating no mitral or aortic valve involvement; and
  - any of the following additional criteria:
    - patient was not an IVDU,
    - evidence of extrapulmonary sites of infection,
    - serum creatinine ≥2.5 mg/dL,
    - MRSA bacteremia.

- Uncomplicated *S. aureus* RIE
  - Definite or Possible IE according to the Modified Duke Criteria; and
  - echocardiographic evidence indicating no mitral or aortic valve involvement; 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 Definite IE according to the Modified Duke Criteria; and
  - *S. aureus* was isolated from blood cultures obtained on at least 2 different calendar days; and/or
  - metastatic foci of infection (deep tissue involvement) were present.
- Uncomplicated *S. aureus* bacteremia
  - Patient did not have Definite IE according to the Modified Duke Criteria; and
  - *S. aureus* was isolated from blood culture(s) obtained on a single calendar day; and
  - no metastatic foci of infection were present; and
  - no infection of prosthetic material.

Patients who entered with Possible IE were ultimately classified by the Adjudication Committee as having RIE, LIE, complicated bacteremia, or uncomplicated bacteremia.

2.1.1.3 Administration of Study Medication

Daptomycin was administered at 6 mg/kg q24h and the SSPs at 2 g q4h. In patients with normal renal function, vancomycin was administered at 1 g q12h; vancomycin dosing was to be adjusted based on renal function and serum drug levels according to the Investigator's standard practice and hospital guidelines. Initial low-dose gentamicin therapy at 1 mg/kg q8h adjusted according to renal function was to be administered for the first 4 days or until blood cultures became negative to all patients randomized to comparator and to LIE patients randomized to daptomycin.

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, which are based on the Modified Duke Criteria, are outlined in Table 5.(75) During the conduct of the study, actual treatment duration was determined by the Investigator based on his or her working diagnosis.

The difficulties in diagnosis of patients at presentation, together with the likelihood of relapse in *S. aureus* infections given inadequate therapy, led to current recommendations for long courses of therapy for most patients. Further, multiple studies have demonstrated a significant failure rate with short-course therapy even for catheter-related *S. aureus* bacteremia. In a meta-analysis, Jernigan *et al.* showed a 6.1% late complication rate with substantial risk of morbidity and mortality.(77) Although some propose using TEE, follow-

up blood culture data, and resolution of fever to help determine who should receive short-course therapy, this approach has not yet been validated.(78, 79)

Table 5: Protocol Guidance for Treatment Duration

Working Diagnosis	Daptomycin	Comparator[a]
Uncomplicated *S. aureus* bacteremia	10-14 days	10-14 days
Uncomplicated *S. aureus* RIE	14-28 days	14-42 days[b]
Complicated *S. aureus* bacteremia or RIE	28-42 days[c]	28-42 days
S. aureus LIE	28-42 days[a]	28-42 days

Based on the Modified Duke Criteria(75)

a Plus initial low-dose (1 mg/kg q8h) gentamicin for 4 days.

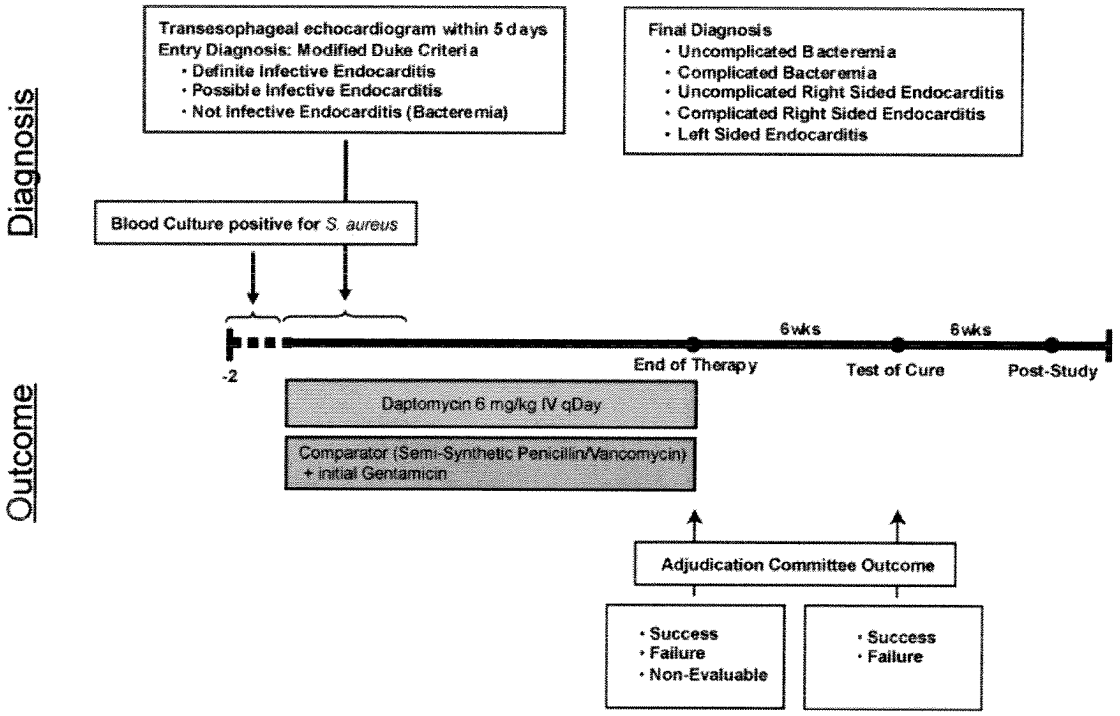
b Uncomplicated RIE: Option of 14 days of SSP + gentamicin or 28-42 days SSP plus low-dose gentamicin for first 4 days.

c Daptomycin patients had the option of 14 to 28 days if MRSA was the only complicating factor.

2.1.1.4 Patient Monitoring

An overall study schematic is provided in Figure 2.

Figure 2: Study Schematic



An overview of efficacy and safety assessments conducted during Study DAP-IE-01-02 is provided in Table 6. Study visits occurred daily during in-patient treatment, at the EOT visit (within 3 days after the last day study medication was administered for patients who completed the minimum duration of treatment), and 6 weeks post-treatment at the TOC visit. An additional post-study (PS) telephone contact or visit was conducted 12 weeks post-treatment for patients who had a successful outcome at the TOC visit. All patients who

terminated study medication early were to have an evaluation performed within 3 days after the last day of study medication administration (EOT). These patients were subsequently followed weekly for documentation of antibiotics received and survival and had a safety visit approximately 6 weeks post-treatment.

Table 6: Efficacy and Safety Assessments Conducted during Study DAP-IE-01-02

Efficacy Parameter	Assessment Time Points
Medical and Antibiotic History	Baseline
Chest Radiograph	Baseline
Concomitant Medications, Antibiotics, and Procedures	Throughout the study to the PS[a] visit (if applicable)
Physical Examination	Baseline, weekly to EOT, EOT, TOC/Day 42P and PS[a]
Transesophageal Echocardiography	One obtained between Baseline and Day 5 and in follow-up as clinically indicated
Blood Cultures	Baseline, repeated daily until negative for 48 hours, EOT, TOC/Day 42P, PS[a]
Clinical Assessments	Baseline, daily to EOT, EOT, TOC/Day 42P, PS[a]
HR, RR, SBP, DBP	Baseline, Days 1 and 7, weekly to EOT, EOT, TOC/Day 42P, PS[a]
Temperature	Baseline, daily to EOT, EOT, TOC/Day 42P, PS[a]
Physical Examination	Baseline, Day 7, weekly to EOT, EOT, TOC/Day 42P, PS[a]
Laboratory Assessments	
Clinical Labs[b]	Baseline, Days 1, 4, 7 and weekly to EOT, EOT, TOC/Day 42P
CPK	Baseline, Days 1, 4, 7 and every other day during treatment to EOT[c], EOT
Adverse Events	Throughout the study to 30 days post-treatment
Serious Adverse Events	Throughout the study to the PS[a] visit (if applicable)

Note: HR=heart rate; RR=respiratory rate; SBP=systolic blood pressure; DBP=diastolic blood pressure; EOT = end-of-therapy; TOC=test-of-cure; PS=post-study.

a Visit conducted for patients with successful outcome at the TOC visit.

b Included hematology, clinical chemistry, coagulation profile, and urinalysis.

c Minimum of 3 days/week; CPK values exceeding 4.0×ULN while the patient was receiving study medication were to be monitored daily until the results returned to within the normal range or the patient's baseline level and <2×ULN. If the patient had completed study medication, CPK values were to be monitored daily until values trended downward, at which point CPK was to be monitored a minimum of 3 days/week.

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 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 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 (Chris Cabell, MD, Duke Echocardiography CORE Lab, Durham, North Carolina) who was blinded to treatment. The independent cardiology assessment was used in the determination of entry and final diagnosis by the independent Adjudication Committee.

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 non-blood foci of infection. Adverse events, including serious events, were assessed throughout the study.

2.1.1.5 Data Safety Monitoring Board

Cubist convened a DSMB to review blinded safety and efficacy data as they related to safety and to recommend continuing, modifying, or stopping the study. No interim statistical analysis of efficacy data was conducted. The DSMB performed 6 interim reviews of the data as planned and recommended continuing the study to completion without modification.

2.1.1.6 Independent External Adjudication Committee

Due to potential bias because of the open-label study design, the heterogeneity of the patient population, and the complexity of diagnosis and treatment outcome assessments in patients with *S. aureus* bacteremia and IE, an external Adjudication Committee was convened to conduct a clinical review of the data. The committee was blinded to treatment assignment in order to provide independent assessments of entry and final diagnosis and outcome at key time points. In accordance with the statistical analysis plan, efficacy was assessed using the Adjudication Committee assessments.

The committee was composed of 5 infectious disease experts, including one chairperson and 4 members:

- G. Ralph Corey, MD, Professor of Internal Medicine & Infectious Disease, Duke University Medical Center (chairperson)
- Elias Abrutyn, MD, Professor of Medicine and Public Health, Associate Provost and Associate Dean for Faculty Affairs, Interim Chief, Infectious Diseases, Drexel University
- Adolf W. Karchmer, MD, Professor of Medicine, Chief, Division of Infectious Diseases, Beth Israel Deaconess Medical Center
- Vance G. Fowler, MD, Associate Professor of Medicine, Duke University Medical Center
- Sara Cosgrove, MD, Assistant Professor, Department of Medicine, Division of Infectious Disease, Johns Hopkins University School of Medicine and Johns Hopkins Bloomberg School of Public Health

The Adjudication Committee was charged with reviewing all available clinical data to establish patient diagnoses and treatment outcomes at both EOT and TOC visits.

Because the extent of *S. aureus* infection is not known at the time therapy is initiated, the Adjudication Committee was charged with retrospectively determining a final diagnosis (complicated or uncomplicated RIE, complicated or uncomplicated bacteremia, LIE) for the purposes of analysis.

All committee members were trained and followed a standard operating procedure in their deliberations and assessments. A chairperson was designated (Dr. Corey), and the remaining 4 members were divided into 2 reviewing teams. All cases that the committee reviewed were blinded to study drug treatment. The chairperson was to review all cases, and the 2 teams

each reviewed 50% of cases. Agreement was required by both team members for each assessment. As an additional quality control measure, cases were reviewed by both teams to ensure consistency.

2.1.1.7 Microbiologic Methods

The local microbiology laboratories were to culture specimens and send isolates to the central microbiology laboratory for re-identification and susceptibility testing. All isolates were identified to species level and tested for antimicrobial susceptibility by the central laboratory using accepted interpretative criteria.(80) *S. aureus* isolates with an MIC to daptomycin of ≥2 µg/mL were considered non-susceptible. These isolates were evaluated with repeat susceptibility testing and pulsed-field gel electrophoresis.

2.1.2 Statistical Considerations

All randomized patients who received at least one dose of study medication were evaluated for safety. The intent-to-treat (ITT) population for analysis of efficacy data included all randomized patients who received at least one dose of study medication, excluding patients who had LIE and were enrolled prior to protocol Amendment 4A. The per protocol (PP) population for analysis of efficacy included all ITT patients with documented strict protocol adherence (see Table 7, page 32), including adherence to dosing, visit schedule, key inclusion and exclusion criteria, and key assessments.

The primary endpoint was success at TOC based on Adjudication Committee-determined outcome; success rate was to be evaluated in both the ITT and PP populations and is a composite endpoint based on clinical success (Cured or Improved) as well as microbiologic eradication.

Patients were classified by the Adjudication Committee as "Success" if they met all of the following criteria:

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

Patients were classified by the Adjudication Committee as "Failure" if they met any one of the following criteria:

- Had persisting or relapsing *S. aureus* infection.
- No blood culture results.
- Died.
- Received a PENS antibiotic that influenced therapeutic outcome.
- Discontinued study medication prematurely due to clinical failure, microbiologic failure, or adverse event.

Patients were classified as "Non-evaluable" 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.

This was a non-inferiority trial. The primary outcome measure was the comparison of the success rates for the 2 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. The non-inferiority test was based upon a comparison of the lower bound of the 95% CI relative to a margin of 20%.

The secondary efficacy endpoint was time to clearance of bacteremia assessed by Kaplan-Meier methods. Additional efficacy analyses included assessment of Adjudication Committee success rates by entry diagnosis, final diagnosis, and baseline pathogen (MRSA and MSSA); Investigator assessment of response, time to defervescence, and survival.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) in each MedDRA System Organ Class (SOC) was compared between treatment groups using Fisher's exact test.

2.2 Patient Disposition

A total of 246 patients were randomized into Study DAP-IE-01-02 between August 2002 and February 2005; 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. These 236 patients were treated at 44 study sites in the US (38) and Europe (6). 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 4 patients who received a longer duration of vancomycin therapy.

The majority of the patients in both treatment groups completed therapy (66.7% and 67.2% in the daptomycin and comparator groups, respectively); a total of 78 patients, including 40 (33.3%) in the daptomycin group and 38 (32.8%) in the comparator group, discontinued treatment early. The primary reason for early treatment discontinuation was adverse event, reported for 16.7% and 18.1% of patients in the daptomycin and comparator groups, respectively. Adverse events leading to treatment withdrawal are discussed in Section 2.8.8.3 (page 81).

A summary of patient populations for analysis is provided in Table 7. All 236 patients enrolled and treated in this study were included in the safety population, and 235 patients were included in the ITT population. The PP population comprised a total of 139 (58.9%) of

the 236 patients who received treatment; a higher proportion of patients in the daptomycin group (65.8%) were included in the PP population compared with the comparator group (51.7%). However, the primary reasons for exclusion from the PP population were similar between the treatment groups, with the exception of exclusion for lack of study medication adherence.

Table 7: Overview of Patient Populations in Study DAP-IE-01-02

Disposition	Daptomycin n (%)	Comparator n (%)
Safety Population	120	116
ITT Population	120 (100%)	115 (99.1%)
Reasons for exclusion from the ITT population		
At risk for LIE prior to Amendment 4A	0	1 (<1%)
PP Population	79 (65.8%)	60 (51.7%)
Reasons for exclusion from the PP population[a]		
Early termination for administrative reasons[b]	29 (24.2%)	34 (29.3%)
Major inclusion/exclusion violation	12 (10.0%)	14 (12.1%)
Non-evaluable per the Adjudication Committee	9 (7.5%)	14 (12.1%)
<4 days of therapy	9 (7.5%)	9 (7.8%)
Non-compliant with visits	7 (5.8%)	6 (5.2%)
Lack of study medication adherence	0	8 (6.9%)

Note: BMI=body mass index; CL_{cr}=creatinine clearance.

a More than one reason for exclusion can occur per patient.

b Patient terminated early from study drug for reasons other than adverse event, microbiological failure, or unsatisfactory clinical response (i.e., withdrew consent, care withdrawn).

2.3 Demographic and Baseline Characteristics

2.3.1 Demographics

Demographic characteristics were well balanced between the daptomycin and comparator groups (Table 8). Mean age was 54.5 years, with a range of 21 to 91 years. The majority of patients in both treatment groups were male (~60%); nearly two-thirds were Caucasian and approximately one-quarter were Black.

Table 8: Summary of Demographic and Other Baseline Characteristics (ITT Population)

Characteristic	Daptomycin (N=120)	Comparator (N=115)
Median Age, years (range)	50.5 (21, 87)	55.0 (25, 91)
Age, years [N (%)]		
≥65	30 (25.0%)	37 (32.2%)
≥75[a]	19 (15.8%)	15 (13.0%)
Gender [N (%)]		
Male	70 (58.3%)	71 (61.7%)
Female	50 (41.7%)	44 (38.3%)
Race [N (%)]		
Caucasian	75 (62.5%)	81 (70.4%)
Black	32 (26.7%)	23 (20.0%)
Other	13 (10.8%)	11 (9.6%)
Median BMI, kg/m^2 (range)	26.90 (17.6, 49.7)	25.67 (17.0, 44.0)
Median CL_{cr}, mL/min[b] (range)	86.44 (28.0, 246.9)	83.61 (17.9, 277.0)
CL_{cr} <50 mL/min[b] [N (%)]	19 (15.8%)	22 (19.1%)
≥75 years of age [n/N (%)]	11/19 (57.9%)	7/22 (31.8%)

Note: BMI=body mass index; CL_{cr}=creatinine clearance.

a Age category ≥75 years is a subset of the category ≥65 years.

b Calculated by the Sponsor using the Cockcroft-Gault equation.

2.3.2 Baseline Disease Characteristics

The patient population enrolled and treated in Study DAP-IE-01-02 was seriously ill, and the baseline disease characteristics were reflective of the complicated nature of the patient population under study (Table 9). Systemic inflammatory response syndrome (SIRS) was present in 74.2% and 75.7% of patients in the daptomycin and comparator groups, respectively. Over one-third of the patients in each of the treatment groups had diabetes mellitus (36.7% and 36.5% in the daptomycin and comparator groups, respectively).

Extravascular and intravascular foreign materials are prime risk factors for *S. aureus* bacteremia and IE. Extravascular foreign material was present in 23.3% and 25.2% of patients in the daptomycin and comparator groups, respectively, and included orthopedic prostheses in 18 and 12 daptomycin and comparator patients, respectively, and other devices (neurological, sternal wires, surgical drains/clamps/stents, non-vascular catheters, chest and endotracheal tubes) in 12 and 22 patients, respectively (note that a patient could have more than one type of material). The orthopedic prostheses were infected in 8 patients (6 daptomycin and 2 comparator); 6 of whom underwent any surgical therapy, including 2 (both daptomycin patients) who had a successful outcome. Permanent intravascular devices, including implanted pacemakers and intravascular grafts, were present in 11.7% of patients in the daptomycin group and 15.7% of patients in the comparator group. Pre-existing valvular heart disease was reported more often in patients in the daptomycin group (13.3%) than in those who received standard of care (7.8%). Prior surgery within 30 days of onset, including reports of incision and drainage or debridement of skin infections, cardiac surgery (coronary artery bypass, angioplasty with and without stent placement), central catheter placement, pacemaker insertion and removal, and orthopedic procedures, also was reported

in a higher proportion of patients in the daptomycin group (40.8%) than in the comparator group (31.3%).

