Cubicin® (daptomycin for injection) for the treatment of *Staphylococcus aureus* bacteremia, including those with known or suspected infective endocarditis

FDA Briefing Document for
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I. INTRODUCTION

Bacteremia and infective endocarditis (IE) due to *Staphylococcus aureus* continue to remain challenging illnesses, both due to limited treatment options and their propensity to develop complications, with ensuing morbidity and mortality. Daptomycin, a lipopeptide was developed by Cubist Pharmaceuticals and approved by the FDA in September 2003 for the indication of complicated skin and skin structure infections. The Sponsor (Cubist Pharmaceuticals Inc.) has submitted a supplemental new drug application (sNDA, 21-572/S-008), seeking an indication of *Staphylococcus aureus* bacteremia, including those with suspected or proven infective endocarditis. Drugs that are FDA-approved for endocarditis are primarily older drugs and their approval for endocarditis was based on small numbers of patients and not on adequate and well-controlled trials. This is the first randomized controlled trial in patients with *S. aureus* bacteremia that has been submitted to the Agency to seek an indication for *S. aureus* bacteremia.

This briefing document provides background information on *S. aureus* bacteremia, and infective endocarditis, and daptomycin, regulatory history regarding bacteremia as an indication, selected analyses of the results of the trial comparing daptomycin to standard of care in the treatment of patients with *S. aureus* bacteremia, including patients with known or suspected IE, and topics for discussion.

II. BACKGROUND

S. aureus bacteremia and infective endocarditis

Rates of both community and hospital acquired bacteremia due to *S. aureus* have increased over the last few years.[1] *S. aureus* has become the second most common bloodstream isolate, contributing to 20% of all hospital-acquired bacteremias.[2] Data show that most patients with bacteremia due to *S. aureus* have a known site of infection.[3] Mylotte et al. reported that a primary focus was identified in 91/114 (80%) episodes of SAB.[4, 5]

Clinical differentiation of *S. aureus* bacteremia (SAB) from infective endocarditis (IE) can be difficult in the absence of typical clinical features of IE, such as a new regurgitant heart murmur, embolic lesions etc. Nolan and Beaty had suggested three useful bedside criteria namely community-acquisition, no apparent primary focus, and metastatic foci to predict underlying IE in patients with SAB.[6] These may not be very helpful with the changing epidemiology of *S. aureus* infections wherein endocarditis has been reported with hospital-acquired disease and in the presence of intravascular catheters. The numbers of patients with SAB who have IE varies among studies.

The frequency of IE due to *S. aureus* seems to be increasing. *S. aureus* was the most common pathogen identified in the International Collaboration on Endocarditis Prospective-Cohort Study. *S. aureus* was identified in about a third of the 1779 cases of definite IE.[7] Patients with *S. aureus* IE were more likely to have healthcare-associated IE than patients with non-*S. aureus* IE. Regional variations in the frequency of *S. aureus* IE have been reported.[8]

Use of intravascular catheters and indwelling prosthetic devices may be contributing to the increasing number of *S. aureus* IE. With the rise in number of serious community-acquired methicillin resistant *S. aureus* (MRSA) infections, it is likely that endocarditis due to such strains will also increase. Increasing numbers of cases of IE are now nosocomially acquired. Clinical differences between patients with community acquired versus hospital acquired IE have been reported. Patients with community acquired disease were more likely to have vascular phenomena and no evident source for bacteremia while those with hospital acquired IE were more likely to have IE due to MRSA. Out of 59 cases of IE due to *S. aureus* identified over a 3-year period, 27 (45.8%) patients had hospital-acquired infection. In over half of the patients an intravascular device was the presumed source of infection. [9]

Right sided IE due to *S. aureus* is usually seen in Intravenous Drug Users (IVDUs) and often involves the tricuspid valve. In non-drug addicts, *S. aureus* primarily causes left-sided IE (LIE). *S. aureus* can cause both native-valve and prosthetic-valve endocarditis. Mortality rates in LIE due to *S. aureus* ranges from 25-40%, while cure rates for right-sided IE (RIE) due to *S. aureus* in IVDUs are > 85%.[9]

Treatment regimens for *S. aureus* IE vary depending on whether the left or right side of the heart is involved and whether the disease is affecting native or prosthetic valves. For oxacillin-susceptible strains, a semi-synthetic penicillin such as oxacillin or nafcillin with optional gentamicin (for 3-5 days) is recommended. Uncomplictated RIE can be treated with shorter regimens while complicated RIE and LIE need longer treatment regimens. For infections due to MRSA, vancomycin is recommended. With rising methicillin resistance among *S. aureus* and the emergence of intermediate- and high-level resistance to vancomycin, treatment options are limited.