Table 9: Summary of Risk Factors and Other Baseline Disease Characteristics (ITT Population)

Risk Factor [N (%)]	Daptomycin (N=120)	Comparator (N=115)
SIRS present	89 (74.2%)	87 (75.7%)
Diabetes mellitus	44 (36.7%)	42 (36.5%)
Injection drug use	25 (20.8%)	25 (21.7%)
Pre-existing valvular heart disease	16 (13.3%)	9 (7.8%)
Prior endocarditis	7 (5.8%)	6 (5.2%)
Extravascular foreign material[a]	28 (23.3%)	29 (25.2%)
Permanent intravascular foreign material[a]	14 (11.7%)	18 (15.7%)
Percutaneous intravascular device[a]	6 (5.0%)	4 (3.5%)
Surgery within 30 days of onset[b]	49 (40.8%)	36 (31.3%)
Trauma within 30 days of onset[b]	22 (18.3%)	18 (15.7%)
Septic pulmonary emboli	10 (8.3%)	13 (11.3%)
HIV positive	8 (6.7%)	1 (<1%)

Notes: SIRS=systemic inflammatory response syndrome; HIV=human immunodeficiency virus.
Patient may have been reported in more than one category.

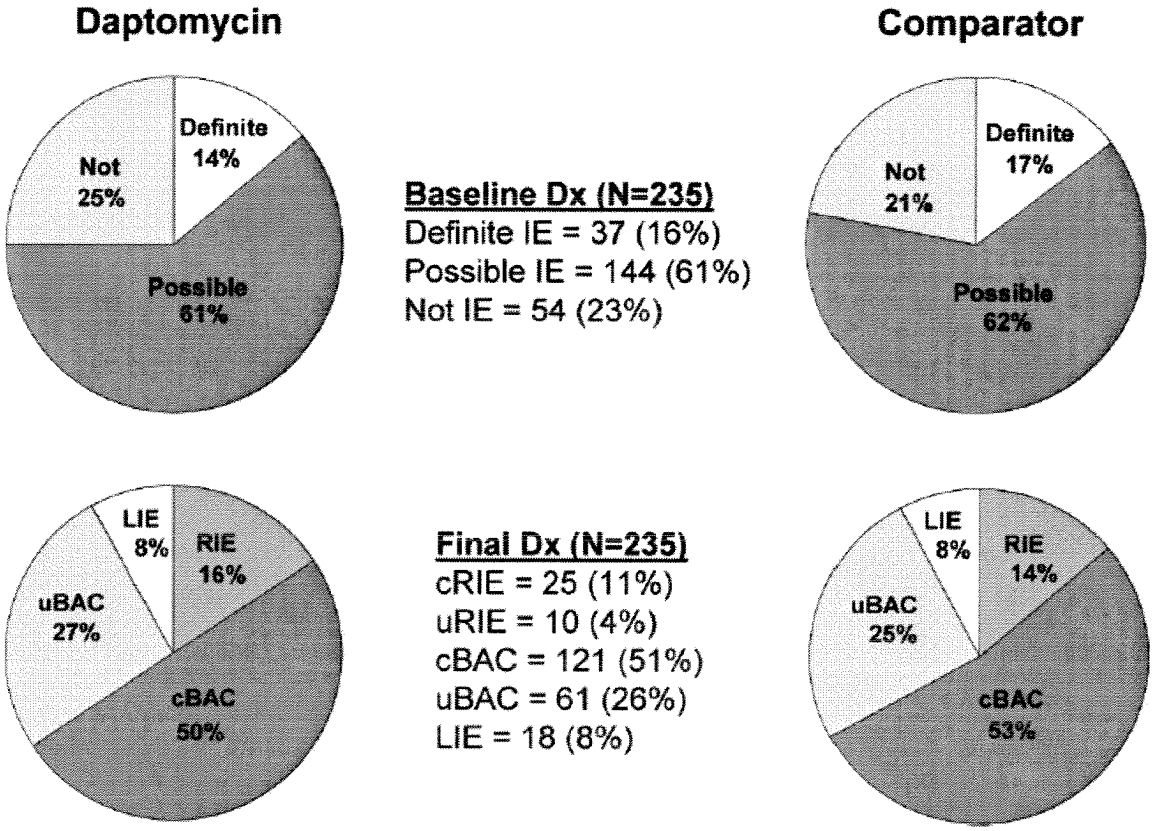
a In place/present at the time of the first positive blood culture for *S. aureus.*

b Within 30 days of onset of *S. aureus* bacteremia.

2.3.3 Diagnosis of Endocarditis

As detailed in Section 2.1.1.2 (page 24), entry and final diagnoses were determined by the Adjudication Committee; results are displayed in Figure 3. The treatment groups were well balanced with regard to both of these diagnostic categories. Known or suspected endocarditis, based on the Modified Duke Criteria categories of Definite or Possible IE, was reported at study entry for 75.0% and 79.1% of the daptomycin and comparator patients, respectively. Final diagnoses also were similar in the 2 treatment groups and reflective of the entry diagnosis. Complicated bacteremia or IE was reported in 73.3% and 74.8% of patients in the daptomycin and comparator groups, respectively, and uncomplicated bacteremia was reported in 26.7% and 25.2%, respectively.

Figure 3: Summary of Adjudication Committee Diagnoses (ITT Population)



Note: cRIE=complicated right-sided IE, uRIE=uncomplicated right-sided IE, cBAC=complicated bacteremia, uBAC=uncomplicated bacteremia, LIE=left-sided IE.

The entry diagnosis as determined by the study Investigators was similar to that reported by the Adjudication Committee. Overall, the Investigators reported known or suspected endocarditis in 182 (77.4%) of the 235 patients, including 74.2% (89 of 120 patients) and 80.9% (93 of 115 patients) of patients in the daptomycin and comparator groups, respectively.

2.3.4 Baseline Pathogens

Similar to recently reported international studies (15, 23), MRSA was well represented in the study population, accounting for 37.5% and 38.3% of infections in daptomycin and comparator groups, respectively (Table 10). 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 62, 96.8%).

Table 10: Oxacillin Susceptibility of the Baseline Pathogen (ITT Population)

Pathogen	Daptomycin (N=120)	Comparator[a] Total (N=115)	Comparator[a] Vancomycin (N=53)	Comparator[a] SSP (N=62)
MSSA	74 (61.7%)	70 (60.9%)	10 (18.9%)	60 (96.8%)
MRSA	45 (37.5%)	44 (38.3%)	43 (81.1%)	1 (1.6%)[b]
No *S. aureus* isolated	1 (<1%)	1 (<1%)	0	1 (1.6%)

a For vancomycin, patients received only this agent during the study; for SSP, patients received SSP with or without initial therapy with vancomycin.

b One patient received 9 days of nafcillin prior to switching to vancomycin, which she received through Day 35; MRSA was isolated at baseline but was not recognized until Day 9.

2.4 Exposure to Study Treatment

Across the 120 daptomycin-treated patients, mean daily dose administered was 5.9 ± 0.30 mg/kg with a median of 6.0 mg/kg, indicating excellent compliance with the once-daily daptomycin dosing regimen.

Study drug adherence was defined as having received ≥80% of the expected daily dose over the duration of study treatment and was assessed for the patients who received dosing on Day 4 of the study or later. All 109 patients in the daptomycin group who received dosing on Day 4 or later (100%) were adherent to study drug dosing, compared with 97 (92.4%) of 105 patients in the comparator group; this difference was significant (p=0.003) and is likely related to the ease of once-daily dosing with daptomycin compared with up to 6 times daily dosing required in the comparator arm. Among the 43 patients who received vancomycin on Day 4 or later, 40 (93.0%) were adherent to the study drug regimen, as were 57 (91.9%) of 62 patients who received SSP.

Across the 63 SSP-treated patients, mean daily dose administered was 11.5 ± 1.4 g/day with a median of 12.0 g/day.

Vancomycin trough levels were reported for a total of 44 (83.0%) of the 53 patients who received this comparator agent; mean trough levels among these patients were 14.1 μg/mL, consistent with current recommendations.

As required by the protocol, the majority of patients who received conventional therapy received initial low-dose gentamicin (108 of 116 patients, 93.1%). Only one patient in the daptomycin group (<1%), with an Adjudication Committee final diagnosis of LIE, was administered gentamicin concomitantly. Median duration of exposure to gentamicin in the comparator group was 4.0 days and was not different among patients who received SSP with or without initial vancomycin (median of 4 gentamicin treatment days) and those who received vancomycin (median of 5 gentamicin treatment days).

As shown in Table 11, the duration of treatment was similar in the 2 treatment groups. The majority of patients in both groups received treatment for 14 or more days (67.5% in the daptomycin group and 68.7% in the comparator group). A total of 56 patients, including 22.5% and 25.2% in the daptomycin and comparator groups, respectively, were dosed for 28

or more days. Maximum duration of treatment was 74 days in the daptomycin group and 57 days in the comparator group.

Table 11: Duration of Treatment (ITT Population)

Duration of Treatment	Daptomycin N=120 n (%)	Comparator N=115 n (%)
1 to 13 Days	39 (32.5%)	36 (31.3%)
14 to 27 Days	54 (45.0%)	50 (43.5%)
≥28 Days	27 (22.5%)	29 (25.2%)

A summary of mean duration of study drug exposure by Adjudication Committee final diagnosis for the patients who completed therapy according to the Investigator is displayed in Table 12. Note that treatment duration was determined by the Investigators and was based on their working diagnosis.

Across all patients who completed therapy, mean duration of therapy was similar in the daptomycin (22.0 days) and comparator (24.2 days) groups. As expected, in both treatment groups mean duration of therapy was higher for patients with complicated infections than for those with uncomplicated infections. An analysis of outcome by duration of treatment is provided in Section 2.5.3.4 (page 45).

Table 12: Mean Duration of Study Drug Exposure (Days) by Adjudication Committee Final Diagnosis (ITT Population, Patients who Completed Therapy)

			Comparator[a]					
	Daptomycin (N=120)		Total (N=115)		Vancomycin (N=53)		SSP (N=62)	
Diagnostic Subgroup	*n*	Mean	*n*	Mean	*n*	Mean	*n*	Mean
Pts who Completed Therapy	*80*	22.0	*77*	24.2	*33*	23.4	*44*	24.8
Uncomplicated bacteremia	*27*	15.7	*25*	18.4	*13*	18.6	*12*	18.3
Uncomplicated RIE	*4*	17.5	*1*	15.0	*0*	--	*1*	15.0
Complicated bacteremia	*37*	25.5	*38*	25.2	*15*	23.3	*23*	26.4
Complicated RIE	*8*	29.5	*9*	33.9	*4*	38.3	*5*	30.4
LIE	*4*	20.5	*4*	30.8	*1*	27.0	*3*	32.0

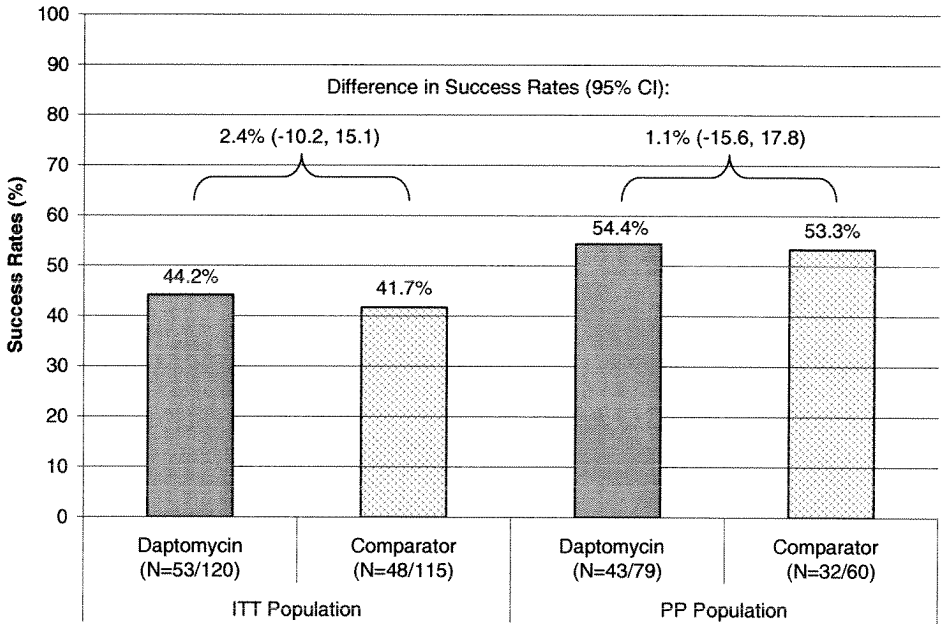
a For vancomycin, patients received only this agent during the study; for SSP, patients received SSP with or without initial therapy with vancomycin.

2.5 Efficacy Results

2.5.1 Primary Efficacy Analysis: Adjudication Committee Outcome at Test of Cure

The primary efficacy endpoint of the study was met (Figure 4). Daptomycin monotherapy was shown to be non-inferior to conventional therapy with SSP and/or vancomycin plus initial low-dose gentamicin in the treatment of patients with *S. aureus* bacteremia and known or suspected endocarditis. The results were robust, with daptomycin meeting the pre-defined primary efficacy endpoint, success at 6 weeks post-treatment (TOC), in the co-primary ITT and PP populations.

Figure 4: Adjudication Committee Success Rates at TOC (ITT and PP Populations)



In the ITT population, a successful outcome was documented by the Adjudication Committee in 44.2% of daptomycin-treated patients compared with 41.7% of comparator-treated patients. Similarly, in the PP population 54.4% of daptomycin-treated patients had a successful outcome 6 weeks post-treatment compared with 53.3% of 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 limit of –20% for the overall pooled analysis and when the results were adjusted for Adjudication Committee entry and final diagnoses (Table 13).

Table 13: Adjudication Committee Outcome at TOC – Results of Statistical Analyses Overall and Weighted by Adjudication Committee Diagnoses (ITT and PP Populations)

Adjudication Committee 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[b] in Success Rates (95% CI)				
Overall	2.4% (–10.2, 15.1)		1.1% (–15.6, 17.8)	
Weighted by Entry Diagnosis[c]	2.4% (–10.5, 15.2)		0.9% (–16.1, 17.9)	
Weighted by Final Diagnosis[c]	2.1% (–10.5, 14.8)		0.9% (–15.5, 17.3)	

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 Daptomycin minus comparator.

c Difference in success rates and the associated 95% CI around the difference (daptomycin minus comparator) with adjustment for Adjudication Committee diagnostic subgroups.

2.5.2 Secondary Efficacy Analysis: Time to Clearance of Bacteremia

A single secondary efficacy endpoint, time to clearance of *S. aureus* bacteremia in the ITT population, was assessed using Kaplan-Meier methods.

There were no statistically significant differences noted between the treatment groups for time to clearance, either overall or for patients with MSSA or MRSA infections, for the ITT population. Median times to clearance of *S. aureus* bacteremia, based on all patients with positive blood cultures on Day 1, were 5 and 4 days in the daptomycin and comparator groups, respectively, in the ITT population. For patients with infections caused by MSSA, median times to clearance were 4 and 3 days in the daptomycin and comparator groups, respectively, and for patients with infections caused by MRSA, 8 and 9 days, respectively.

2.5.3 Additional Efficacy Analyses of Outcome

2.5.3.1 Adjudication Committee Outcome at Test of Cure by Entry and Final Diagnoses

Figure 5 and Figure 6 provide summaries of Adjudication Committee-determined success rates at 6 weeks post-treatment (TOC) by entry and final diagnostic categories, respectively, for the ITT population; complete results for all entry and final diagnoses are displayed in Table 14 and Table 15, respectively.

As detailed in Section 2.1.1.2 (page 24), at entry into the study it is difficult to determine the patient's ultimate diagnosis (e.g., complicated RIE); therefore, the Adjudication Committee was asked to review baseline and post-baseline data to determine a final diagnosis. Although this diagnosis is based on post-baseline data, it is a clinically important group of patients to evaluate for response.

As shown below, daptomycin treatment effect was demonstrated across all clinically important subgroups, including patients with entry diagnoses of Definite or Possible (known or suspected) IE according to the Modified Duke Criteria and patients with final diagnoses of RIE or complicated bacteremia.

Figure 5: Adjudication Committee Success Rates at TOC by Entry Diagnosis (ITT Population)

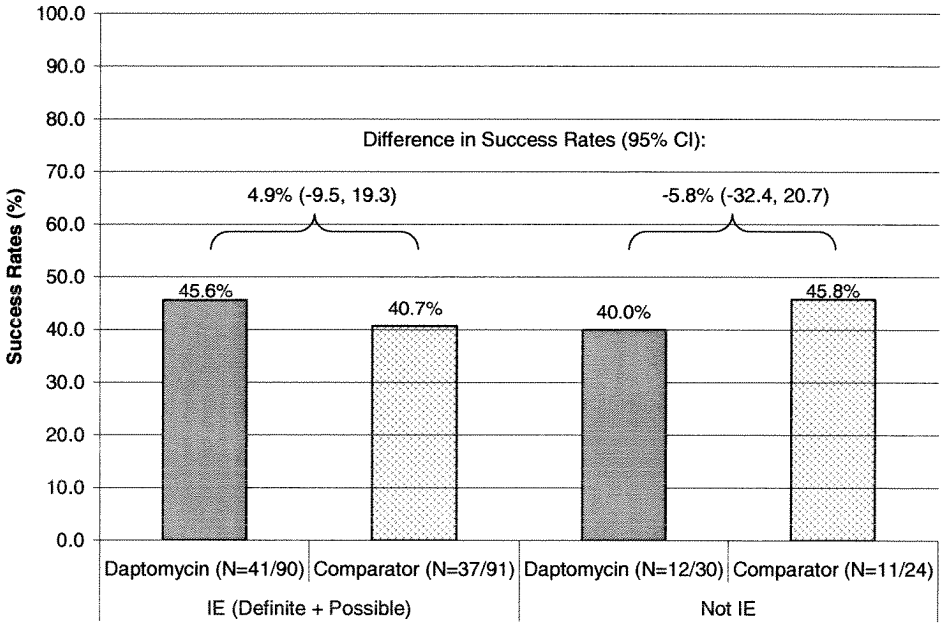
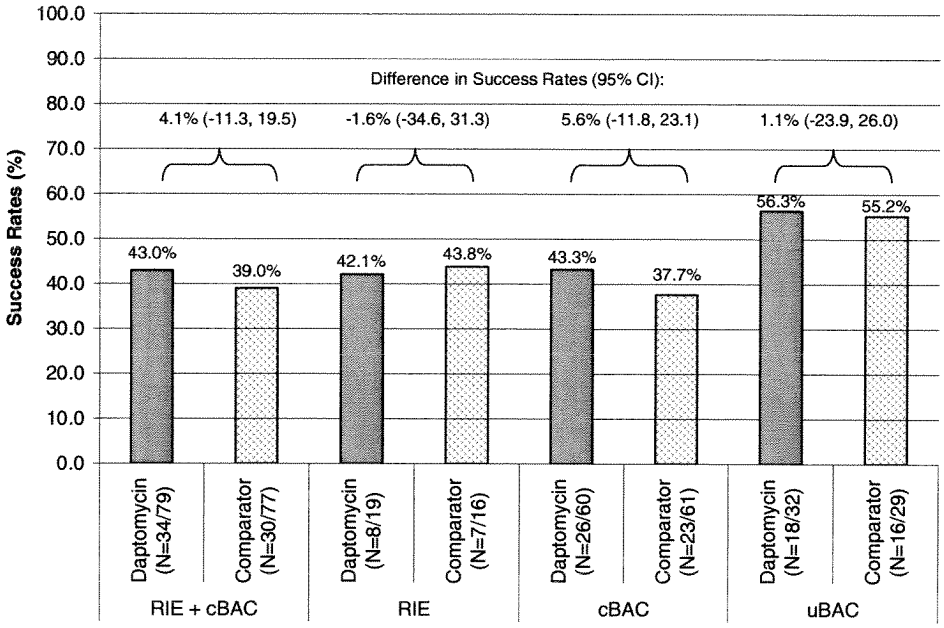


Table 14: Adjudication Committee Success Rates at TOC by Entry Diagnosis (ITT Population)

Population Entry Diagnostic Subgroup	Daptomycin n/N (%)	Comparator n/N (%)	Difference in Success Rate (95% CI)
Overall	53/120 (44.2%)	48/115 (41.7%)	2.4% (–10.2, 15.1)
IE (Definite + Possible)	41/90 (45.6%)	37/91 (40.7%)	4.9% (–9.5, 19.3)
Definite IE	7/17 (41.2%)	8/20 (40.0%)	1.2% (–30.6, 32.9)
Possible IE	34/73 (46.6%)	29/71 (40.8%)	5.7% (–10.4, 21.9)
Not IE	12/30 (40.0%)	11/24 (45.8%)	–5.8% (–32.4, 20.7)

Figure 6: Adjudication Committee Success Rates at TOC by Final Diagnosis (ITT Population)



Note: RIE=right-sided IE, cBAC=complicated bacteremia, uBAC=uncomplicated bacteremia, LIE=left-sided IE.

Table 15: Adjudication Committee Success Rates at TOC by Final Diagnosis (ITT Population)

Population Final Diagnostic Subgroup	Daptomycin n/N (%)	Comparator n/N (%)	Difference in Success Rate (95% CI)
Overall	53/120 (44.2%)	48/115 (41.7%)	2.4% (–10.2, 15.1)
RIE + Complicated bacteremia	34/79 (43.0%)	30/77 (39.0%)	4.1% (–11.3, 19.5)
RIE	8/19 (42.1%)	7/16 (43.8%)	–1.6% (–34.6, 31.3)
Complicated RIE	5/13 (38.5%)	6/12 (50.0%)	–11.5% (–50.3, 27.2)
Uncomplicated RIE	3/6 (50.0%)	1/4 (25.0%)	25.0% (–33.3, 83.3)
Complicated bacteremia	26/60 (43.3%)	23/61 (37.7%)	5.6% (–11.8, 23.1)
Uncomplicated bacteremia	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)

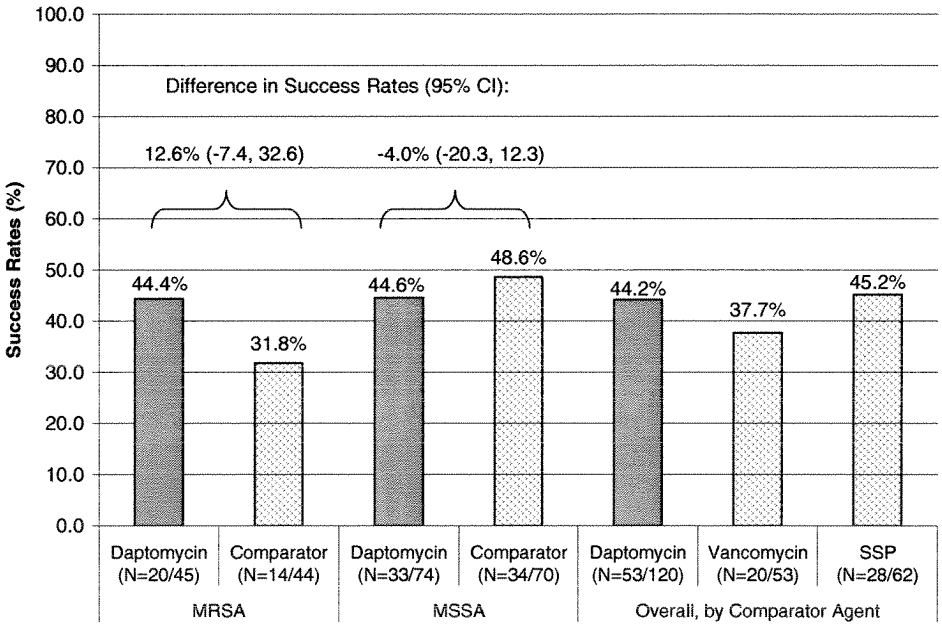
2.5.3.2 Adjudication Committee Outcome at Test of Cure by Oxacillin Susceptibility of the Baseline Infecting Pathogen

Figure 7 provides a summary of the Adjudication Committee success rates at the 6-week post-treatment TOC evaluation for the ITT population by oxacillin susceptibility of the baseline infecting pathogen; results are also presented overall, by comparator agent.

Compared with standard of care, daptomycin demonstrated the greatest relative benefit in patients with infections caused by MRSA, the subpopulation with the fewest treatment options and the highest unmet medical need. In patients with MRSA included in the ITT population, the success rates were 44.4% and 31.8% in the daptomycin and comparator

groups, respectively. Success rates at TOC were similar between the treatment groups for patients with infections caused by MSSA (44.6% and 48.6% in the daptomycin and comparator groups, respectively). These results are also reflected in review of success rates by comparator agent. The success rate in the ITT population was similar for patients who received daptomycin (44.2%) and those who received SSP (45.2%), but was lower for the patients who received vancomycin (37.7%).

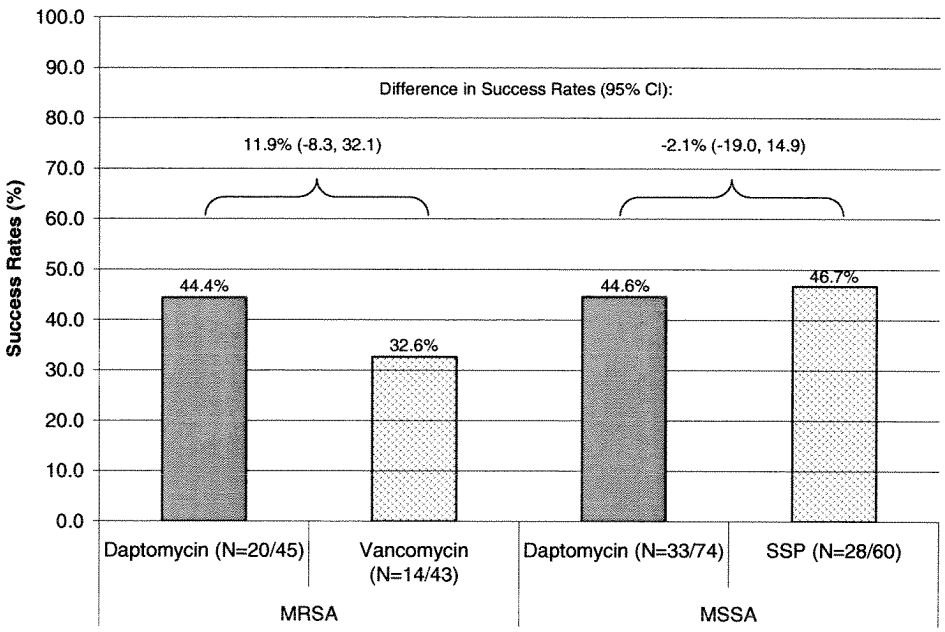
Figure 7: Adjudication Committee Success Rates at TOC by Oxacillin Susceptibility and Comparator Agent (ITT Population)



Similar overall results were noted in the PP population, with success rates of 52.9% and 44.4% for patients with MRSA in the daptomycin and comparator groups, respectively, and 55.6% and 57.1%, respectively, for patients with MSSA.

Among the patients who received pathogen-specific therapy in the comparator group, i.e., vancomycin for MRSA and SSP for MSSA, success rates for MRSA were 44.4% and 32.6% for daptomycin and vancomycin, respectively, and for MSSA were 44.6% and 46.7% for daptomycin and SSP, respectively (Figure 8).

Figure 8: Adjudication Committee Success Rates at TOC for MRSA and MSSA According to Pathogen-Specific Therapy (ITT Population)



Success rates by oxacillin susceptibility were also assessed by entry and final diagnosis, as displayed in Table 16.

Table 16: Adjudication Committee Success Rates at TOC by Entry and Final Diagnosis and by Oxacillin Susceptibility (ITT Population)

Group Pathogen Diagnosis	Daptomycin (N=120) n/N (%)	Comparator (N=115) n/N (%)	Difference in Success Rate (95% CI)
Entry Diagnosis			
MRSA			
Definite + Possible IE	15/36 (41.7%)	11/38 (28.9%)	12.7% (–8.9, 34.3)
Not IE	5/9 (55.6%)	3/6 (50.0%)	5.6% (–46.0, 57.1)
MSSA			
Definite + Possible IE	26/54 (48.1%)	26/53 (49.1%)	–0.9% (–19.8, 18.0)
Not IE	7/20 (35.0%)	8/17 (47.1%)	–12.1% (–43.7, 19.6)
Final Diagnosis			
MRSA			
RIE + Complicated bacteremia	14/30 (46.7%)	9/29 (31.0%)	15.6% (–8.9, 40.2)
Uncomplicated bacteremia	6/10 (60.0%)	5/11 (45.5%)	14.5% (–27.7, 56.8)
MSSA			
RIE + Complicated bacteremia	20/49 (40.8%)	21/48 (43.8%)	–2.9% (–22.6, 16.7)
Uncomplicated bacteremia	12/21 (57.1%)	11/17 (64.7%)	–7.6% (–38.6, 23.5)

Note: One patient in each treatment group did not have *S. aureus* isolated at baseline.

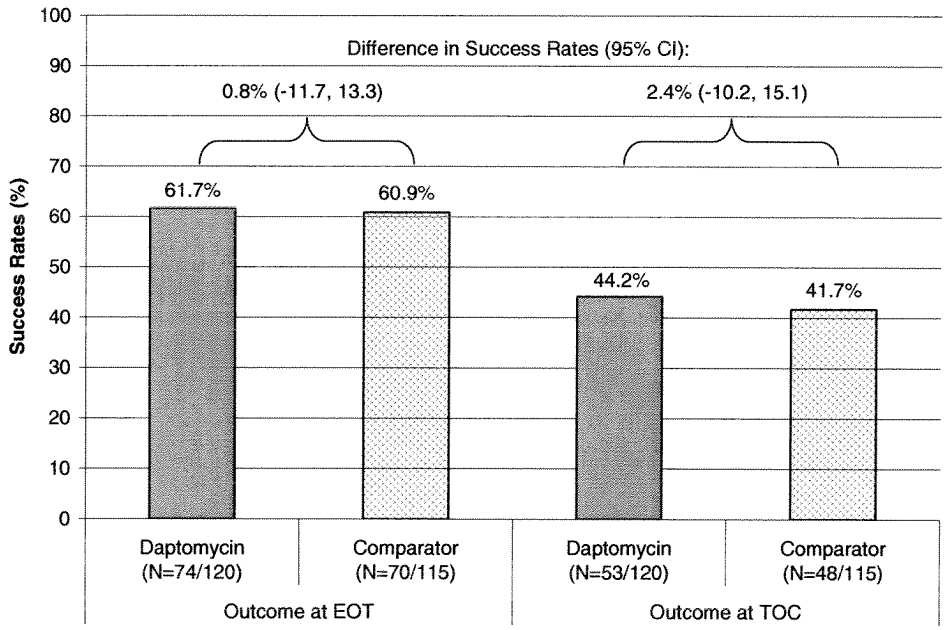
2.5.3.3 Adjudication Committee Outcome at End of Therapy

Adjudication Committee outcome also was reported for the evaluation conducted at the EOT visit; results of this analysis are provided in Figure 9 for the ITT population (note that results at TOC also are displayed).

The success rates in the ITT population at EOT as determined by the Adjudication Committee were 61.7% for daptomycin and 60.9% for the comparator. Note that the EOT results are consistent with response rates reported in recent *S. aureus* bacteremia and endocarditis studies (>60%).(19, 29, 81)

A total of 43 patients, including 21 in the daptomycin group and 22 in the comparator group, who were reported as successes at the end of therapy were determined to be failures 6 weeks later at the TOC visit. The primary reasons for failure at TOC for these 43 patients were receipt of non-study antibiotics that may have influenced outcome (17 patients, 8 and 9 in the daptomycin and comparator groups, respectively), microbiologic or clinical failure (14 patients, 7 in each treatment group), and lack of blood culture at the TOC visit (13 patients, 7 and 6 patients, respectively).

Figure 9: Adjudication Committee Success Rates at EOT and TOC (ITT Population)



Adjudication Committee outcome at EOT was also assessed by entry and final diagnosis and by oxacillin susceptibility of the baseline *S. aureus* isolate. As shown in Table 17, results were consistent with those reported at TOC and with the overall EOT results.

Table 17: Adjudication Committee Success Rates at EOT by Entry and Final Diagnosis and by Oxacillin Susceptibility (ITT Population)

Analysis Group	Daptomycin (N=120) n/N (%)	Comparator (N=115) n/N (%)	Difference in Success Rate (95% CI)
Entry Diagnostic Subgroup			
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)
Final Diagnostic Subgroup			
RIE + Complicated bacteremia	45/79 (57.0%)	45/77 (58.4%)	–1.5% (–17.0, 14.0)
Uncomplicated bacteremia	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[a]			
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)

a Based on 119 and 114 patients in the daptomycin and comparator groups, respectively. One patient in each treatment group did not have *S. aureus* isolated at baseline.

2.5.3.4 Adjudication Committee Success Rates at Test of Cure by Duration of Treatment

Increased duration of dosing with daptomycin and the comparator agents was associated with a higher success rate, especially in patients with complicated infections.

Figure 10 presents a summary of Adjudication Committee success rates at TOC by duration of treatment; results across final diagnostic subgroups are displayed in Table 18.

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 15.4%, 55.6%, and 63.0% for patients who received dosing for 1 to 13 days, 14 to 27 days, and ≥28 days, respectively; in the comparator group, success rates were 16.7%, 46.0%, and 65.5%, respectively.

Figure 10: Adjudication Committee Success Rates at TOC by Duration of Treatment (ITT Population)

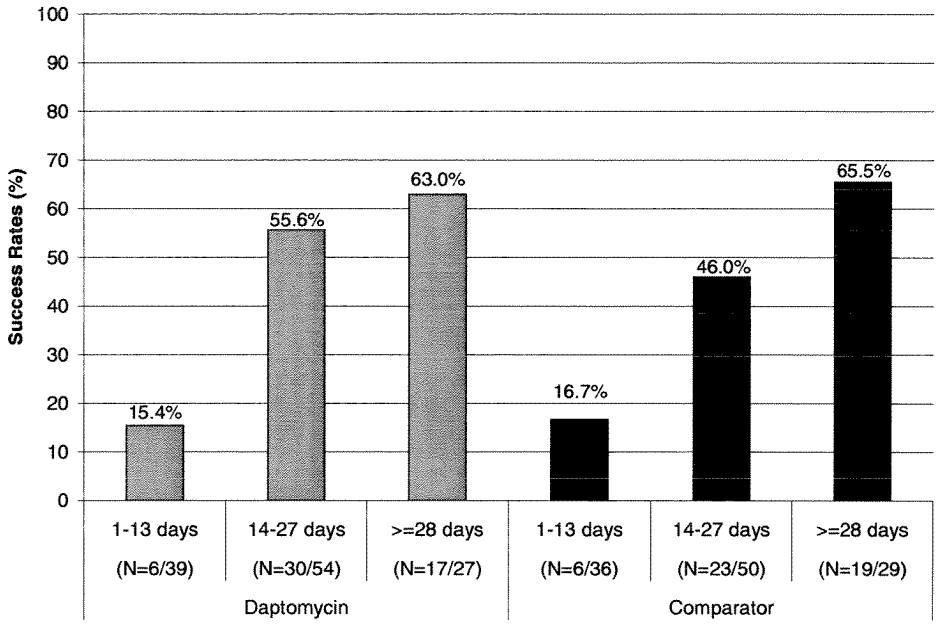


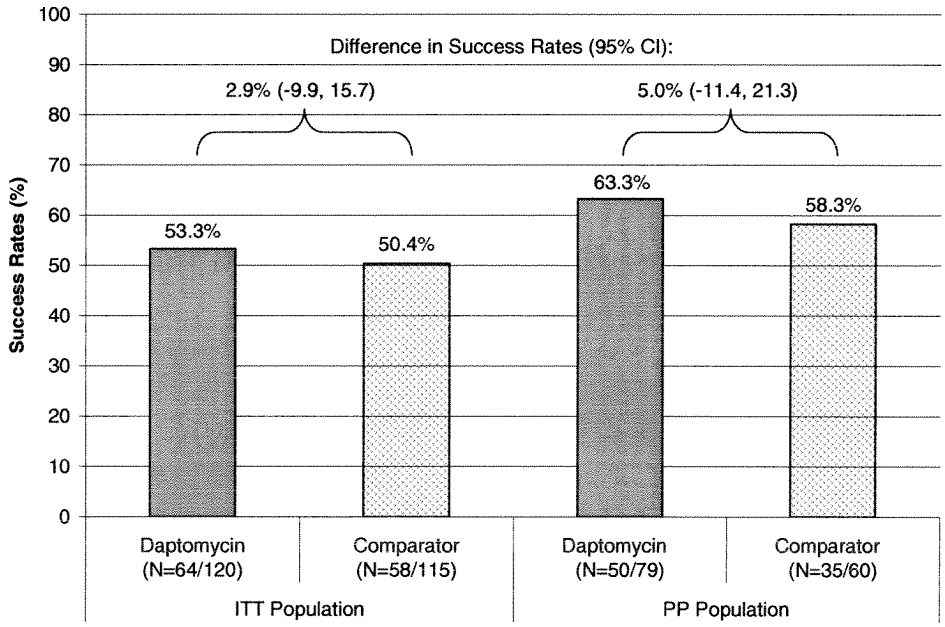
Table 18: Adjudication Committee Success Rates at TOC by Duration of Treatment and Final Diagnosis (ITT Population)