In 2005, the American Heart Association published a scientific statement on diagnosis, antimicrobial therapy, and management of complications in IE. [10]The recommended therapies for adults with staphylococcal endocarditis in the absence of prosthetic valves are outlined in Table 1:

Table 1: Treatment regimens for *S. aureus* infective endocarditis

Regimen	Dosage* and Route	Duration
Oxacillin-susceptible strains		
Nafcillin or oxacillin	12 g/24 h IV in 4–6 equally divided doses	6 wk
with		
Optional addition of gentamicin sulfate	3 mg/kg per 24 h IV/IM in 2 or 3 equally divided doses	3–5 d
For penicillin-allergic (nonanaphylactoid type) patients:		
Cefazolin	6 g/24 h IV in 3 equally divided doses	6 wk
with		
Optional addition of gentamicin sulfate	3 mg/kg per 24 h IV/IM in 2 or 3 equally divided doses	3–5 d
Oxacillin-resistant strains		
Vancomycin	30 mg/kg per 24 h IV in 2 equally divided doses	6 wk

*Dosages recommended for patients with normal renal function

Daptomycin

Daptomycin is a cyclic lipopeptide that acts by disrupting the plasma membrane resulting in loss of membrane potential and cell death. Daptomycin was approved in September 2003 for the treatment of complicated skin and skin structure infections (cSSSI).

Daptomycin is not effective in the treatment of pneumonia. Cubist had conducted two controlled clinical trials of similar design to evaluate daptomycin in the treatment of moderate to severe community-acquired pneumonia due to *Streptococcus pneumoniae*, including penicillin-resistant strains. Each study was a randomized, multicenter, multinational, double-blinded, parallel group, active-treatment controlled trial using a dosage of 4 mg/kg q24h. The comparator in each trial was ceftriaxone 2 g q24h. In both trials, non-inferiority of daptomycin to comparator was not demonstrated. Daptomycin has been shown to interact *in vitro* with pulmonary surfactant. [11]

In a Phase 2 study conducted by Lilly, the clinical efficacy of daptomycin 3 mg/kg q12 hours as treatment of *S. aureus* infective endocarditis was lower than that of comparator (usually nafcillin/gentamicin). It was postulated that the lower efficacy rate in the treatment of *S. aureus* endocarditis was due to low daptomycin levels with q 12 hour dosing.

Cubist had conducted a randomized, open-label, multicenter, Phase 2 study comparing three doses of intravenous daptomycin (4 mg/kg every 24 hour, 6 mg/kg every 24 hours, 3 mg/kg every 12 hours following a single 6 mg/kg loading dose) with a comparator agent (either i.v. vancomycin, or i.v. nafcillin/oxacillin) in patients with bacteremia caused by gram-positive pathogens. This Phase 2 study was terminated early due to slow enrollment. The efficacy of daptomycin 4 mg/kg q24h was similar to comparator for patients with bacteremia due to gram-positive pathogens. The daptomycin 3 mg/kg q12h regimen appeared to be less effective than either of those regimens. The Sponsor's

assessment was that these observations were consistent with the pharmacodynamic characteristics of daptomcyin and support the utility of once daily dosing for the treatment of serious infections due to gram-positive pathogens. Success rates in patients in the daptomycin 6 mg/kg q24h treatment group were also lower than that of the comparator. The Sponsor postulated that other confounding clinical factors, including delayed adjunctive treatments (e.g., surgical drainage and removal of foreign bodies) affected outcomes among these patients.

III. REGULATORY HISTORY

Prior to 1992, the labeling of anti-infective drugs included the terms *bacteremia* and *septicemia*. Analyses of clinical data used in granting those indications involved pooling data from patients with infections associated with *concurrent* bacteremia, often from diverse unrelated infections (e.g., UTI, pneumonia).

In 1992, the FDA published the "Guidance to Industry on Clinical Development and Labeling of Anti-Infective Drug Products" (also called the "Points to Consider" document) to assist sponsors in formulating development plans for anti-infective drug products. [12] At that time, FDA raised questions about the appropriateness of "bacteremia" indications as they related to infections at specific body sites.

These questions resulted in a meeting of the Anti-Infective Drugs Advisory Committee (AIDAC) in 1993. Committee members discussed issues related to "bacteremic sepsis" as a potential new anti-infective drug product indication. [13] The then-proposed new indication incorporated definitions of sepsis and bacteremia, as provided in a consensus document of the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) published in 1992. [14] Following extensive discussion, the committee recommended elimination of "bacteremic sepsis" as an indication, continuing to use the site of infection in defining an indication for an anti-infective drug, and including bacteremia in product labeling in the context of site-specific infection (e.g., "community-acquired pneumonia with concurrent bacteremia").

During the five years following the 1993 AIDAC meeting until the AIDAC meeting in 1998, there were no anti-infective drugs approved for the indication of bacteremia. However, the issue of bacteremia as an indication was again considered by the 1998 AIDAC. [15] Following extensive discussion, the 1998 AIDAC members concluded that product labeling regarding "bacteremia", secondary to an identified site of infection, should *not* be considered as a separate indication. Rather, the Committee advised the Agency that it should be retained within the context of the site-specific indications. In addition, the 1998 AIDAC identified primary bacteremia (including catheter-related bloodstream infections) as a potential area for study. Catheter-related bloodstream infections (CRBSI) were considered a potential focus for future investigation. Committee members considered this indication a potential source of useful information, due to the increased incidence of CRBSI in hospitals, growing antimicrobial drug resistance among bacteria with limited treatment options for such infections, and the lack

of controlled clinical trials for antimicrobial drugs for the treatment and prevention of CRBSI. Since the 1998 AIDAC meeting, no drug has been approved for the indication of CRBSI. Several Sponsors have attempted to conduct trials with systemic drugs in pursuit of this indication, but to date none have come to fruition.