	Daptomycin (N=120)			Comparator (N=115)		
Group	**1-13 days**	**14-27 days**	**≥28 days**	**1-13 days**	**14-27 days**	**≥28 days**
Overall ITT	6/39 (15.4%)	30/54 (55.6%)	17/27 (63.0%)	6/36 (16.7%)	23/50 (46.0%)	19/29 (65.5%)
RIE + Complicated bacteremia	5/26 (19.2%)	15/30 (50.0%)	14/23 (60.9%)	2/26 (7.7%)	12/27 (44.4%)	16/24 (66.7%)
Complicated RIE	0/2	2/5 (40.0%)	3/6 (50.0%)	0/2	1/2 (50.0%)	5/8 (62.5%)
Uncomplicated RIE	0/2	2/3 (66.7%)	1/1 (100%)	0/1	1/3 (33.3%)	0
Complicated bacteremia	5/22 (22.7%)	11/22 (50.0%)	10/16 (62.5%)	2/23 (8.7%)	10/22 (45.5%)	11/16 (68.8%)
Uncomplicated bacteremia	1/8 (12.5%)	15/21 (71.4%)	2/3 (66.7%)	4/8 (50.0%)	10/18 (55.6%)	2/3 (66.7%)
LIE	0/5	0/3	1/1 (100%)	0/2	1/5 (20.0%)	1/2 (50.0%)

2.5.3.5 Investigator Assessment of Outcome at Test of Cure

Results as determined by the site Investigators were similar between the treatment groups and approximately 5% to 10% higher than those reported by the Adjudication Committee, which was more conservative (Figure 11). In the ITT population, success at 6 weeks post-treatment (TOC) was reported in 64 (53.3%) of 120 daptomycin patients and in 58 (50.4%) of 115 comparator patients; the lower bound on the 95% CI on the difference in success rates was -9.9%, indicating non-inferiority of daptomycin to comparator. Similar results were noted in the PP population.

Figure 11: Investigator-Reported Success Rates at TOC (ITT and PP Populations)



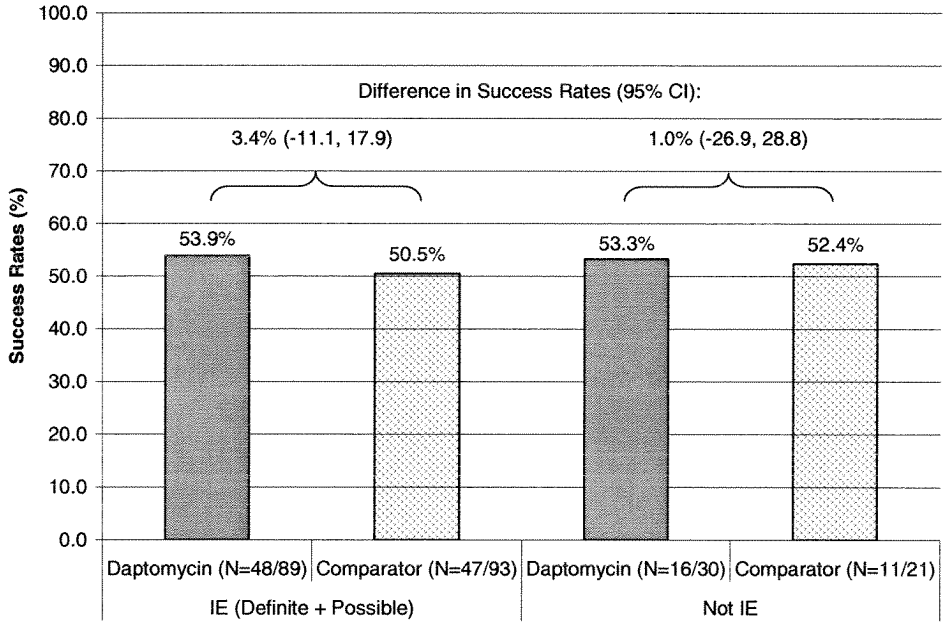
A concordance analysis of Investigator and Adjudication Committee outcomes was conducted. Data from a total of 157 of the 235 ITT patients were included in the analysis at TOC; 78 patients who terminated early from the study were excluded.

At TOC, the Investigator and Adjudication Committee outcomes agreed in 130 of 157 cases and disagreed in 27. Among the 27 disagreements, 26 were cases in which the Adjudication Committee was more conservative and assessed the patient as a treatment failure, whereas the Investigator reported success. The majority of these 26 patients were reported as failures by the Adjudication Committee because the patients had been administered non-study antibiotics that may have influenced outcome (15 cases); 4 were reported as failures by the committee due to persistent or relapsing infection, 4 had no blood cultures to document success, and 3 were assessed as non-evaluable by the committee. In one case, the Adjudication Committee reported success at TOC and the Investigator reported that the patient had not been seen at the clinic. This patient was incarcerated, was contacted, and was

well at TOC; a subsequent visit was conducted with a negative blood culture, resulting in an Adjudication Committee outcome of success.

Investigator outcomes were also determined by Investigator-reported diagnosis at study entry (based on the Modified Duke Criteria) (Figure 12). These results were similar between the treatment groups and were 5% to 10% higher than those reported by the Adjudication Committee, which was more conservative in its assessments. By Investigator Entry diagnosis, success rates at TOC for patients with Definite or Possible IE were 53.9% and 50.5% in the daptomycin and comparator groups, respectively, and for patients unlikely to have IE, success rates were 53.3% and 52.4%, respectively.

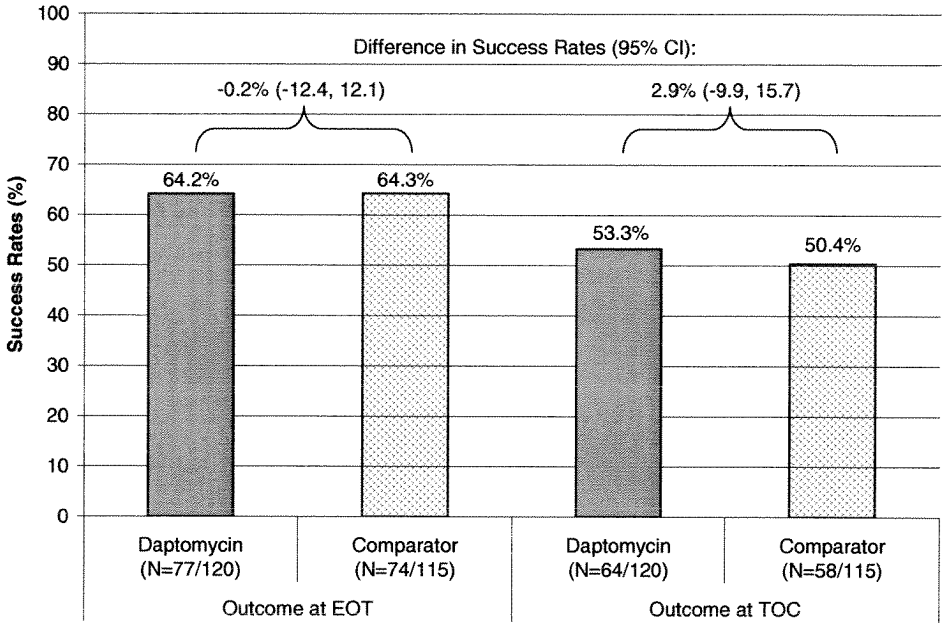
Figure 12: Investigator-Reported Success Rates at TOC by Investigator-Determined Entry Diagnosis (ITT Population)



2.5.3.6 Investigator Assessment of Outcome at End of Therapy

Figure 13 presents Investigator-determined success rates at EOT; results at TOC are displayed for reference. At EOT, the success rates as determined by the clinical Investigators were similar between the treatment groups and to those reported by the Adjudication Committee (64.2% for daptomycin and 64.3% for the comparator). Note that the EOT results are consistent with response rates reported in recent *S. aureus* bacteremia and endocarditis studies (>60%).(19, 29, 81)

Figure 13: Investigator-Reported Success Rates at EOT and TOC (ITT Population)



2.5.4 Reasons for Treatment Failure

The Adjudication Committee assessed all reasons for failure in each patient. As shown in Table 19, the overall treatment failure rates in the ITT population were similar in the daptomycin (55.8%) and comparator (58.3%) groups (note that more than one reason may apply). No differences were noted between the treatment groups in the proportion of patients who failed treatment due to receipt of non-study antibiotics that may have influenced outcome (16.7% and 13.9% in the daptomycin and comparator groups, respectively) or in the number of patient deaths (10.8% and 11.3%, respectively). Patients in the daptomycin group were more likely to be reported by the Adjudication Committee as failures at TOC due to persisting/relapsing *S. aureus* (PRSA) and/or clinical failure (19.2% in the daptomycin group and 13.0% in the comparator group), and 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).

Table 19: Adjudication Committee Reasons for Failure/Non-Evaluable at TOC (ITT Population)

Reason for Failure	Daptomycin N=120 n (%)	Comparator N=115 n (%)
Overall Failure[a]	67 (55.8%)	67 (58.3%)
Reason for failure[b]		
Persisting/relapsing *S. aureus* infection and/or clinical failure	23 (19.2%)	15 (13.0%)
Persisting or relapsing *S. aureus* infection	19 (15.8%)	11 (9.6%)
Clinical failure without persistence/relapse	4 (3.3%)	4 (3.5%)
Discontinued due to adverse event	8 (6.7%)	17 (14.8%)
Received non-study antibiotics that influenced outcome	20 (16.7%)	16 (13.9%)
Patient died	13 (10.8%)	13 (11.3%)
No blood culture drawn at TOC	9 (7.5%)	12 (10.4%)
Non-evaluable (withdrew consent, left against medical advice)	9 (7.5%)	14 (12.2%)

a Overall failure includes non-evaluable cases.

b Patients can have more than one reason for failure/non-evaluable.

A total of 30 patients, including 19 in the daptomycin group and 11 in the comparator group (9 receiving vancomycin and 2 SSP), experienced persistent or relapsing *S. aureus* infection. Mean treatment durations in these patients were 12.7 and 12.4 days in the daptomycin and comparator groups, respectively.

Among the 19 daptomycin patients with persisting or relapsing *S. aureus*, 6 had *S. aureus* isolates with increases in daptomycin MIC. Five of these isolates were MRSA. In all 6 patients, the baseline isolates had daptomycin MIC values of 0.25 µg/mL (4 patients) or 0.5 µg/mL (2 patients) and rose to 2 µg/mL (5 patients) or 4 µg/mL (1 patient).

Among the 9 vancomycin patients with persisting or relapsing *S. aureus*, one had an *S. aureus* isolate with an increase in vancomycin MIC to 2 µg/mL.

No association was found between plasma daptomycin (see Table 29, page 61) or vancomycin levels and microbiologic failure.

Most patients who failed due to persisting or relapsing *S. aureus* or who had clinical failure had deep-seated infections and did not or could not receive necessary surgical intervention. Major foci of infection included complications of endocarditis, intravascular infection, bone and joint infection, inadequately drained abscesses, infected ulcers, empyema and septic pulmonary emboli, high-grade *S. aureus* bacteremia, and intravenous port and pacemaker infections. Patients were not and could not be stratified by foci of infection at entry; note that in most of these patients, evidence of foci was present at entry but the foci were not diagnosed until after randomization.

A total of 25 patients, including 8 (6.7%) in the daptomycin group and 17 (14.8%) in the comparator group, were assessed by the Adjudication Committee as failures due to treatment-limiting adverse events. The most common treatment-limiting adverse events leading to treatment failure in the comparator group were hypersensitivity-type events, including rash, red man syndrome and anaphylaxis (6 patients), and renal toxicities

(5 patients). In the daptomycin group, the most common treatment-limiting adverse events leading to treatment failure were rash (2 patients), increased CPK (2 patients), and gastrointestinal (2 patients).

2.5.5 Evaluation of Patients with Endocarditis

A total of 37 patients were reported to have Definite IE at study entry based on the Adjudication Committee entry diagnosis; all 37 of these patients had a final diagnosis of IE as determined by the Adjudication Committee, including 18 patients with complicated RIE, 7 with uncomplicated RIE, and 12 with LIE. Furthermore, a total of 17 additional patients had a final diagnosis of IE, including 7 patients with complicated RIE, 3 with uncomplicated RIE, and 7 with LIE. A review of the data from these 54 patients with IE is provided below.

Patients with RIE

A total of 35 patients treated in this study had an Adjudication Committee final diagnosis of RIE, including 25 patients with complicated RIE and 10 with uncomplicated RIE.

Among the 35 patients with RIE, 19 received daptomycin and 16 received the comparator agent. Eight (42.1%) of the 19 daptomycin-treated patients and 7 (43.8%) of the 16 comparator-treated patients had RIE caused by MRSA.

As expected, the majority of these 35 patients were intravenous drug users; other risk factors included diabetes mellitus, prior episodes of IE, HIV, hepatitis C infection, underlying cardiac conditions, and pacemakers.

Potential complications and or foci of infection noted among the 25 patients with complicated RIE included tricuspid vegetations, abscess/empyema, septic pulmonary emboli or infarct, osteomyelitis, septic arthritis, and infected pacemaker/automatic implantable cardioverter defibrillator (AICD).

The TOC success rates in patients with RIE were similar between the treatment groups (8 of 19 patients, 42.1%, in the daptomycin group; 7 of 16 patients, 43.8%, in the comparator group). Among patients with complicated RIE, success was reported in 5 (38.5%) of 13 daptomycin patients and 6 (50.0%) of 12 comparator patients, and among those with uncomplicated RIE, success was reported in 3 (50.0%) of 6 patients and 1 (25.0%) of 4 patients, respectively.

Among patients with MRSA RIE, success was reported in 4 (50.0%) of 8 patients in the daptomycin group and 3 (42.9%) of 7 comparator patients.

Failure due to persisting or relapsing *S. aureus* infection was reported in a total of 6 patients with RIE, including 3 in each treatment group.

None (0%) of 19 daptomycin patients with RIE died during the study, compared with 2 (12.5%) of 16 comparator patients.

Patients with LIE

Although initially excluded from entry into the study, a total of 19 patients in the safety population with Adjudication Committee final diagnoses of LIE were treated in this study,

including 9 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 excluded from the ITT population in accordance with the Statistical Analysis Plan, but is included in this discussion.

Complications in these patients included valve perforation in 1 daptomycin patient and 3 comparator patients; none of the patients in the daptomycin group and 3 in the comparator group developed perivalvular abscesses. Other complications included osteomyelitis and post-surgical infections.

It is noteworthy that so many of these patients did not or could not receive surgical therapy, because several studies have demonstrated improved outcomes with early valve replacement surgery.(22, 82-86) Among the 19 patients with LIE, 3 underwent valve replacement surgery — 1 on study (comparator) and 2 following study (daptomycin).

Among the 19 patients with an Adjudication Committee final diagnosis of LIE, 10 had infections caused by MSSA, including 4 patients in the daptomycin group and 6 in the comparator group, and 9 had infections caused by MRSA, including 5 in the daptomycin group and 4 in the comparator group. Among the patients with LIE caused by MSSA, 1 of 4 daptomycin-treated patients and 2 of 6 comparator-treated patients had successful outcomes at TOC. None of the 9 patients with LIE caused by MRSA had successful outcomes at TOC.

Failure due to persisting or relapsing *S. aureus* infection was reported in a total of 6 patients, including 4 in the daptomycin group and 2 in the comparator group.

A total of 9 of the 19 patients with LIE died, including 3 (33.3%) of 9 patients in the daptomycin group and 6 (60.0%) of 10 patients in the comparator group.

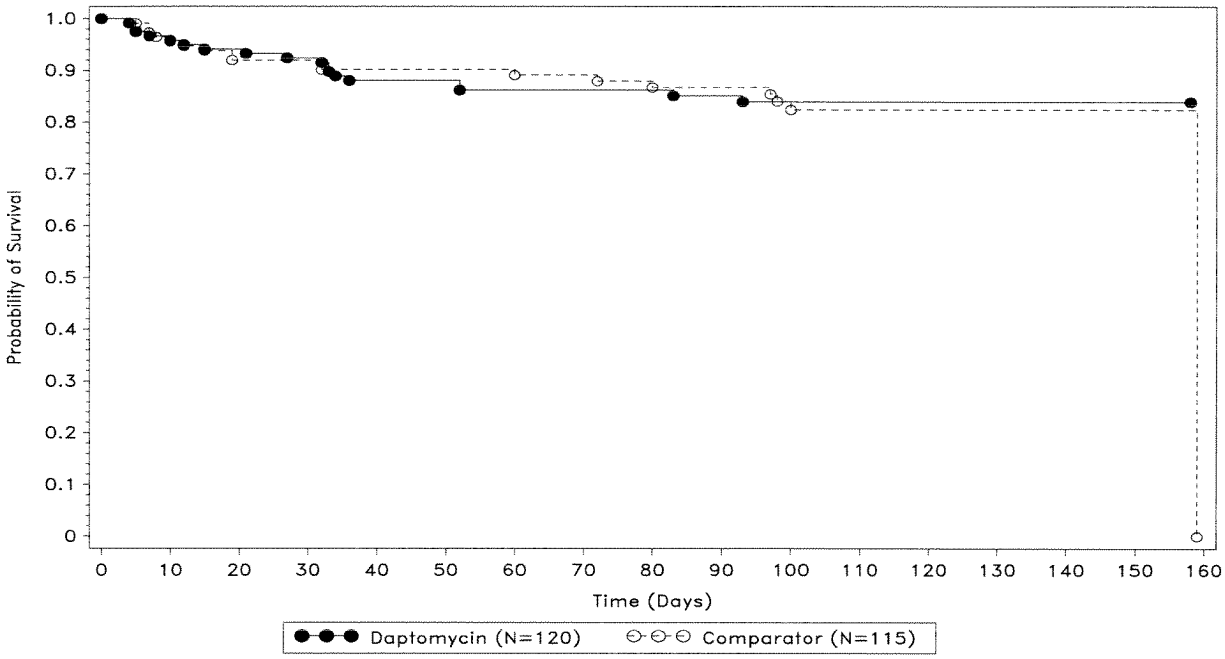
2.5.6 Time to Defervescence and Survival

Time to defervescence and survival were assessed in this study using Kaplan-Meier methods.