In April 2004, FDA co-sponsored a workshop with the Infectious Diseases Society of America (IDSA) and the International Society of Antimicrobial Pharmacologists (ISAP) that addressed issues in study design of primary bacteremia due to *S. aureus* (PBSA). The issues discussed included the fact that bacteremia by itself was often not a disease, and that drug efficacy is most often related to the underlying primary source of the disease. Thus, drug efficacy may be different in pneumonia compared to complicated skin infections although bacteremia may accompany both diseases. Participants discussed that disease with a primary focus and concomitant *S. aureus* bacteremia should be considered under the indication for the primary focus (e.g. pneumonia, complicated skin infection, etc.). They cited the need for clinical data from a serious disease indication as well as appropriate pre-clinical information before proceeding with clinical trials in PBSA, due to the seriousness of the PBSA indication and high mortality rate in untreated disease.

In October 2004, the feasibility of PBSA as an indication was discussed at an AIDAC meeting. The committee members concluded that PBSA as an indication was acceptable and that the disease definition for PBSA would include patients with *S. aureus* bacteremia without an obvious focus of infection. Patients with indwelling intravascular catheters would be included in the category of PBSA. The study of daptomycin versus vancomycin/semi-synthetic penicillins in the treatment of patients with bacteremia due to *S. aureus* is the first reviewed by FDA in pursuit of a PBSA claim.

IV. STUDY DESIGN

This was a multicenter, randomized (1:1), open-label study in patients with *S. aureus* bacteremia, including those with known or suspected IE. According to the original protocol, patients with a high likelihood of left-sided IE were to be excluded. Following a protocol amendment in April 2004, patients with LIE were allowed in the study and were separately randomized to the two treatment groups.

Intravenous daptomycin was compared with semi-synthetic penicillins (nafcillin, oxacillin, cloxacillin, or flucloxacillin) or vancomycin. The study was initiated in 76 sites in the US, Belgium, France, Germany, Italy, and Spain. Patients were enrolled at 48 study sites. The study was conducted from 8/28/2002 to 02/16/05. An independent external adjudication committee (IEAC), consisting of five infectious disease physicians (four members and one chair person) was convened. The IEAC conducted a clinical review of the data and made assessments of diagnosis and outcomes at pre-specified time points in the study. The IEAC was blinded to treatment assignment. The primary efficacy endpoint, clinical success at the test of cure visit was based on the IEAC assessment.

Study Visits

Baseline: Within two calendar days prior to the first infusion of study medication. At baseline, patients were classified as having definite IE, possible IE, or not IE based on the Modified Duke criteria. [16]

End of Therapy (EOT) - within 3 days after the last day study medication was administered for patients who completed the minimum duration of treatment.

Test of Cure (TOC) - 38 to 46 days after completion of study medication for all patients who completed the minimum duration of study treatment and who were considered to have a successful outcome at the EOT evaluation.

Post Study (PS) - 80 to 88 days after completion of study medication for all patients who completed the minimum duration of study medication and who were considered to have a successful outcome at the TOC.

Blood cultures

The Investigator could initiate study treatment based on a single blood culture positive for *S. aureus* on Day -2 or -1. At baseline, a blood culture was to be obtained from a fresh venipuncture site. Blood cultures were to be obtained daily by fresh venipuncture during the treatment period until previous cultures had remained negative for 48 hours.
Two blood cultures from separate, fresh venipuncture sites were to be obtained at the EOT, TOC, and PS visits. For patients not completing study treatment, two blood cultures from separate fresh venipuncture sites were to be obtained at the early termination visit and at the safety follow-up visit.

Echocardiography

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

Disease Definitions

The following definitions were used by the investigator at EOT and by the IEAC at EOT and TOC to define different diagnostic subgroups:

***S. aureus* LIE**

- Definite **or** possible IE according to the Modified Duke Criteria; and
- echocardiographic evidence of involvement or predisposing pathology of the mitral or aortic valve.

Complicated *S. aureus* RIE

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

Uncomplicated *S. aureus* RIE

- Definite **or** possible IE according to the Modified Duke Criteria and
- echocardiographic evidence indicating no predisposing pathology or active involvement of either the mitral valve or the aortic valve; and
- history of intravenous drug use; and
- no evidence of extrapulmonary sites of infection; and
- serum creatinine <2.5 mg/dL; and
- blood cultures yielded only MSSA.