No statistically significant differences were noted between the treatment groups for time to defervescence in any analysis. Median time to defervescence, based on all patients with temperature >38.0°C on Day -1 or Day 1, was 3 days in both treatment groups overall and for patients with infections caused by MSSA and by MRSA.

The Kaplan-Meier survival curve, including all available survival data, is provided in Figure 14. There was no difference between the treatment groups in overall survival (p=0.976; log-rank statistic). As of last follow-up, a total of 18 (15.0%) of the 120 patients in the daptomycin group and 18 (15.7%) of the 115 patients in the comparator group had died.

Figure 14: Kaplan-Meier Survival Curve (ITT Population)



Note: The drop in the curve observed in the comparator group at Day 159 was related to the death of one patient, with no further data available for any other patients.

2.5.7 Sensitivity Analyses

At the request of the FDA, 2 sensitivity analyses were conducted to further document the robustness of the efficacy results. Success rates at TOC as determined by the Adjudication Committee were analyzed for the ITT population excluding patients with a diagnosis of LIE, and success rates for the PP population were analyzed excluding patients with a TOC visit outside the strict protocol-defined TOC window of Days 38 to 42P. Results are displayed in Table 20 and were consistent with the primary endpoint showing that daptomycin was non-inferior to the comparator agents in the treatment of patients with *S. aureus* bacteremia, including those with known or suspected endocarditis.

Table 20: Pre-specified Sensitivity Analysis for Adjudication Committee Success Rates at TOC

Analysis:	Daptomycin (N=120) n/N (%)	Comparator (N=115) n/N (%)	Difference in Success Rate (95% CI)
Excluding Patients with LIE	52/111 (46.8%)	46/106 (43.4%)	3.5% (–9.8, 16.7)
Excluding Patients with TOC outside Days 38 to 42P	32/65[a] (49.2%)	24/48[a] (50.0%)	–0.8% (–19.4, 17.9)

a Results based on the PP population.

Cubist conducted additional post-hoc sensitivity analyses, based on inclusion and exclusion of non-evaluable patients from analyses (Table 21) and including only specific patient subsets as failures based on the Adjudication Committee-reported reasons for failure (Table 22). As shown, all sensitivity analyses yielded results that were consistent with the

primary efficacy results showing that daptomycin was non-inferior to the comparator agents in the treatment of patients with *S. aureus* bacteremia, including those with known or suspected endocarditis.

Table 21: Additional Sensitivity Analysis for Adjudication Committee Success Rates at TOC Based on Inclusion/Exclusion of Non-evaluable Cases (ITT Population)

Analysis:	Daptomycin (N=120) n/N (%)	Comparator (N=115) n/N (%)	Difference in Success Rate (95% CI)
Including Non-evaluable as Success	62/120 (51.7%)	62/115 (53.9%)	–2.2% (–15.0, 10.5)
Excluding Non-evaluable from Analysis	53/111 (47.7%)	48/101 (47.5%)	0.2% (–13.2, 13.7)

Table 22: Additional Sensitivity Analyses for Adjudication Committee Success Rates at TOC Based on Reported Reasons for Failure (ITT Population)

Analysis:	Daptomycin (N=120) n/N (%)	Comparator (N=115) n/N (%)	Difference in Success Rate (95% CI)
Considers only patients with PRSA as failures[a]	92/120 (76.7%)	90/115 (78.3%)	–1.6% (–12.3, 9.1)
Considers only patients with PRSA or death as failures[a]	86/120 (71.7%)	81/115 (70.4%)	1.2% (–10.4, 12.8)
Considers only patients with PRSA or death or clinical failure as failures[a]	84/120 (70.0%)	79/115 (68.7%)	1.3% (–10.5, 13.1)
Considers only patients with PRSA or death or clinical failure or withdrawal due to AE as failures[a]	77/120 (64.2%)	67/115 (58.3%)	5.9% (–6.5, 18.3)

PRSA=persisting/relapsing *S. aureus*.

a Based on reasons for failure as reported by the Adjudication Committee; also includes non-evaluable patients as failures.

Additional sensitivity analyses were conducted that included individual reasons for failure analyzed as success or excluded them from the analysis. These results also were consistent with the primary efficacy results showing that daptomycin was non-inferior to the comparator agents in the treatment of patients with *S. aureus* bacteremia, including those with known or suspected endocarditis.

2.5.8 Success Rates in Patient Subgroups

2.5.8.1 Success Rates by Demographic Characteristics

Table 23 provides a summary of Adjudication Committee success rates at the TOC evaluation for patient subgroups in the ITT population, including gender, age, race, geographic region, and renal function at study entry.

Although differences are noted between the treatment groups, many of the baseline factors are likely to be interrelated, including decreased renal function and age. Given the small sample sizes in many of the individual subgroups, no definitive conclusions can be drawn.

Table 23: Adjudication Committee Success Rates at TOC by Demographic Characteristics (ITT Population)

Subgroup	Daptomycin n/N (%)	Comparator n/N (%)
ITT Population Overall	53/120 (44.2%)	48/115 (41.7%)
Gender		
Male	35/70 (50.0%)	30/71 (42.3%)
Female	18/50 (36.0%)	18/44 (40.9%)
Age		
<65 years	47/90 (52.2%)	35/78 (44.9%)
≥65 years	6/30 (20.0%)	13/37 (35.1%)
Race		
Caucasian	27/75 (36.0%)	35/81 (43.2%)
Black	21/32 (65.6%)	10/23 (43.5%)
Other	5/13 (38.5%)	3/11 (27.3%)
Renal Function		
CL_{cr} >80 mL/min	38/67 (56.7%)	25/59 (42.4%)
CL_{cr} ≤80 mL/min	15/53 (28.3%)	23/56 (41.1%)
Geographic Region		
US	46/100 (46.0%)	47/99 (47.5%)
Europe	7/20 (35.0%)	1/16 (6.3%)

2.5.8.2 Success Rates by Endocarditis Risk Factors

Table 24 provides a summary of Adjudication Committee success rates at the TOC evaluation for patient subgroups in the ITT population based on risk factors for endocarditis. Success rates were similar between the treatment groups for patients with diabetes, SIRS, injection drug use, permanent intravascular foreign material, and trauma within 30 days as baseline risk factors. A higher response (>10% difference) was noted in the daptomycin group for patients with extravascular foreign material, septic pulmonary emboli, and surgery within 30 days, and a higher response was noted in the comparator group for patients with pre-existing valvular heart disease and percutaneous intravascular devices present. Note, however, that the sample size for many of these subgroups was small, making it difficult to draw any definitive conclusions.

Table 24: Adjudication Committee Success Rates at TOC by Endocarditis Risk Factors (ITT Population)

Subgroup	Daptomycin n/N (%)	Comparator n/N (%)
ITT Population Overall	53/120 (44.2%)	48/115 (41.7%)
Diabetes Mellitus	18/44 (40.9%)	17/42 (40.5%)
SIRS present	38/89 (42.7%)	37/87 (42.5%)
Injection Drug Use	13/25 (52.0%)	12/25 (48.0%)
Pre-existing Valvular Heart Disease	3/16 (18.8%)	3/9 (33.3%)
Extravascular Foreign Material	12/28 (42.9%)	8/29 (27.6%)
Permanent Intravascular Foreign Material	7/15 (46.7%)	7/18 (38.9%)
Percutaneous Intravascular Device	2/6 (33.3%)	3/4 (75.0%)
Septic Pulmonary Emboli	6/10 (60.0%)	6/13 (46.2%)
Surgery within 30 Days	23/49 (46.9%)	13/36 (36.1%)
Trauma within 30 Days	12/22 (54.5%)	10/18 (55.6%)

2.6 Microbiology Results

2.6.1 Minimum Inhibitory Concentrations of Baseline Infecting Pathogens

The DAP-IE-01-02 Central Microbiology Laboratory was responsible for receiving study isolates from clinical study sites, identifying each isolate to the species level, and performing antimicrobial susceptibility testing according to NCCLS criteria (80) for all isolates identified as *S. aureus*. A total of 1459 isolates of *S. aureus* were reported by the study sites on the CRF, with 1256 isolates received and processed by the Central Laboratory for patients in the ITT population. All baseline infecting pathogens that were methicillin-resistant were *mecA*-positive.

A summary of MIC results for daptomycin, oxacillin, and vancomycin for all *S. aureus* isolated during Study DAP-IE-01-02 is provided in Table 25. The MIC values are consistent with those seen in contemporaneous surveillance studies.

Table 25: Summary of MIC Data for All *S. aureus* Isolates from Patients in Study DAP-IE-01-02 (ITT population)

Pathogen	N	Antibiotic	MIC Value Range (µg/mL)	MIC_{50} Value (µg/mL)	MIC_{90} Value (µg/mL)
All *S. aureus*	1256	Daptomycin	0.12 – 4	0.25	0.5
		Oxacillin	≤0.06 – >8	0.5	>8
		Vancomycin	0.25 – 2	0.5	1
MSSA	690	Daptomycin	0.12 – 4	0.25	0.25
		Oxacillin	≤0.06 – 2	0.25	0.5
		Vancomycin	0.25 – 2	0.5	1
MRSA	566	Daptomycin	0.12 – 2	0.25	0.5
		Oxacillin	≤0.06 – >8[a]	>8	>8
		Vancomycin	0.5 – 2	0.5	1

a Twelve *S. aureus* isolates were classified as MRSA based on the results of *mecA* testing by polymerase chain reaction and pulsed-field gel electrophoresis. These isolates had oxacillin MIC values of ≤0.06 to 2 µg/mL.

2.6.2 Efficacy Results by Baseline Minimum Inhibitory Concentration

Table 26 and Table 27 present a summary of Adjudication Committee success rates overall and by oxacillin susceptibility of the baseline infecting pathogen by baseline MIC values for daptomycin and vancomycin, respectively. No trends were observed among the baseline *S. aureus* daptomycin or vancomycin MIC values and outcome.

Table 26: Summary of Adjudication Committee Success Rates, by Pathogen and by Baseline Daptomycin Broth Microdilution MIC Value (ITT Population)

Pathogen	Baseline Daptomycin MIC[a] (µg/mL)	Daptomycin		Comparator	
		N	Success Rate	N	Success Rate
All *S. aureus*	Overall	119	53/119 (44.5%)	114	48/114 (42.1%)
	n.d.[b]	2	2/2 (100.0%)	1	0/1 (0.0%)
	0.12	3	1/3 (33.3%)	13	5/13 (38.5%)
	0.25	93	40/93 (43.0%)	74	33/74 (44.6%)
	0.5	21	10/21 (47.6%)	25	10/25 (40.0%)
	1	0	0	1	0/1 (0.0%)
MSSA	Overall	74	33/74 (44.6%)	70	34/70 (48.6%)
	n.d.[b]	2	2/2 (100.0%)	1	0/1 (0.0%)
	0.12	3	1/3 (33.3%)	13	5/13 (38.5%)
	0.25	58	24/58 (41.4%)	47	24/47 (51.1%)
	0.5	11	6/11 (54.5%)	9	5/9 (55.6%)
	1	0	0	0	0
MRSA	Overall	45	20/45 (44.4%)	44	14/44 (31.8%)
	0.12	0	0	0	0
	0.25	35	16/35 (45.7%)	27	9/27 (33.3%)
	0.5	10	4/10 (40.0%)	16	5/16 (31.3%)
	1	0	0	1	0/1 (0.0%)

Note: n.d.=not done.

a Baseline daptomycin microdilution MIC values were determined at the Central Microbiology Laboratory for each patient's baseline infecting pathogen.

b Three patients did not have a baseline *S. aureus* isolate sent to the Central Microbiology Laboratory.

Table 27: Summary of Adjudication Committee Success Rates, by Pathogen and by Baseline Vancomycin Broth Microdilution MIC Value (ITT Population)

Pathogen	Baseline Vancomycin MIC[a] (µg/mL)	Daptomycin		Comparator	
		N	Success Rate	N	Success Rate
All *S. aureus*	Overall	119	53/119 (44.5%)	114	48/114 (42.1%)
	n.d.[b]	2	2/2 (100.0%)	1	0/1 (0.0%)
	0.5	70	28/70 (40.0%)	68	29/68 (42.6%)
	1	47	23/47 (48.9%)	45	19/45 (42.2%)
MSSA	Overall	74	33/74 (44.6%)	70	34/70 (48.6%)
	n.d.[b]	2	2/2 (100.0%)	1	0/1 (0.0%)
	0.5	49	19/49 (38.8%)	45	21/45 (46.7%)
	1	23	12/23 (52.2%)	24	13/24 (54.2%)
MRSA	Overall	45	20/45 (44.4%)	44	14/44 (31.8%)
	0.5	21	9/21 (42.9%)	23	8/23 (34.8%)
	1	24	11/24 (45.8%)	21	6/21 (28.6%)

Note: n.d.=not done.

a Baseline vancomycin MIC values were determined at the Central Microbiology Laboratory for each patient's baseline infecting pathogen.

b Three patients did not have a baseline *S. aureus* isolate sent to the Central Microbiology Laboratory.

2.6.3 Emergence of Daptomycin Non-Susceptible Isolates

S. aureus isolates that demonstrated increased daptomycin MIC values exceeding the current susceptible breakpoint of ≤1 µg/mL were recovered from 8 different patients. The isolates from 7 of the patients went to an MIC value of 2 µg/mL, while the isolate from 1 patient went to 4 µg/mL. Seven of the 8 patients were in the daptomycin group (including 6 patients who failed therapy and one patient with success), and 1 patient who received vancomycin was in the comparator group.

Additional studies are ongoing with the baseline and non-susceptible strains from these patients. The goals of these studies are to identify any factors intrinsic to the infecting *S. aureus* strains and any biological differences between the baseline isolates and the isolates with MIC values of 2 or 4 µg/mL. These studies include *in vitro* growth curves, *in vitro* time-kill curves, genetic analyses, and *in vivo* animal model studies.

2.7 Pharmacokinetic and Pharmacodynamic Results

2.7.1 Pharmacokinetic Results

A population pharmacokinetic model, including data from 10 Phase 1 and 8 Phase 2/3 clinical trials, was conducted. The Phase 1 clinical trials included adult and elderly healthy subjects, moderately and extremely obese subjects, subjects with varying degrees of renal function, and subjects with impaired hepatic function. The Phase 2/3 clinical trials included patients with Gram-positive bacterial infections, including patients in Study DAP-IE-01-02.

The population pharmacokinetics of daptomycin in healthy subjects and in patients with Gram-positive infections (cSSSI, IE, and/or bacteremia) were described by a two-compartment model. The model parameters were daptomycin clearance (CL), volume of the central compartment (V_1), intercompartmental clearance (Q), and volume of the peripheral compartment (V_2). The major covariate affecting the pharmacokinetics of daptomycin was renal function (CL_{cr} or dialysis on CL).

A review of patients from Study DAP-IE-01-02 indicated that the model was performing equally well in this population as it was overall. Individual PK parameters for DAP-IE-01-02 patients were estimated, and derived parameters were calculated (Table 28).

Total exposure to daptomycin in patients with bacteremia or IE as assessed by AUC is lower than that seen in healthy subjects at the same dose at steady-state. In patients with infections, the volume of distribution at steady-state (V_{ss} [L/kg]) is markedly increased, and the total CL (mL/h/kg) is higher than in healthy subjects. However, C_{max}, terminal half-life ($T_{1/2}$), and trough ($C_{24,ss}$) values are generally similar to those in normal volunteers.

Table 28: Summary of Pharmacokinetic Parameters (PK Population)

Parameter	N	Mean (CV%)	Median	Minimum, Maximum
$C_{24,ss}$ (µg/mL)	106[a]	10.3 (66.4)	8.16	2.26, 35.1
$C_{max,ss}$ (µg/mL)	106[a]	101 (118.2)	72.3	18.5, 1070
$AUC_{0-24,ss}$ (µg*h/mL)	108	622 (48.8)	543	242, 2210
V_{ss} (L)	108	12.6 (45.7)	11.6	4.61, 56.5
V_{ss} (L/kg)	108	0.158 (39.4)	0.152	0.046, 0.508
CL (L/h)	108	0.927 (41.3)	0.879	0.272, 2.77
CL (mL/h/kg)	108	11.6 (41.5)	11.1	2.71, 25
$T_{1/2}$ (h)	108	11.0 (36.7)	9.92	6.22, 25.8

a Two patients were not at steady-state (defined as 5 half-lives) on the day of PK sampling and are not included in these analyses.

AUC values in patients with bacteremia or IE who received 6 mg/kg were proportionately higher as predicted than values for patients with cSSSI who received 4 mg/kg; in general CL, volume of distribution and $T_{1/2}$ were similar in patients with infections at these 2 dose levels.

2.7.2 Pharmacokinetic and Pharmacodynamic Association with Efficacy

Several animal models of infection have demonstrated that the parameters C_{max}/MIC and AUC_{0-24}/MIC are those most closely correlated with *in vivo* efficacy. These observations are consistent with daptomycin's concentration-dependent bactericidal activity noted *in vitro*. The population PK model provided estimates for each patient's steady-state daptomycin PK parameters, specifically C_{max} 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.

PK/PD parameters by Adjudication Committee outcome at EOT are shown in Table 29. The EOT time point was selected for the analysis because it is less confounded by patients deemed failures at TOC for reasons not related to daptomycin therapy (e.g., missing blood culture, other antibiotics). No relationship was noted between the daptomycin PK/PD parameters examined and outcome at EOT. Similar C_{max}, AUC_{0-24}, and resultant C_{max}/MIC and AUC_{0-24}/MIC values were observed in both the Adjudication Committee success and failure groups at EOT.

Table 29: Summary of Daptomycin PK/PD Parameters by Adjudication Committee Outcome at EOT

PK/PD Parameter	Success (Mean ± SD)	Failure (Mean ± SD)	P-value[a]
N[b]	73	33	
C_{max} (µg/mL)	108.1 ± 140.38	84.1 ± 41.00	0.337
AUC_{0-24} (µg*h/mL)	592.6 ± 249.84	616.9 ± 261.12	0.648
C_{max} / Baseline MIC value	375.8 ± 391.70	306.9 ± 160.41	0.334
AUC_{0-24} / Baseline MIC value (h)	2168.0 ± 1025.33	2229.2 ± 930.49	0.771

a P-values determined by a t-test.

b The population for analysis included patients in the PK population who reached steady-state and had microbiology data available.

2.7.3 Pharmacokinetic and Pharmacodynamic Association with Safety

The population PK data were also used to characterize the exposure-response relationship for daptomycin and CPK in patients (DAP-IE-01-02 plus all other data) using AUC, C_{max}, clearance, and trough ($C_{24,ss}$) as measures of exposure.

A trend toward increasing CPK with increasing exposure to daptomycin as measured by AUC_{ss} and $C_{min,ss}$ was noted. However, this trend was observed for CPK levels within the range of normal and is therefore of unclear clinical significance. There were a limited number of observations of CPK above the upper limit of normal.

A complete discussion of CPK results for this study, including patients with elevations in CPK, is provided in Section 2.8.7.7 (page 73).

2.8 Safety Results

2.8.1 Overview

The currently approved dose for daptomycin in the treatment of complicated skin and skin structure infections is 4 mg/kg administered by i.v. infusion over 30 minutes once daily for 7 to 14 days. The proposed dose of daptomycin for the indication sought in this supplemental New Drug Application (sNDA) (i.e., the treatment of patients with *S. aureus* bacteremia, including those with known or suspected endocarditis caused by methicillin-susceptible and methicillin-resistant strains) is 6 mg/kg administered as a 30-minute i.v. infusion once per day for a minimum duration of 2 to 6 weeks, depending on the clinical condition.

The safety information reviewed in the sNDA was derived primarily from the pivotal Phase 3 Study DAP-IE-01-02, which treated a total of 236 patients with endocarditis or bacteremia; these results are summarized in the sections below. Additional supportive safety data derived from 12 clinical studies sponsored by Cubist and 3 Lilly-sponsored studies that treated a total of 619 subjects and patients, including 414 who received at least one dose of daptomycin ≥6 mg/kg per day, were included in the sNDA. The data from Study DAP-IE-01-02 were not pooled with data from other studies because this was the only study that specifically evaluated the proposed dose of 6 mg/kg q24h in the specific indication of *S. aureus* bacteremia and endocarditis sought in the sNDA.

2.8.2 Non-clinical Safety Review

The non-clinical safety profile of daptomycin is consistent across species for both pharmacokinetic and toxicologic effects. At clinically relevant dose levels, daptomycin was well tolerated when administrated to rats, dogs, and monkeys for up to 6 months. No clinical signs of toxicity or effects on growth (body weight), food consumption, hematology, serum chemistry, or urinalysis were observed, and no significant histopathological changes were evident. Daily administration of daptomycin to rhesus monkeys at dose levels up to 10 mg/kg (resulting in a daily AUC comparable to that in patients at 6 mg/kg q24h) for 1 month was not associated with any adverse clinical or histopathological effects.

At higher doses, daptomycin administration has been associated with effects on skeletal muscle, with no histopathologic changes in cardiac or smooth muscle. Skeletal muscle effects were characterized from very minimal to minimal degenerative/regenerative changes, with less than <0.1% of muscle fibers affected. Serum CPK was a very sensitive measure of daptomycin-associated muscle effects. Mild effects (minimal degenerative changes and increases in serum CPK levels, generally without clinical signs of muscle weakness) were noted at doses ranging from 20 to 75 mg/kg/day. 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), representing exposures (daily AUC) of approximately 10-fold and 6-fold, respectively, the predicted human exposure for the 6 mg/kg q24h dose. The degree of skeletal myopathy showed no increase when treatment was extended from 1 month to up to 6 months. 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 losses of patellar reflex, gag reflex, and pain perception) were observed at doses 4- to 6-fold higher than those associated with skeletal myopathy. The C_{max} values at the dose levels associated with peripheral nerve effects are approximately 16 times the peak plasma levels in humans at the proposed *S. aureus* bacteremia and endocarditis clinical dose of 6 mg/kg q24h (mean C_{max} = 108 µg/mL). Peripheral nerve effects are reversible, consistent with the absence of a microscopic effect on the neuronal cell body.

Daptomycin-related effects on the kidney were limited to the rat and are considered species-specific.

No other daptomycin-related effects were apparent across the non-clinical safety studies.

2.8.3 Morbidity Associated with Bacteremia and Infective Endocarditis Caused by **Staphylococcus aureus** *and with the Therapies Administered for the Disease*

The clinical manifestations of *S. aureus* endocarditis are highly variable and are characterized by local, embolic, and systemic manifestations.(33, 87) The local complications include valve destruction, which may be associated with a new or worsening regurgitant murmur, and signs and symptoms of valvular insufficiency. Because of the acute nature of the evolving valvular insufficiency, rapid cardiac decompensation can ensue, with evidence of both forward and congestive heart failure. Additional local complications include progression of infection into deeper cardiac tissues with resultant abscess formation, conduction disturbances and arrhythmias, myocardial infarction, and pericarditis (which can lead to cardiac tamponade). Surgical removal of the infected valve is often required to manage these complications effectively, even with optimal antibiotic therapy.(22, 85)

The embolic manifestations of IE are based on the location of the infected valve. In LIE affecting the mitral or aortic valve, vegetations are liberated into the systemic circulation. Central nervous system symptoms, including acute stroke, may result from septic emboli to the middle cerebral artery or due to septic emboli causing brain abscess or mycotic aneurysm. Less commonly, patients may present with purulent meningitis. More typically,

patients develop metastatic deep tissue infection, such as visceral abscesses, vertebral osteomyelitis, septic arthritis, and psoas abscess. Surgical intervention at the site of the embolic complication is sometimes needed. In RIE affecting the pulmonic or tricuspid valve, the site of embolization involves the pulmonary vascular beds, with resultant pulmonary embolism, infarction, and abscess often associated with empyema.

The systemic manifestations of acute IE include signs and symptoms of infection with fever (or hypothermia), chills, rigors, arthralgia, myalgia, and hypotension. Sepsis may be associated with clinical signs of poor peripheral perfusion and diffuse organ system dysfunction, including acute renal failure and cardiorespiratory compromise. Additional clinical features of IE include splenomegaly, petechiae (including on mucosal surfaces), and clubbing of the fingers (usually associated with longer duration infections). Renal insufficiency is common in IE and may be the result of renal abscess, infarction, or glomerulonephritis.

Normochromic, normocytic anemia is a common presenting hematologic feature of IE and is more marked when the presentation of IE is subacute. Leukocytosis is more commonly seen with acute staphylococcal IE. The erythrocyte sedimentation rate is typically elevated, as is C-reactive protein, reflecting the underlying inflammatory response. Circulating immune complexes and positive rheumatoid factor are commonly observed and may be associated with proteinuria, microscopic hematuria, and hypocomplementemia accompanying renal impairment caused by diffuse glomerulonephritis.

Currently employed treatments for IE are often associated with side effects. Adverse events due to SSPs include drug allergy (including anaphylaxis, interstitial nephritis, rash, eosinophilia), gastrointestinal side effects (including nausea, vomiting, diarrhea, and elevated liver function tests [LFTs]), and bone marrow suppression.(88) Vancomycin administered via rapid infusion can result in histamine-mediated reactions manifested as hypotension and, rarely, cardiac arrest. Other infusion-related events can include wheezing, dyspnea, urticaria, rash, muscle spasm of the chest and back, and flushing of the upper body and neck (red man syndrome). Rare toxicities include ototoxicity, nephrotoxicity, reversible neutropenia, and allergic reactions. Gentamicin, often added to these regimens, has the attribute of significant nephrotoxicity, particularly when combined with vancomycin.(89) The risk of nephrotoxicity of gentamicin is increased in the presence of renal impairment. Gentamicin can also result in permanent ototoxicity, both vestibular and auditory.(90)

2.8.4 Safety Evaluations Conducted during Study DAP-IE-01-02

Careful safety evaluations were conducted throughout the treatment phase and during the follow-up period in Study DAP-IE-01-02 (see Table 6, page 28). Visits were conducted daily during in-patient treatment, at the end of therapy, and 6 weeks post-treatment. An additional post-study telephone contact or visit was conducted 12 weeks post-treatment for patients who had a successful outcome at the TOC visit. All patients who terminated study medication early were to have an evaluation performed within 3 days after the last day of study medication administration. These patients were subsequently followed weekly for

documentation of antibiotics received and survival and had a safety visit approximately 6 weeks post-treatment.

Baseline evaluations included medical, antibiotic and medication history, physical examination, blood cultures, chest x-ray, ECG, and clinical laboratory tests. Patients were monitored daily during the treatment period for the occurrence of adverse events and the use of concomitant medications. ECGs were obtained at baseline, weekly during treatment to the EOT visit, and at follow-up visits. CPK assessments were conducted on 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. If the subject had completed study medication, CPK values were to be monitored daily until values trended downward, at which point CPK was to be monitored a minimum of 3 days per week. The medical monitor was to be contacted whenever CPK exceeded 4.0 x ULN. Other clinical laboratory tests, including hematology, clinical chemistry, and urinalysis, were to be obtained on Days 1, 4, and 7, weekly to EOT and during follow-up.

2.8.5 Overview of Adverse Events

During Study DAP-IE-01-02, treatment with daptomycin was well tolerated at a dose of 6 mg/kg once daily for 2 to 6 weeks in a seriously ill patient population with *S. aureus* bacteremia and endocarditis.

The reported rates of TEAEs, drug-related events, severe events, deaths, SAEs, and events leading to treatment withdrawal were similar between the daptomycin and comparator groups (Table 30). As expected in a seriously ill patient population, the majority of patients experienced at least one adverse event during the study. Most events were assessed as unrelated to study treatment and were reported as mild to moderate in severity by the Investigators.

Table 30: Overview of Adverse Events (Safety Population)

Patients with:	Daptomycin (N=120) n (%)	Comparator (N=116) n (%)
Any TEAE	115 (95.8%)	110 (94.8%)
Any drug-related TEAE	42 (35.0%)	49 (42.2%)
Any severe/marked TEAE	55 (45.8%)	53 (45.7%)
Death	18 (15.0%)	19 (16.4%)
Any SAE	62 (51.7%)	52 (44.8%)
Any drug-related SAE	3 (2.5%)	6 (5.2%)
Terminated study drug due to TEAE	20 (16.7%)	21 (18.1%)
Terminated study drug due to drug-related TEAE	10 (8.3%)	13 (11.2%)

2.8.6 Common Adverse Events

Table 31 presents the most commonly reported adverse events, i.e., the events reported in 10% or more of patients in either treatment group by MedDRA preferred term; the table also

includes the drug-related and severe incidence of these events. Adverse events reported in ≥5% of patients in either treatment group are displayed by MedDRA SOC and preferred term in Table 32.

There were no statistically significant differences between the treatment groups with regard to the incidence of adverse events by MedDRA SOC, with the exception of the *General Disorders and Administration Site Conditions* SOC. In this SOC, a higher proportion of patients in the comparator group (59.5%) experienced at least one adverse event than in the daptomycin group (44.2%) (p=0.020). The most commonly reported types of events in this SOC were edema, pain and discomfort, febrile disorders, asthenic conditions, and injection and infusion site reactions. Each of these types of events was reported at a higher incidence in the comparator group than in the daptomycin group.

The most commonly reported events during the study were gastrointestinal in nature and included diarrhea, nausea, vomiting, and constipation. Other events reported in ≥10% of patients in either treatment group included anemia, hypokalemia, peripheral edema, headache, and arthralgia. All of these events were reported at a similar or lower incidence in the daptomycin group relative to the comparator group. The majority of the most commonly reported events were assessed as mild to moderate in severity and unrelated to study treatment.

Drug-related adverse events were reported in 35.0% and 42.2% of patients in the daptomycin and comparator groups, respectively. The most commonly reported drug-related adverse event overall was diarrhea, occurring in 1.7% and 9.5% of patients in the daptomycin and comparator groups, respectively. Other drug-related events reported in ≥5% of patients in either treatment group by MedDRA preferred term included increased blood CPK (5.0% and 0% in the daptomycin and comparator groups, respectively), renal failure (1.7% and 6.0%, respectively), and nausea (1.7% and 5.2%, respectively).

Adverse events judged by the Investigators to be severe or marked in intensity were reported in 45.8% and 45.7% of patients in the daptomycin and comparator groups, respectively. The most commonly reported severe event was sepsis, reported in 5.0% and 2.6% of patients in the daptomycin and comparator groups, respectively. In 2 of the 6 patients in the daptomycin arm, the severe sepsis was reported on Days 1 or 2 of therapy; all other reports of severe sepsis occurred on the last day of therapy or post-treatment. All other severe events were reported in <5% of patients in both treatment groups. Severe drug-related adverse events were reported in 6 (5.0%) of the 120 daptomycin-treated patients and 13 (11.2%) of the 116 comparator-treated patients.

Table 31: Incidence of the Most Common (≥10%) Adverse Events: Overall, Drug-Related, and Severe (Safety Population)

MedDRA Preferred Term	Daptomycin (N=120)			Comparator (N=116)		
	Any Event	Drug-Related	Severe	Any Event	Drug-Related	Severe
Pts with one event	*115 (95.8%)*	*42 (35.0%)*	*55 (45.8%)*	*110 (94.8%)*	*49 (42.2%)*	*53 (45.7%)*
Diarrhoea NOS	14 (11.7%)	2 (1.7%)	0	21 (18.1%)	11 (9.5%)	2 (1.7%)
Nausea	12 (10.0%)	2 (1.7%)	0	23 (19.8%)	6 (5.2%)	3 (2.6%)
Anaemia NOS	15 (12.5%)	0	1 (<1%)	18 (15.5%)	0	0
Vomiting NOS	14 (11.7%)	1 (<1%)	2 (1.7%)	15 (12.9%)	2 (1.7%)	2 (1.7%)
Constipation	13 (10.8%)	1 (<1%)	0	14 (12.1%)	0	0
Hypokalaemia	11 (9.2%)	1 (<1%)	0	15 (12.9%)	1 (<1%)	0
Oedema peripheral	8 (6.7%)	0	0	16 (13.8%)	1 (<1%)	1 (<1%)
Headache	8 (6.7%)	1 (<1%)	0	12 (10.3%)	0	2 (1.7%)
Arthralgia	4 (3.3%)	0	0	13 (11.2%)	2 (1.7%)	0

Note: NOS = not otherwise specified.

Table 32: Incidence of Treatment-Emergent Adverse Events Reported in ≥5% of Patients in Either Treatment Group by MedDRA SOC and Preferred Term (Safety Population)

MedDRA SOC Preferred Term	Daptomycin (N=120) n (%)	Comparator (N=116) n (%)	p-value[a]
Infections and infestations	65 (54.2%)	56 (48.3%)	0.435
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%)	0.194
Diarrhoea NOS	14 (11.7%)	21 (18.1%)	
Vomiting NOS	14 (11.7%)	15 (12.9%)	
Constipation	13 (10.8%)	14 (12.1%)	
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%)	0.020
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%)	

(continued)

Table 32: Incidence of Treatment-Emergent Adverse Events Reported in ≥5% of Patients in Either Treatment Group by MedDRA SOC and Preferred Term (Safety Population)

MedDRA SOC Preferred Term	Daptomycin (N=120) n (%)	Comparator (N=116) n (%)	p-value[a]
Respiratory, thoracic and mediastinal disorders	38 (31.7%)	43 (37.1%)	0.412
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%)	0.488
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%)	0.269
Pain in extremity	11 (9.2%)	11 (9.5%)	
Back pain	8 (6.7%)	10 (8.6%)	
Arthralgia	4 (3.3%)	13 (11.2%)	
Psychiatric disorders	35 (29.2%)	28 (24.1%)	0.462
Insomnia	11 (9.2%)	8 (6.9%)	
Anxiety	6 (5.0%)	6 (5.2%)	
Nervous system disorders	32 (26.7%)	32 (27.6%)	0.885
Headache	8 (6.7%)	12 (10.3%)	
Dizziness	7 (5.8%)	7 (6.0%)	
Investigations	30 (25.0%)	33 (28.4%)	0.560
Blood creatine phosphokinase increased	8 (6.7%)	1 (<1%)	
Blood and lymphatic system disorders	29 (24.2%)	24 (20.7%)	0.537
Anaemia NOS	15 (12.5%)	18 (15.5%)	
Metabolism and nutrition disorders	26 (21.7%)	38 (32.8%)	0.059
Hypokalaemia	11 (9.2%)	15 (12.9%)	
Hyperkalaemia	6 (5.0%)	10 (8.6%)	
Vascular disorders	21 (17.5%)	20 (17.2%)	>0.999
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%)	0.181
Renal failure NOS	4 (3.3%)	11 (9.5%)	
Renal failure acute	4 (3.3%)	7 (6.0%)	

Note: NOS = not otherwise specified.

a p-value is from Fisher's exact test comparing the incidence of events by MedDRA SOC between the treatment groups.

2.8.7 Adverse Events of Clinical Importance

This section highlights the events associated with antibiotic therapy and events of interest based on the clinical and non-clinical safety profile of daptomycin and on the known clinical safety profiles of the comparator agents. Specifically, gastrointestinal disorders, including

reports of antibiotic-associated colitis; infections, including those potentially related to *S. aureus* pneumonia; peripheral nerve events; rashes, and other allergic-type reactions; renal toxicity; and elevations in CPK and possible associated musculoskeletal events, are reviewed.

2.8.7.1 Gastrointestinal Disorders

Gastrointestinal disorders occurred in 50.0% and 58.6% of patients in the daptomycin and comparator groups, respectively (p=0.194).

Gastrointestinal events reported in the daptomycin group included diarrhea (11.7%), vomiting (11.7%), constipation (10.8%), and nausea (10.0%). The incidence of gastrointestinal events was similar or higher in the comparator group (diarrhea [18.1%], vomiting [12.9%], constipation [12.1%], and nausea [19.8%]) relative to the daptomycin group.

The majority of the gastrointestinal disturbances were assessed as unrelated to study treatment and were mild to moderate in severity. Although commonly reported, gastrointestinal events rarely led to discontinuation of study treatment; 1.7% of patients in the daptomycin group and none of the patients in the comparator group discontinued due to gastrointestinal disorders.