Complicated *S. aureus* bacteremia

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

Uncomplicated *S. aureus* bacteremia

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

Study Drugs

Daptomycin was administered at 6 mg/kg q24h and semi-synthetic penicillins at 2 g q4h. In patients with normal renal function, vancomycin was administered 1 g q12h; dose was to be adjusted based on renal function and plasma levels. Patients randomized to comparator and LIE patients randomized to daptomycin were to receive initial synergistic gentamicin. If susceptibility results were unknown at the time of randomization, patients

in the comparator arm received vancomycin. If the organism isolated was oxacillin-susceptible therapy was changed to semi-synthetic penicillins, unless contraindicated by beta-lactam allergy.

Treatment Regimens

The duration of study treatment was based on the patient's diagnosis as determined by the investigator. The protocol-defined regimens are outlined in the Table 2:

Table 2: Protocol-defined treatment regimens

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

Source: Study report, Table 9-2

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

IEAC Outcome definitions at TOC

Success: Patients were classified as success if they met all of the following criteria:

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

Failures: Patients were classified as failures if they met any one of the following criteria:

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

Patients classified by the IEAC as "Non-evaluable" at EOT were considered "Non-evaluable" by the IEAC at TOC. Patients classified by the IEAC as "Failures" at EOT were considered "Failures" at TOC.

V. STUDY RESULTS

OVERALL POPULATION

A total of 246 patients were enrolled in the study, 206 from sites in the United States and 40 from all European sites combined. Of 246 patients enrolled, 236 were randomized and treated including 120 who received daptomycin and 116 who received a comparator regimen. One patient in the comparator group was enrolled with a suspicion of LIE prior to Amendment 4A and was excluded from the Intent-To-Treat (ITT) population. The Per Protocol (PP) population consisted of 139 patients, which included 79 in the daptomycin group and 60 in the comparator group. Patient populations for analysis are provided in the following table:

Table 3: Patient Populations

Study Population	Daptomycin n, (%)	Comparator (total) n, (%)	Vancomycin n, (%)	SSP+/- Vancomycin n, (%)
ITT (n =235)	120 (100)	115 (99.1)	53 (100)	62 (98.4)
PP (n =139)	79 (65.8)	60 (51.7)	22 (41.5)	38 (60.3)
Safety Population	120 (100)	116 (100)	53 (100)	63 (100)

SSP = semi-synthetic penicillin

It is noteworthy that only 44% of all study patients completed treatment with study medication and completed study participation to the TOC visit, thus limiting the number

of patients in whom complete data were available. The percentage of patients who discontinued study therapy or those who completed therapy and prematurely discontinued study were similar in the two treatment arms. Premature discontinuations due to microbiologic failures were more common in patients in the daptomycin arm. Patient disposition as reported by the investigators is summarized in the Table 4.

Table 4: Patient Disposition

Disposition	Daptomycin N=120 n (%)	Comparator N=116 n (%)
Completed therapy	80 (66.7%)	78 (67.2%)
Prematurely discontinued therapy	40 (33.3%)	38 (32.8%)
Adverse event	20 (16.7%)	21 (18.1%)
Microbiologic failure	9 (7.5%)	3 (2.6%)
Withdrew consent	1 (<1%)	2 (1.7%)
Discontinued therapy against medical advice	1 (<1%)	2 (1.7%)
Unsatisfactory clinical response	1 (<1%)	1 (<1%)
Care transferred to another physician	1 (<1%)	1 (<1%)
Other	7 (5.8%)	8 (6.9%)
Completed therapy and study	54 (45.0%)	50 (43.1%)
Completed therapy, prematurely discontinued study	26 (21.7%)	28 (24.1%)
Lost to follow-up	7 (5.8%)	9 (7.8%)
Adverse event	6 (5.0%)	5 (4.3%)
Withdrew consent	1 (<1%)	0
Other	12 (10.0%)	14 (12.1%)

Source: Sponsor Table 10-1, final study report

Distribution of patients in the two treatment arms, based on the IEAC determined Entry Diagnosis and Final Diagnosis subgroups for the ITT population are outlined in the following table:

Table 5: Entry and Final Diagnostic Subgroups (ITT)

	Daptomycin (N=120)	Comparator (N=115)	Total (N=235)
IEAC Entry Diagnostic Subgroup [N (%)]			
Possible IE	73 (60.8%)	71 (61.7%)	144 (61.3%)
Definite IE	17 (14.2%)	20 (17.4%)	37 (15.7%)
Not IE	30 (25.0%)	24 (20.9%)	54 (23.0%)
IEAC Final Diagnostic Subgroup [N (%)]			
Complicated bacteremia	60 (50.0%)	61 (53.0%)	121 (51.5%)
Uncomplicated bacteremia	32 (26.7%)	29 (25.2%)	61 (26.0%)
Complicated RIE	13 (10.8%)	12 (10.4%)	25 (10.6%)
Uncomplicated RIE	6 (5.0%)	4 (3.5%)	10 (4.3%)
LIE	9 (7.5%)	9 (7.8%)	18 (7.7%)

Source: Sponsor Table 11-4, final study report

Although, the majority of patients had an entry diagnosis of definite or possible IE, the number of patients with a final diagnosis of IE was small (28 in the daptomycin arm and 25 in the comparator arm). Using the modified Duke criteria at study entry to classify all-comers who have at least one positive blood culture for *S. aureus* within 2 calendar days prior to initiation of study drug, the study population appeared to be relatively homogeneous (>70% of all patients were classified as possible IE or definite IE).