Serious gastrointestinal disorders were reported in 2 patients (1.7%) in the daptomycin group and 6 patients (5.2%) in the comparator group. These included reports of diabetic gastroparesis and acute abdominal pain in the setting of Crohn's disease in the 2 patients in the daptomycin group and 4 reports of gastrointestinal hemorrhage and 1 report each of pancreatitis and vomiting in the 6 patients in the comparator group. None of the serious gastrointestinal events were assessed as drug-related by the investigators.

The incidence of *Clostridium difficile* colitis was low in both treatment groups, occurring in 1 (<1%) of 120 daptomycin-treated patients and 3 (2.6%) of 116 comparator-treated patients. Three of the events, including the 1 report in the daptomycin group and 2 in the comparator group, were moderate in severity and assessed as unrelated to study treatment. One event in the comparator group, reported in a patient receiving nafcillin followed by vancomycin, was serious in nature and assessed as drug-related by the Investigator.

2.8.7.2 Infections

The overall incidence of infections was similar in the daptomycin and comparator groups (p=0.435); at least 1 infection was reported in 54.2% and 48.3% of patients in the daptomycin and comparator groups, respectively. The majority of these events were assessed as unrelated to study treatment; 6.7% and 1.7% of patients in the daptomycin and comparator groups, respectively, had an infection that was assessed as drug-related by the Investigators. Not unexpectedly in these seriously ill patients, many of the infections were reported as severe in intensity. The incidence of severe infections was 21.7% in the daptomycin group and 19.8% in the comparator group.

Although the overall incidence of infections and the incidence of severe infections were similar in the 2 treatment groups, a higher proportion of patients in the daptomycin group (31.7%) experienced infections that were reported as serious in nature than in the comparator group (19.8%) (see Section 2.8.8.2, page 79). Discontinuation of treatment due to infections was reported in 8 patients (6.7%) in the daptomycin group and 1 patient (<1%) in the comparator group.

Not unexpectedly given the disease under study, the types of infections most commonly reported were in the category of sepsis, bacteremia, and viremia, with these events reported in 15 patients (12.5%) and 8 patients (6.9%) in the daptomycin and comparator groups, respectively. Sepsis, bacteremia, and viremia events were reported as severe in intensity in 7.5% and 6.0% of patients in the daptomycin and comparator groups, respectively, and were serious in nature in 8.3% and 6.0%, respectively (see Section 2.8.8.2, page 79).

2.8.7.3 Patients with Lower Respiratory Tract Infections/Events

Similar proportions of patients in both treatment groups had events potentially related to *S. aureus* pneumonia (daptomycin, 9.2%; comparator, 11.2%). This is reassuring, given that in studies conducted with daptomycin in patients with community-acquired pneumonia, the protocol-specified non-inferiority criterion was not met against the comparator. It was subsequently shown that daptomycin is inactivated by pulmonary surfactant *in vitro,* thus providing an explanation for the outcome in the community-acquired pneumonia studies.(1)

None of the pneumonia events were assessed as drug-related by the Investigators, and all were reported as resolved. One patient in the daptomycin group was discontinued from the study due to pneumonia.

The majority of the patients with events potentially related to *S. aureus* pneumonia (14 of 24) had an Adjudication Committee final diagnosis of IE, including 7 patients with RIE and 7 with LIE; 8 patients had a final diagnosis of complicated bacteremia, and 2 had a final diagnosis of uncomplicated bacteremia. Eighteen of the 24 patients, including 9 in each treatment group, were reported as failures at TOC by the Adjudication Committee.

2.8.7.4 Peripheral Nervous System Events

At high animal exposures, peripheral nerve is a target organ of toxicity of daptomycin; therefore, all events indicative of possible peripheral nerve toxicity from the pivotal trial were reviewed. A total of 11 patients (9.2%) in the daptomycin group and 2 (1.7%) in the comparator group were identified who had experienced adverse events associated with the peripheral nervous system. The most commonly reported type of peripheral nerve event was paraesthesia, reported in 3 (2.5%) and 1 (<1%) daptomycin and comparator patients, respectively.

All peripheral nerve events were classified as mild to moderate in severity; most were of short duration (≤3 days) and resolved during continued treatment with daptomycin or were considered unrelated to treatment by the Investigators.

2.8.7.5 Rashes, Hypersensitivity Reactions, and Other Allergic-Type Events

An overview of rashes, hypersensitivity, and other allergic-type events was conducted. A total of 13 (10.8%) of the 120 daptomycin patients and 18 (15.5%) of the 116 comparator patients experienced rash (including reports of rash NOS, exanthem, and macular, maculo-papular, vesicular, erythematous, or follicular rashes) or dermatitis (including reports of bullous or medicamentosa). The majority of the rashes were mild to moderate in severity. Two patients in the daptomycin group experienced severe rashes during the study; both were assessed as probably related to treatment and both occurred during the second week of therapy. The rashes were reported as resolved 10 and 22 days after treatment discontinuation, respectively.

Other allergic-type reactions included hypersensitivity NOS, drug hypersensitivity, anaphylactic reaction, and red man syndrome; all were reported in comparator-treated patients. Three of the events (hypersensitivity NOS, anaphylactic reaction, and red man syndrome) were severe in intensity and assessed as treatment-related by the Investigators, including one event, anaphylaxis, that was serious in nature. In addition, 2 patients in the comparator group were discontinued from the study due to drug-related fever.

2.8.7.6 Adverse Events Indicative of Potential Renal Toxicity

Adverse events in the *Renal and Urinary Disorders* SOC were reviewed for events indicative of renal toxicity; results are presented in Table 33. As required by the protocol, the majority of patients who received conventional therapy received concomitant treatment with gentamicin (108 of 116, 93.1%), including 49 (92.5%) of 53 patients who received vancomycin and 59 (93.7%) of 63 patients who received SSP.

The overall incidence of adverse events in the *Renal and Urinary Disorders* SOC was 15.0% in the daptomycin group and 22.4% in the comparator group. Adverse events in the MedDRA High Level Term (HLT) category of *Renal failure and impairment* were reported in 6.7% of patients in the daptomycin group, compared with 16.4% of patients in the comparator group. Within the comparator group, the overall incidence of *Renal and Urinary Disorders* was similar between patients who received vancomycin (24.5%) and those who received SSP (20.6%), as was the incidence of events in the HLT of *Renal failure and impairment* (18.9% and 14.3%, respectively).

Table 33: Treatment-Emergent Adverse Events Potentially Related to Renal Toxicity (Safety Population)

MedDRA HLT Preferred Term	Daptomycin (N=120) n (%)	Comparator[a] Total (N=116) n (%)	Vancomycin (N=53) n (%)	SSP (N=63) n (%)
At least 1 renal or urinary disorder event	*18 (15.0%)*	*26 (22.4%)*	*13 (24.5%)*	*13 (20.6%)*
Renal failure and impairment	8 (6.7%)	19 (16.4%)	10 (18.9%)	9 (14.3%)
Acute prerenal failure	1 (<1%)	0	0	0
Renal failure NOS	4 (3.3%)	11 (9.5%)	6 (11.3%)	5 (7.9%)
Renal failure acute	4 (3.3%)	7 (6.0%)	4 (7.5%)	3 (4.8%)
Renal failure chronic	0	1 (<1%)	1 (1.9%)	0
Renal impairment NOS	1 (<1%)	3 (2.6%)	1 (1.9%)	2 (3.2%)
Renal vascular and ischaemic conditions[b]	0	1 (<1%)	0	1 (1.6%)
Renal tubular necrosis	0	1 (<1%)	0	1 (1.6%)
Nephritis NEC	0	1 (<1%)	0	1 (1.6%)
Nephritis interstitial	0	1 (<1%)	0	1 (1.6%)
Nephropathies and tubular disorders NEC	0	1 (<1%)	0	1 (1.6%)
Nephropathy toxic	0	1 (<1%)	0	1 (1.6%)

Note: NOS=not otherwise specified; NEC=not elsewhere classified.

a For vancomycin, patients received only this agent during the study; for SSP, patients received SSP with or without initial therapy with vancomycin.

b Excludes the preferred term of renal artery stenosis.

Potential renal toxicity events were further reviewed to assess the overall incidence, the incidence of serious renal toxicity, and discontinuations due to these events both in the overall population and in elderly patients; results are summarized in Table 34. Within all categories, including all events, serious events, and events leading to discontinuation, the incidence of these potential renal toxicity events was higher in the comparator group than in the daptomycin group. The difference in the incidence rates was more pronounced in patients who were 65 years of age or older, occurring in 31.6% of comparator patients compared with 6.7% of daptomycin patients.

Table 34: Potential Renal Toxicity Adverse Events (Safety Population)

Renal toxicity events:[a]	Daptomycin (N=120) n (%)	Comparator (N=116) n (%)
At least one renal toxicity event	8/120 (6.7%)	21/116 (18.1%)
Events in patients ≥65 years of age	2/30 (6.7%)	12/38 (31.6%)
At least one drug-related event	3/120 (2.5%)	13/116 (11.2%)
At least one serious event	1/120 (<1%)	9/116 (7.8%)
SAEs in patients ≥65 years of age	0/30	6/38 (15.8%)
Discontinuations of study drug	1/120 (<1%)	5/116 (4.3%)

a Renal toxicity events include events in the HLTs of renal failure and impairment, renal vascular and ischaemic conditions (excluding the preferred term of renal artery stenosis), nephritis NEC, and nephropathies and tubular disorders.

Laboratory results for serum creatinine and creatinine clearance were consistent with adverse event reporting for renal toxicity. A summary of mean values and changes from baseline to on-study time points for serum creatinine is provided in Table 35.

At baseline, mean serum creatinine levels were 1.10 and 1.16 mg/dL in the daptomycin and comparator groups, respectively. At the majority of time points assessed, mean changes from baseline in serum creatinine were statistically significantly higher in the comparator group than in the daptomycin group. Statistically significant increases in serum creatinine in the comparator group were observed as early as Day 4.

Table 35: Actual Mean (SD) Values at Baseline and Mean (SD) Changes from Baseline for Serum Creatinine (mg/dL) (Safety Population)

Time Point	Daptomycin (N=120)			Comparator (N=116)			p-value[a]
	N	Actual Mean (SD)	Mean Change (SD)	N	Actual Mean (SD)	Mean Change (SD)	
Baseline	118	1.10 (0.379)		113	1.16 (0.449)		
Day 4	100	1.04 (0.357)	-0.06 (0.208)	96	1.18 (0.590)	0.03 (0.456)	0.046
Day 7	102	1.10 (0.493)	0.02 (0.349)	93	1.30 (0.628)	0.19 (0.561)	0.009
Day 14	39	1.09 (0.339)	0.01 (0.326)	59	1.35 (0.784)	0.23 (0.754)	0.048
Day 21	31	1.08 (0.308)	0.05 (0.324)	44	1.42 (0.857)	0.35 (0.849)	0.041
Day 28	13	0.95 (0.304)	-0.05 (0.357)	20	1.46 (0.614)	0.37 (0.540)	0.011
EOT	114	1.16 (0.535)	0.07 (0.462)	100	1.38 (0.564)	0.24 (0.451)	0.004
TOC	83	1.11 (0.358)	0.02 (0.373)	76	1.29 (0.530)	0.11 (0.411)	0.041

a Comparison of change from baseline using ANCOVA with baseline value as a covariate.

The proportion of patients with decreased renal function on study, defined as patients with a creatinine clearance level <50 mL/min if baseline clearance was ≥50 mL/min or those with a decrease of ≥10 mL/min if baseline clearance was <50 mL/min, was assessed (Table 36). As shown, a significantly higher proportion of patients in the comparator group had renal failure by Day 7 and at the EOT visit based on creatinine clearance levels.

Table 36: Summary of Patients with Decreased Renal Function Based on Creatinine Clearance Levels (Safety Population)

Study Interval	Daptomycin (N=120) n/N (%)	Comparator (N=116) n/N (%)	p-value[a]
Days 2 to 4	2/96 (2.1%)	6/90 (6.7%)	0.159
Days 2 to 7	6/115 (5.2%)	16/113 (14.2%)	0.026
Days 2 to EOT	13/118 (11.0%)	30/114 (26.3%)	0.004

Note: Decreased renal function was defined as patients with a creatinine clearance level <50 mL/min if baseline clearance was ≥50 mL/min or those with a decrease of ≥10 mL/min if baseline clearance was <50 mL/min.

a Fisher's exact test.

2.8.7.7 Analysis of CPK, Musculoskeletal Events, and Asthenic Conditions

Table 37 (page 75) presents an overview of CPK elevations reported as adverse events, including overall incidence, incidence of drug-related reports, severe events, and events that were serious in nature or led to early termination of treatment. The table also includes

musculoskeletal events (specifically, HLTs representing potential muscle toxicity) and asthenic conditions.

A total of 8 (6.7%) of the 120 daptomycin-treated patients and 1 (<1%) of the 116 comparator-treated patients had elevated blood CPK reported as an adverse event during the study. All reports were mild to moderate in severity, with 6 events assessed as drug-related in the daptomycin group. In 4 of the patients with CPK elevations reported as adverse events, including 3 in the daptomycin group and 1 in the comparator group, all of the reported CPK levels were <500 U/L.

Three patients in the daptomycin group discontinued treatment due to elevations in CPK.

There did not appear to be a difference in the incidence of musculoskeletal events between the treatment groups. In general, the incidence of musculoskeletal events and asthenic conditions was similar or lower in the daptomycin group relative to the comparator group for each MedDRA HLT, including musculoskeletal and connective tissue signs and symptoms (19.2% and 25.9% in the daptomycin and comparator groups, respectively), muscle-related signs and symptoms (1.7% and 5.2%, respectively), asthenic conditions (8.3% and 12.1%, respectively), muscle pains (<1% in each group), and myopathies (<1% and 0%, respectively). No musculoskeletal events or asthenic conditions were reported as serious in nature in the daptomycin group.

Table 37: Overview of Treatment-Emergent CPK Events, Musculoskeletal Events, and Asthenic Conditions (Safety Population)

MedDRA HLT Preferred Term	Daptomycin (N=120) Total n (%)	Drug-Related n (%)	Severe n (%)	Serious n (%)	DC[a] n (%)	Comparator (N=116) Total n (%)	Drug-Related n (%)	Severe n (%)	Serious n (%)	DC[a] n (%)
Blood CPK increased	8 (6.7%)	6 (5.0%)	0	1 (<1%)	3 (2.5%)	1 (<1%)	0	0	0	0
Musculoskeletal and connective tissue signs and symptoms NEC	23 (19.2%)	0	3 (2.5%)	0	0	30 (25.9%)	2 (1.7%)	2 (1.7%)	1 (<1%)	0
Pain in extremity	11 (9.2%)	0	1 (<1%)	0	0	11 (9.5%)	1 (<1%)	0	0	0
Back pain	8 (6.7%)	0	2 (1.7%)	0	0	10 (8.6%)	0	2 (1.7%)	1 (<1%)	0
Neck pain	4 (3.3%)	0	1 (<1%)	0	0	5 (4.3%)	1 (<1%)	0	0	0
Chest wall pain	3 (2.5%)	0	0	0	0	1 (<1%)	0	0	0	0
Extremity contracture	1 (<1%)	0	0	0	0	0	0	0	0	0
Flank pain	0	0	0	0	0	3 (2.6%)	0	0	0	0
Limb discomfort	1 (<1%)	0	0	0	0	0	0	0	0	0
Muscle spasms	2 (1.7%)	0	0	0	0	1 (<1%)	0	0	0	0
Musculoskeletal stiffness	1 (<1%)	0	0	0	0	2 (1.7%)	0	0	0	0
Nodule on extremity	0	0	0	0	0	2 (1.7%)	0	0	0	0
Nuchal rigidity	0	0	0	0	0	1 (<1%)	0	0	0	0
Muscle related signs and symptoms NEC	2 (1.7%)	0	0	0	0	6 (5.2%)	0	0	0	0
Muscle cramp	2 (1.7%)	0	0	0	0	5 (4.3%)	0	0	0	0
Muscle stiffness	0		0	0	0	1 (<1%)	0	0	0	0
Muscle pains	1 (<1%)	1 (<1%)	0	0	0	1 (<1%)	0	0	0	0
Myalgia	1 (<1%)	1 (<1%)	0	0	0	1 (<1%)	0	0	0	0
Myopathies	1 (<1%)	0	0	0	0	0	0	0	0	0
Rhabdomyolysis	1 (<1%)	0	0	0	0	0	0	0	0	0

(continued)

Table 37: Overview of Treatment-Emergent CPK Events, Musculoskeletal Events, and Asthenic Conditions (Safety Population)

MedDRA HLT Preferred Term	Daptomycin (N=120)					Comparator (N=116)				
	Total n (%)	Drug-Related n (%)	Severe n (%)	Serious n (%)	DC[a] n (%)	Total n (%)	Drug-Related n (%)	Severe n (%)	Serious n (%)	DC[a] n (%)
Asthenic conditions	10 (8.3%)	1 (<1%)	1 (<1%)	0	0	14 (12.1%)	1 (<1%)	1 (<1%)	1 (<1%)	0
Asthenia	6 (5.0%)	1 (<1%)	0	0	0	6 (5.2%)	0	1 (<1%)	1 (<1%)	0
Fatigue	4 (3.3%)	0	0	0	0	4 (3.4%)	1 (<1%)	0	0	0
Lethargy	2 (1.7%)	0	1 (<1%)	0	0	3 (2.6%)	0	0	0	0
Malaise	1 (<1%)	0	0	0	0	2 (1.7%)	0	0	0	0

Notes: NEC=not elsewhere classified.
Includes only HLTs potentially associated with muscle toxicity; HLTs associated with joint or bone disorders are not included.

a Discontinued from study treatment.

A total of 11 daptomycin patients (9.2%) had treatment-emergent elevations in CPK to >500 U/L on study; elevations were reported between Days 2 and 3P (Table 38). Maximum reported CPK on study was 5548 U/L.

Table 38: Maximum CPK (U/L) in Patients with CPK Elevations on Treatment (Safety Population)

Maximum CPK (U/L)	Daptomycin (N=120) n (%)	Comparator (N=116) n (%)
>500 – 1000	4 (3.3%)	1 (<1%)
>1000 – 2000	3 (2.5%)	0
>2000 – 3000	1 (<1%)	1 (<1%)
>3000 – 4000	2 (1.7%)	0
>4000 – 5000	0	0
>5000	1 (<1%)	0

Note: Maximum CPK reported on study = 5548 U/L.

Three of the 11 daptomycin patients with CPK >500 U/L on study had CPK levels decrease from baseline during continued daptomycin treatment, 6 had values return to the normal range during follow-up, 1 had values returning toward baseline at the last assessment, and 1 did not have follow-up values reported. Six of the 11 patients with treatment-emergent CPK elevations >500 U/L had medical or surgical reasons for the elevated CPK, including trauma in 2 patients and 1 patient each with cerebrovascular accident and shock, gout with inflammation, exploratory laparotomy, and chronic steroid use with evidence of osteoporosis.

A total of 6 patients in the daptomycin group had CPK levels >500 U/L at study entry; all 6 of these patients showed decreases from baseline in their CPK levels during daptomycin therapy, with 5 of 6 patients having CPK returning to ≤ULN during treatment (from Day 3 to Day 12).

In the comparator group, 2 patients with CPK levels ≤ULN at baseline had treatment-emergent elevations to CPK >500 U/L. One of these patients had no obvious cause for the elevation, and 1 had received a blood transfusion and had decubitus ulcers. CPK levels improved to <ULN during continued therapy in both patients. A total of 3 comparator patients had CPK levels >500 U/L at study entry; all 3 of these patients showed decreases in CPK levels during treatment or within 1 day post-treatment.

A total of 24 daptomycin patients entered the study with baseline CPK levels ≥ULN, including 8 patients with levels >500 U/L; 20 (83.3%) of these 24 patients had CPK return to the normal range during treatment (18 patients) or during the follow-up period (2 patients), including 7 of 8 patients with levels >500 U/L at baseline.

An additional analysis was conducted for the patients with any elevation of CPK ≥ULN during therapy (through Day 3P) to determine if there was a temporal relationship between CPK elevation and reported musculoskeletal events or asthenia. Three daptomycin patients had musculoskeletal or asthenia events reported that were temporally related to the elevations in CPK; all 3 of these patients had CPK elevations to >500 U/L. One patient had upper

extremity weakness in association with the CPK elevation and discontinued daptomycin due to the elevation in CPK. One patient who had elevated CPK at baseline had lower extremity weakness noted on physical examination on the day CPK increased from baseline. He discontinued the study due to the elevation in CPK and subsequently developed back pain and asthenia in association with spinal cord compression. One patient had rhabdomyolysis secondary to heroin overdose in association with the CPK elevation. None of the patients in the comparator group with elevated CPK had musculoskeletal or asthenia events reported in association with the elevation.

In summary, across all 116 patients in the daptomycin group with CPK assessments conducted at baseline and post-baseline, 3 (2.6%) had an elevation in CPK >500 U/L with an associated musculoskeletal or asthenia event, 2 of whom had an alternative etiology for the events. None of the 111 patients in the comparator group with baseline and post-baseline CPK assessments had an elevation in CPK >500 U/L with an associated musculoskeletal or asthenia event.

2.8.8 Deaths, Other Serious Adverse Events, and Discontinuations from the Study due to Adverse Events

2.8.8.1 Deaths

A total of 37 (15.7%) of the 236 patients died during Study DAP-IE-01-02 or in post-study follow-up, including 18 (15.0%) of the 120 daptomycin-treated patients and 19 (16.4%) of the 116 comparator-treated patients (Table 39). Twenty-six of these patients died within 30 days of the last dose of study treatment, including 14 (11.7%) of 120 daptomycin patients and 12 (10.3%) of 116 comparator patients. A total of 5 patients, including 2 in the daptomycin group and 3 in the comparator, died on-therapy (i.e., last dosing day).

Table 39: Summary of Deaths (Safety Population)

Patient Category	Daptomycin (N=120) n (%)	Comparator (N=116) n (%)
All patient deaths	18/120 (15.0%)	19/116 (16.4%)
Deaths within 30 days	14/120 (11.7%)	12/116 (10.3%)
Deaths by Day 42P	15/120 (12.5%)	13/116 (11.2%)

Thirty-six of the 37 deaths were reported as unrelated to study treatment; one death, cardiac arrest reported in a patient in the daptomycin group, was judged to be possibly related to treatment by the Investigator. This patient was an 87-year-old female with medical history significant for diabetes, heart failure, atrial fibrillation, and hypertension who was hospitalized for weakness, dizziness, and loss of balance; she was enrolled in the study for treatment of MSSA bacteremia. The patient was transferred to a long-term care facility on Day 8 following clinical improvement. On Day 10, the patient experienced acute dyspnea and collapsed. Resuscitation efforts were not successful.

In the daptomycin group, the cause of death was cardiac-related in 6 of the 18 patients who died, was associated with infection in 4, was respiratory-related in 2, and was reported as

multisystem organ failure in 2; other causes of death were pulmonary embolism, thrombocytopenia with coagulopathy, progression of multiple myeloma, and depression (suicide). In the comparator group, infection was reported as the cause of death in 7 of the 19 patients who died, cardiac events were reported in 3, respiratory failure was reported in 3, and neoplasm (progression of lung cancer or prostate cancer and end-stage mycosis fungoides) was reported in 3; other causes of death were exacerbation of chronic renal insufficiency, cerebrovascular accident, and complications of diabetes mellitus.

2.8.8.2 Other Serious Adverse Events

An overview of the most commonly reported serious adverse events is provided in Table 40. A total of 114 of the 236 patients treated in Study DAP-IE-01-02 experienced at least one serious adverse event during the study, including 62 (51.7%) of 120 daptomycin-treated patients and 52 (44.8%) of 116 comparator-treated patients. Serious renal and urinary disorders were reported at a higher incidence in the comparator group (9 of 116 patients, 7.8%) than in the daptomycin group (1 of 120 patients, <1%) (p=0.009). The incidence of serious infections was higher in the daptomycin group (31.7%) than in the comparator group (19.8%) (p=0.053).

The most commonly reported serious adverse event in both treatment groups was osteomyelitis, reported in 5.8% and 3.4% of patients in the daptomycin and comparator groups, respectively. All other serious events were reported in <5% of patients in both treatment groups.

The majority of SAEs were assessed as unrelated to study treatment. A total of 9 patients, including 3 in the daptomycin group (2.5%) and 6 in the comparator group (5.2%), experienced SAEs that were reported by the Investigators as possibly or probably related to study treatment. Drug-related serious adverse events in the daptomycin group included an elevation in CPK that resolved within 6 days, atrial flutter/fibrillation and renal failure in a patient who entered the study with renal insufficiency, and cardiac arrest leading to death (as described above). In the comparator group, serious drug-related events included renal failure or renal tubular necrosis in 4 patients and 1 patient each with antibiotic-associated diarrhea and anaphylaxis.

Table 40: Treatment-Emergent SAEs Reported in ≥2 Patients in Either Treatment Group by MedDRA System Organ Class and Preferred Terms (Safety Population)

MedDRA SOC Preferred Term	Daptomycin (N=120) n (%)	Comparator (N=116) n (%)	p-value[a]
Patients with at least 1 SAE	*62 (51.7%)*	*52 (44.8%)*	
Infections and infestations	38 (31.7%)	23 (19.8%)	0.053
Osteomyelitis NOS	7 (5.8%)	4 (3.4%)	
Sepsis NOS	5 (4.2%)	3 (2.6%)	
Staphylococcal bacteraemia	5 (4.2%)	2 (1.7%)	
Pneumonia NOS	3 (2.5%)	1 (<1%)	
Bacteraemia	3 (2.5%)	0	
Endocarditis infective	2 (1.7%)	2 (1.7%)	
Epidural abscess	2 (1.7%)	0	
Septic shock	1 (<1%)	3 (2.6%)	
Arthritis bacterial	0	2 (1.7%)	
Myocardiac abscess	0	2 (1.7%)	
Cardiac disorders	9 (7.5%)	8 (6.9%)	>0.999
Cardiac arrest	2 (1.7%)	2 (1.7%)	
Cardiac failure NOS	2 (1.7%)	0	
Cardio-respiratory arrest	2 (1.7%)	0	
Angina pectoris	0	2 (1.7%)	
Respiratory, thoracic and mediastinal disorders	8 (6.7%)	5 (4.3%)	0.571
Hypoxia	2 (1.7%)	0	
Pulmonary embolism	2 (1.7%)	0	
Respiratory failure	1 (<1%)	4 (3.4%)	
Nervous system disorders	4 (3.3%)	5 (4.3%)	0.746
Cerebrovascular accident	2 (1.7%)	2 (1.7%)	
Psychiatric disorders	4 (3.3%)	1 (<1%)	0.370
Mental status changes	3 (2.5%)	0	
General disorders and administration site	3 (2.5%)	4 (3.4%)	0.718
Multiorgan failure	2 (1.7%)	0	
Chest pain aggravated	0	2 (1.7%)	
Investigations	3 (2.5%)	0	0.247
Gastrointestinal disorders	2 (1.7%)	6 (5.2%)	0.166
Gastrointestinal haemorrhage NOS	0	4 (3.4%)	
Metabolism and nutrition disorders	2 (1.7%)	5 (4.3%)	0.275
Dehydration	0	2 (1.7%)	
Injury, poisoning and procedural complications	2 (1.7%)	3 (2.6%)	0.680
Vascular disorders	2 (1.7%)	2 (1.7%)	>0.999
Renal and urinary disorders	1 (<1%)	9 (7.8%)	0.009
Renal failure NOS	1 (<1%)	4 (3.4%)	
Renal failure acute	0	4 (3.4%)	
Blood and lymphatic system disorders	1 (<1%)	3 (2.6%)	0.363
Anaemia NOS	0	2 (1.7%)	
Neoplasms benign, malignant and unspecified	1 (<1%)	3 (2.6%)	0.363
Malignant neoplasm progression	1 (<1%)	2 (1.7%)	

a p-value is from Fisher's exact test for comparison of the incidence of events between treatment groups within each MedDRA SOC.

In this open-label trial, infections were reported as serious adverse events more often in the experimental treatment arm than in the comparator arm. In order to assess the potential difference between the treatment groups, serious events in the *Infections and Infestations* SOC were reviewed by the medical monitor, the events that were potentially related to *S. aureus* bacteremia or IE were identified, and the incidence of these events was tabulated (Table 41). The incidence of these events was 25.8% in the daptomycin group and 16.4% in the comparator group (p=0.082, Fisher's exact test).

In order to assess the possible relationship of these reported events to the outcome of study treatment, an analysis was conducted to evaluate Adjudication Committee outcome at TOC for the subset of patients who experienced infections potentially related to *S. aureus* bacteremia or IE (Table 41). At TOC, the failure rate for patients with these infections was higher than for the overall population, at 80.6% in the daptomycin group and 89.5% in the comparator group. Among the 8 patients who were reported as success, 3 patients had Gram-negative infections, 4 patients had infections present at baseline with diagnosis confirmed on study, and 1 patient had a potentially delayed diagnosis of osteomyelitis.

Table 41: Incidence of SAEs Potentially Related to *S. aureus* Bacteremia and IE and Adjudication Committee Outcome (Safety Population)

Parameter	Daptomycin (N=120) n (%)	Comparator (N=116) n (%)
SAE Potentially Related to *S. aureus* Bacteremia/IE	31 (25.8%)	19 (16.4%)
Outcome at TOC		
Success	6 (19.4%)	2 (10.5%)
Failure	25 (80.6%)	17 (89.5%)

Note: Failure includes patients assessed as non-evaluable by the Adjudication Committee.

2.8.8.3 Discontinuations due to Adverse Events

Similar proportions of patients in both treatment groups discontinued study treatment due to adverse events, including 20 (16.7%) of the 120 patients in the daptomycin group and 21 (18.1%) of the 116 patients in the comparator group. Table 42 presents all adverse events leading to treatment withdrawal.

The majority of events leading to treatment withdrawal were assessed as possibly or probably related to study treatment. A total of 10 (8.3%) of 120 patients in the daptomycin group and 13 (11.2%) of 116 patients in the comparator group had a drug-related event that led to treatment discontinuation. Drug-related events leading to treatment withdrawal in the daptomycin group included 3 reports of increased blood CPK (2.5%), 3 patients with rash (2.5%), and 1 report (<1%) each of vomiting, renal failure, thrombocytopenia, and cardiac arrest. In the comparator group, drug-related events leading to treatment withdrawal included rashes and hypersensitivity reactions in 7 patients (6.0%) (including one report of red man syndrome and one anaphylactic reaction), 4 patients with renal toxicity (3.4%), and 2 with pyrexia (1.7%).

Table 42: Incidence of Treatment-Emergent Adverse Events Leading to Discontinuation by MedDRA System Organ Class and Preferred Term (Safety Population)

MedDRA SOC Preferred Term	Daptomycin (N=120) n (%)	Comparator (N=116) n (%)
Patients Discontinuing due to Adverse Event	*20 (16.7%)*	*21 (18.1%)*
Infections and infestations	8 (6.7%)	2 (1.7%)
Bacteraemia	2 (1.7%)	0
Septic shock	1 (<1%)	1 (<1%)
Osteomyelitis NOS	1 (<1%)	0
Pneumonia staphylococcal	1 (<1%)	0
Epidural abscess	1 (<1%)	0
Urinary tract infection bacterial	1 (<1%)	0
Staphylococcal bacteraemia	1 (<1%)	0
Sepsis NOS	0	1 (<1%)
Skin and subcutaneous tissue disorders	3 (2.5%)	5 (4.3%)
Rash NOS	2 (1.7%)	2 (1.7%)
Rash vesicular	1 (<1%)	0
Dermatitis medicamentosa	0	1 (<1%)
Rash erythematous	0	1 (<1%)
Dermatitis bullous	0	1 (<1%)
Renal and urinary disorders	1 (<1%)	5 (4.3%)
Renal failure NOS	1 (<1%)	2 (1.7%)
Renal failure acute	0	1 (<1%)
Nephropathy toxic	0	1 (<1%)
Nephritis interstitial	0	1 (<1%)
Investigations	3 (2.5%)	0
Blood creatine phosphokinase increased	3 (2.5%)	0
General disorders and administration site	0	3 (2.6%)
Pyrexia	0	2 (1.7%)
Red man syndrome	0	1 (<1%)
Gastrointestinal disorders	2 (1.7%)	0
Vomiting NOS	1 (<1%)	0
Diabetic gastroparesis	1 (<1%)	0
Cardiac disorders	1 (<1%)	1 (<1%)
Cardiac arrest	1 (<1%)	1 (<1%)
Respiratory, thoracic and mediastinal disorders	1 (<1%)	1 (<1%)
Hypoxia	1 (<1%)	0
Respiratory failure	0	1 (<1%)
Immune system disorders	0	2 (1.7%)
Anaphylactic reaction	0	1 (<1%)
Hypersensitivity NOS	0	1 (<1%)
Vascular disorders	0	1 (<1%)
Circulatory collapse	0	1 (<1%)
Nervous system disorders	0	1 (<1%)
Cerebrovascular accident	0	1 (<1%)
Blood and lymphatic system disorders	1 (<1%)	0
Thrombocytopenia	1 (<1%)	0

2.8.9 Other Safety Evaluations

In Study DAP-IE-01-02, no clinically significant differences were noted between the treatment groups for changes from baseline to the EOT evaluation for any hematology, clinical chemistry analyte, or coagulation parameter, or for any vital signs parameter. No apparent differences were noted between the treatment groups for the incidence of adverse events associated with ECG abnormalities.

3. CONCLUSIONS

Infections due to *S. aureus,* particularly those due to MRSA, constitute a growing public health threat because of the increasing incidence of these infections in hospitals and in the community, and the increase in associated morbidity and mortality. Infective endocarditis is the most serious manifestation of *S. aureus* infection and may occur in patients with structurally normal heart valves after a clinically inapparent bacteremia. Recently reported mortality rates associated with *S. aureus* bacteremia and endocarditis are between 11% and 43% in patients receiving conventional therapy, and no decrease in mortality rates has been seen for more than 15 years. The problem is compounded by the emergence of CA-MRSA infections in patients not suspected of having MRSA. Recent cases of patients presenting with rapid-onset sepsis, purpura fulminans, toxic shock, and death have been reported.

Currently, few options are available for patients with *S. aureus* bacteremia, who often require a prolonged course of i.v. therapy. Standard of care, as was evaluated in the pivotal study, consists of empiric therapy with vancomycin, with switch to SSP for MSSA infections, along with adjunctive therapy with low-dose gentamicin. Both agents have limitations, including frequent dosing, need for plasma concentration monitoring, hypersensitivity reactions, and renal toxicity.

The properties of daptomycin made it an excellent candidate for evaluation in the treatment of *S. aureus* infections. Its bactericidal activity; potency against both MRSA and MSSA, including stationary phase bacteria; proven efficacy in *S. aureus* infections; efficacy in animal models of endocarditis; tolerability for long-term therapy; and suitability for outpatient administration led to the initiation of the landmark study of daptomycin versus standard of care in the treatment of *S. aureus* bacteremia, with known or suspected endocarditis.

The population included in the pivotal study reflects the population currently in greatest need of therapy for *S. aureus* bacteremia and IE. In general, the population was a seriously ill, hospitalized patient population with many 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.

Daptomycin 6 mg/kg as monotherapy (once daily i.v.) met the pre-specified non-inferiority criteria in both the ITT and PP populations. Efficacy was demonstrated in infections caused by both MRSA and MSSA. In MRSA infections, the response rates for daptomycin were higher than those observed in the comparator group. In MSSA infections, the response rates for daptomycin were similar to those observed in patients who received SSP 6 times daily.

Daptomycin was well tolerated at 6 mg/kg administered i.v. once daily in patients with *S. aureus* bacteremia or endocarditis, and the safety profile was similar to that of daptomycin at the currently approved dose of 4 mg/kg once daily. There was significantly less nephrotoxicity observed in daptomycin-treated patients than in those treated with standard of care. The potential for transient daptomycin-induced muscle effects associated with CPK elevation is low and easily managed through monitoring of CPK. In comparison with the

known safety profile of daptomycin at 4 mg/kg, no new safety issues were identified with daptomycin at a dose of 6 mg/kg once daily for up to 6 weeks.

In conclusion, daptomycin administered i.v. at 6 mg/kg once daily is an effective alternative to standard of care in the treatment of patients with *S. aureus* bacteremia with known or suspected endocarditis, with several advantages over current therapy, including:

- rapid bactericidal activity
- activity in stationary phase bacteria
- proven efficacy in *S. aureus* bacteremia with known or suspected endocarditis, including infections caused by MRSA and MSSA
- demonstrated tolerability for long-term therapy
- significantly less nephrotoxicity than standard of care
- convenient once-daily administration, allowing for outpatient therapy

In an era of limited therapeutic options and in the face of an emerging public health threat, daptomycin 6 mg/kg once daily provides a much-needed treatment option for patients with *S. aureus* bacteremia with known or suspected endocarditis.

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