However, this approach to characterization of all-comers in the study population overestimated the actual number of IE cases. In the daptomycin arm, 63/73 (86.3%) patients with "Possible IE" at entry had a final diagnosis of bacteremia. In the comparator arm, 66/71 (92.9%) patients with "Possible IE" at entry had a final diagnosis of bacteremia. The following table summarizes the distribution of all-comers at study entry based on IEAC assessment and correlates the IEAC Entry Diagnosis with the IEAC Final Diagnosis.

Table 6: Correlation between IEAC Entry and Final Diagnosis Subgroups (ITT)

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

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

Thus, it is evident that using the modified Duke criteria for IE to classify all-comers into diagnostic groups at study entry does not characterize fully the heterogeneity of the all-comers population due to differences in underlying pathophysiology between primary bacteremias, secondary bacteremias, and IE, and it does not take into consideration the possible portal(s) of entry for the *S. aureus* bloodstream infections as observed in the study population.

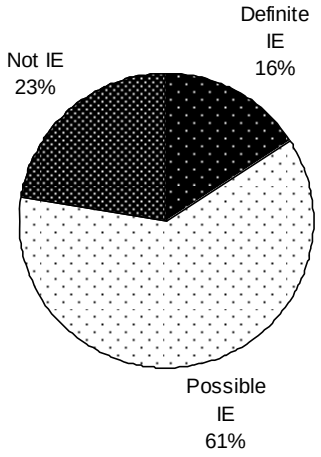
Discrete data relevant to potential portals of entry was not collected prospectively as part of the study design. Patients with bacteremias that develop secondary to an identifiable portal of entry frequently need adjunctive treatment (such as incision and drainage procedures, surgical debridement, etc.)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

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

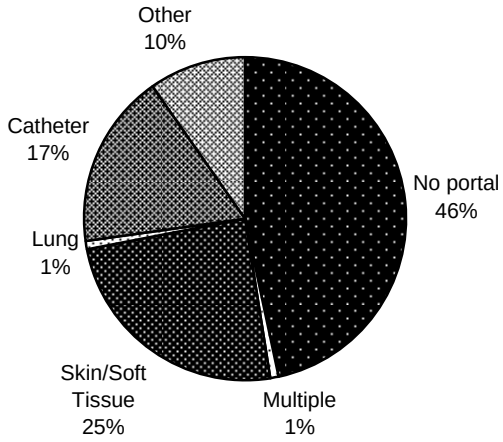
The FDA conducted a post-hoc review of all the case report forms and patient profiles in order to compile data relevant to potential portals of entry. The following diagrams contrast the relative homogeneity of the all-comers study population as assessed based on IEAC Entry Diagnosis subgroups using the modified Duke criteria compared to the underlying heterogeneity of the same population that is evident when characterized by potential portals of entry. Of note, approximately 25% of the patients with staphylococcal bacteremias in the study had a probable skin/soft tissue portal of entry and 17% were likely catheter-related. The proportion of patients with no identifiable portal of entry (46%) is likely an overestimate due to the limited information available in the source documents on some patients.

Figure 1: IEAC Entry Diagnosis versus Possible portals of Entry

IEAC Entry Diagnosis Subgroups



FDA Post-hoc Analysis of Portals of Entry



Clinical Efficacy Results

Selected analyses performed by the Sponsor are reproduced in this briefing document. In addition, certain analyses performed by the FDA are also presented. As stated previously, given the limited number of patients in the several diagnostic categories, no formal statistical analyses were performed in any of these subgroups.

The following table summarizes the Sponsor's results for the primary efficacy endpoint of IEAC outcome at TOC in the overall ITT and PP population:

Table 7: Sponsor Primary Efficacy Analysis

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

Source: Sponsor Table 11-10, final study report

In the overall population, including cases with bacteremia and endocarditis, the study met its pre-defined endpoint of IEAC success in the ITT and PP population using a non-inferiority margin of -20. This was evidenced by the lower bound of the 95% confidence limits not exceeding -20 and the confidence intervals including the value zero.

Based on a review of the case report forms and patient profiles for the study patients, the FDA Medical Officer re-adjudicated the outcomes of 14 study patients. The overall success rates in the FDA analysis for the overall population in both treatment groups declined compared to the Sponsor's analysis, but still met the primary endpoint using pre-defined criteria. The 95% confidence interval included zero and the lower bound of the 95% confidence interval did not exceed -20. In the IEAC Final Diagnosis subgroups, a decrease in the point estimates for both treatment groups in patients with bacteremia and a decrease in the point estimates for patients with IE treated with daptomycin was noted.

The following table summarizes the FDA analysis of treatment outcomes at TOC in the overall population (at least one positive blood culture for *S. aureus* within 2 calendar days prior to initiation of study drug) in the ITT population:

Table 8: FDA Efficacy Analysis at TOC (Overall*, ITT)

	Daptomycin N (%)	Comparator N (%)	Difference in success rates (95 % CI)
ITT			
Total	120	115	
Success	46/120 (38.3)	44/115 (38.3)	0.1% (-12.4, 12.5)
Failure	68/120 (56.7)	57/115 (49.6)	
Non-evaluable	6/120 (5)	14/115 (12.2)	

*at least one positive blood culture for *S. aureus* within 2 calendar days prior to initiation of study drug

The following table summarizes the Sponsor's efficacy data based on IEAC outcome at TOC in the ITT population for the IEAC Final Diagnostic Subgroups:

Table 9: Success Rates by IEAC Final Diagnostic Subgroup (ITT)

IEAC Final Diagnostic Subgroup	Daptomycin n/N (%)	Comparator n/N (%)
Right sided IE	8/19 (42.1%)	7/16 (43.8%)
Complicated RIE	5/13 (38.5%)	6/12 (50.0%)
Uncomplicated RIE	3/6 (50.0%)	1/4 (25.0%)
Left sided IE	1/9 (11.1%)	2/9 (22.2%)
Bacteremia	44/92 (47.8%)	39/90 (43.3%)
Complicated bacteremia	26/60 (43.3%)	23/61 (37.7%)
Uncomplicated bacteremia	18/32 (56.3%)	16/29 (55.2%)

Source: Sponsor Table 11-12, final study report

Success Rates by Oxacillin Susceptibility of Baseline Pathogen

A total of 144/235 patients had methicillin susceptible *S. aureus* (MSSA) as baseline pathogen, including 74 (61.7%) in the daptomycin group and 70 (60.9%) in the comparator group. A total of 89/235 patients had MRSA at baseline, including 45 (37.5%) in the daptomycin arm 44 (38.3%) in the comparator arm. One patient in each treatment group in the ITT population did not have *S. aureus* documented from a baseline blood culture. IEAC success rates by oxacillin susceptibility are summarized in the following table:

Table 10: Success Rates by oxacillin Susceptibility (All-Comers*, ITT)

Pathogen	Daptomycin (N=120) n/N (%)	Comparator N=(115) n/N (%)
MSSA	33/74 (44.6)	34/70 (48.6)
MRSA	20/45 (44.4)	14/44 (31.8)
Total*	53/119 (44.5)	48/114 (42.1)

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

INFECTIVE ENDOCARDITIS

The following section describes characteristics and outcomes for patients with an IEAC final diagnosis of right or left sided endocarditis. As the total number of patients with IE was small and the study was not powered to detect statistical differences between the two treatment arms in patients with endocarditis, only descriptive results are provided.

Patient Characteristics

Although the majority of patients in both treatment arms had an IEAC entry diagnosis of definite or possible IE, only a total of 53 patients had an IEAC Final Diagnosis of IE in the ITT population, 28 in the daptomycin arm and 25 in the comparator arm. The number of patients with IE by the two treatment arms is provided in the table below:

Table 11: IEAC Final Diagnosis of Infective Endocarditis (ITT)

	Daptomycin	Comparator
LIE	9	9
RIE	19	16
Uncomplicated RIE	6	4
Complicated RIE	13	12
Total	**28**	**25**

The demographic variables were generally comparable in the two groups. There were fewer patients younger than 65 years in the comparator arm. Over 75% of patients in both treatment groups had systemic inflammatory response syndrome (SIRS). Overall, about 55% of patients had MSSA and 45% had MRSA infections.

The table below summarizes selected demographic characteristics of patients with IE:

Table 12: Demographics of Patients with Infective Endocarditis

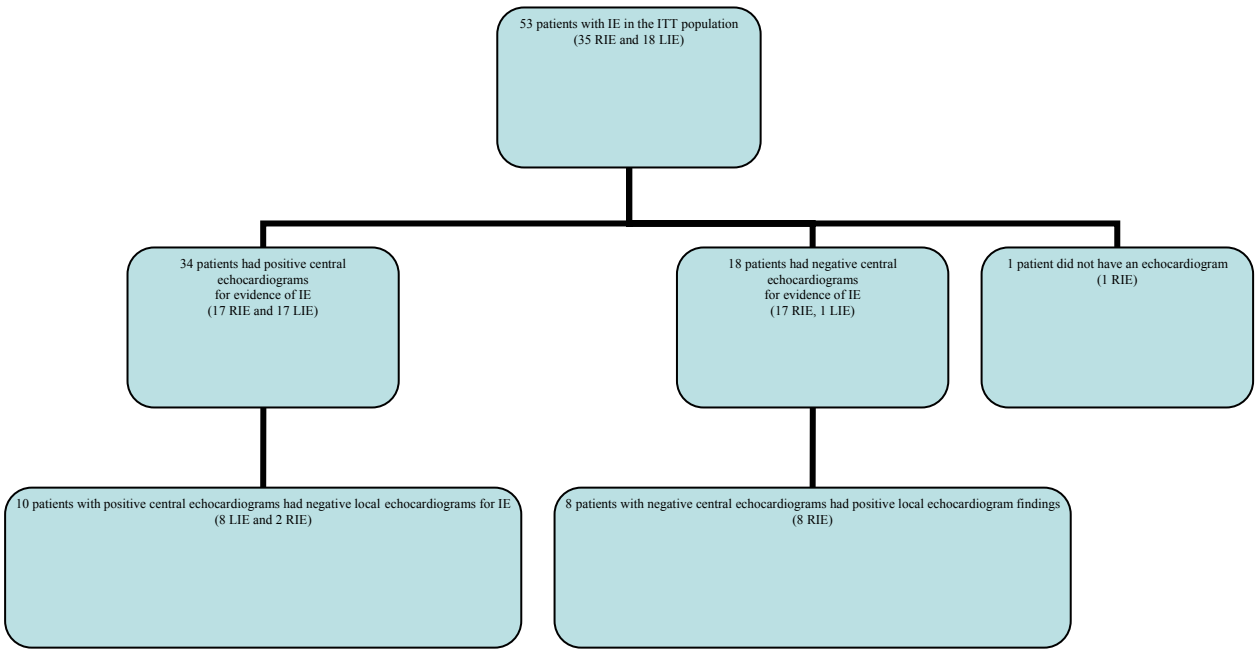
Characteristic	Daptomycin	Comparator
	N = 28 n (%)	N = 25 n (%)
Baseline Demographics		
Age		
Median	45	41
Mean ± S.D.	46.7 ± 15.7	49.6 ± 18.9
<65 years	23 (82)	18 (72)
≥65 – 74 years	2 (7.1)	5 (20)
≥75 years	3 (10.7)	2 (8)
Gender		
Male	14 (50)	11 (44)
Female	14 (50)	14 (56)
Diabetes Mellitus	4 (14.2)	5 (20)
Prior Endocarditis	4 (14.2)	5 (20)
Shock	1 (3.6)	0
SIRS	22 (78.6)	21 (84)
HIV (+)	4 (14.2)	0
IVDA	17 (60.7)	14 (56)
Baseline Pathogen		
MSSA	15 (53.6)	14 (56)
MRSA	13 (46.4)	11 (44)
IEAC Entry Diagnosis		
Definite IE	17 (60.7)	20 (80)
Possible IE	10 (35.7)	5 (20)
Not IE	1(3.6)	0

All patients in the study were to have had local echocardiography (TEE or TTE) performed by the end of Day 5. The local study site was to send a copy of the echocardiogram to the central echocardiography laboratory, the Duke CORE Echo laboratory, Durham, NC, for blinded, independent evaluation. The assessment by the Duke CORE Echo laboratory was to be used by the IEAC for determination of Entry and Final diagnoses.

During the FDA review, discrepancies were identified involving IEAC determinations of Entry Diagnosis using Duke Criteria. Two patients in the comparator group with findings compatible with Definite IE by modified Duke criteria were categorized as Possible IE by the IEAC at Entry, and one patient with findings compatible with Possible IE by modified Duke criteria was categorized as Definite IE by the IEAC at Entry. In the daptomycin group, one patient with findings compatible with Not IE by modified Duke criteria was categorized as Definite IE by the IEAC at Entry, and one subject with findings compatible with Possible IE by modified Duke criteria was categorized as Definite IE by the IEAC at Entry.

Among the patients with IE, the FDA review identified incongruities between the local echocardiography and the Duke Core Echo laboratory assessments for 18 patients (35%), including eight patients with an IEAC Final Diagnosis of LIE and ten patients with an IEAC Final Diagnosis of RIE. The following chart summarizes the discrepancies in echocardiographic interpretations from the local and central echocardiogram readings among the 53 cases of IE in the ITT population. The actual number of patients with echocardiographically-demonstrable valvular vegetations and/or perforations varied depending on whether the local or central echocardiogram readings are considered definitive. Accordingly, there may be as few as 32 to as many as 42 patients with IE who have echocardiographically-demonstrable valvular vegetations and perforations in the entire ITT study population. Thus, the discrepancies in echocardiographic interpretation pose difficulties in accurately defining in a well-characterized group of patients with IE.

Figure 2: Echocardiographic interpretation in IE patients



Clinical Efficacy Results in Patients with IE

Success rates for patients with IE, based on the Sponsor's analysis are depicted in the following table for the ITT and PP populations:

Table 13: Clinical Success Rates in Patients with Infective Endocarditis

	ITT (N=53)		PP (N=33)	
IEAC Final Diagnosis	**Daptomycin n/N (%)**	**Comparator n/N (%)**	**Daptomycin n/N (%)**	**Comparator n/N (%)**
Uncomplicated RIE	3/6 (50)	1 /4 (25)	1 /2 (50)	0/2 (0)
Complicated RIE	5/13 (38.5)	6/12 (50)	5/10 (50)	4/6 (66.7)
Left IE	1/9 (11)	2/9 (22)	1/7 (14.2)	2/6 (33.3)

One comparator-treated and two daptomycin- treated patients had valve replacement surgery for LIE. The comparator-treated patient was a failure at TOC. One daptomycin-treated patient was a failure at TOC and the other was non-evaluable at TOC.

FAILURE ANALYSIS

A total of 58 (48.3%) patients in the daptomycin arm and 53 (46.1%) in the comparator arm had an outcome of failure at TOC. An additional 9 (7.5%) patients in the daptomycin arm and 14 (12.2%) in the comparator arm were non-evaluable. In the ITT analysis, non-evaluable patients were considered failures. They were excluded from the PP population. The Sponsor has provided a detailed analysis of the IEAC's reasons for treatment failure at EOT and TOC among all patients in the ITT population.

Details on all failures including non-evaluable patients are summarized in Table 14:

Table 14: Sponsor's Reasons for Failure in Overall Population (ITT)

Reason for failure	Daptomycin N=120 n/N (%)	Comparator N=115 n/N (%)
Overall Failure [a]	**67 (55.8%)**	**67 (58.3%)**
Microbiologic failure	**28 (23.3%)**	**23 (20.0%)**
Persisting or relapsing bacteremia	18 (15.0%)	10 (8.7%)
No blood culture drawn at TOC	9 (7.5%)	12 (10.4%)
Positive culture from non-blood source (e.g., abscess)	1 (<1%)	1 (<1%)
Clinical failure	**21 (17.5%)**	**14 (12.2%)**
Discontinued study medication prematurely	**27 (22.5%)**	**25 (21.7%)**
Adverse event	8 (6.7%)	17 (14.8%)
Microbiologic failure (positive culture) [b]	14 (11.7%)	5 (4.3%)
Clinical failure [c]	13 (10.8%)	7 (6.1%)
Other	6 (5.0%)	3 (2.6%)
Received non-study antibiotics that influenced outcome	**20 (16.7%)**	**16 (13.9%)**
Patient died	**13 (10.8%)**	**13 (11.3%)**
Non-evaluable	9 (7.5%)	14 (12.2%)
Transfer of care to another physician	1 (<1%)	0
Withdrew consent; placed on other antibiotic	1 (<1%)	3 (2.6%)
Patient discontinued against medical advice	1 (<1%)	2 (1.7%)
Other administrative reason	6 (5.0%)	9 (7.8%)

Source: Sponsor Table 11-21, final study report
a Patients can have more than one reason for failure/non-evaluable. b All patients except one in this category were also reported as microbiologic failures. c All patients in this category were also reported as clinical failures.

Based on the Sponsor's data, failures due to persistent or relapsing bacteremias were more common in the daptomycin arm, while discontinuations due to adverse events were more frequent in the comparator group. The use of potentially effective non-study antibiotics (PENS) as a reason for failure was slightly more frequent in the daptomycin arm. There were comparable numbers of deaths in the two treatment groups. No statistically significant differences were noted between the two treatment arms.

FDA Analysis of Microbiological Failures

Patients with microbiologic failures due to persistent/relapsing bacteremia were analyzed in detail. Based on the re-adjudication of cases by the FDA Medical Officer a re-analysis of this group of patients was performed. A total of 20 patients in the daptomycin arm and 10 patients in the comparator arm had persisting or relapsing bacteremias compared to 18 and 10 respectively in the Sponsor's analysis.

The following table summarizes the FDA Medical Officer's analysis of patients with persisting or relapsing bacteremia or persistent infections in the ITT population:

Table 15: FDA Analysis of Microbiologic Failures (ITT)

IEAC Final Diagnosis Category	Daptomycin N= 21		Comparator N = 11	
	MRSA	MSSA	MRSA	MSSA
Total IE	**4**	**4**	**4**	**1**
Complicated RIE	-	1	2	1
Uncomplicated RIE	-	3*	-	-
Left IE	4	-	2	-
Total bacteremia	**8**	**5**	**5**	**1**
Complicated bacteremia	8	4	5	-
Uncomplicated Bacteremia	-	-	-	-
Persistent Infections	**-**	**1****	**-**	**1**[§]**
Total	12	9	9	2

*includes 1 post-study relapse at Day 85P; ** persistent knee infection; persistent urinary tract infection

As depicted in the table above, there were a total of 21 failures in the daptomycin group attributable to persistent and relapsing bacteremias and persistent infections (at other sites) compared to 11 failures among patients treated with comparator. Data summarized in the table above includes two additional patients re-adjudicated as failures by the FDA Medical Officer in the daptomycin group, including one subject (034-078) with a post-study relapse at Day 85P and one subject for whom the investigator stopped study medication due to persistently positive blood cultures (027-095) after six days of treatment.

Among patients with IE, there were eight failures (8/28, 28.6%) in the daptomycin group and five (5/25, 20%) in the comparator group due to persistent/relapsing bacteremia. In the daptomycin group, failures were equally distributed among infections due to MSSA and MRSA, whereas failures in the comparator arm were more common in infections due to MRSA compared to those due to MSSA. Of these 32 patients, 10 died by TOC, including seven in the daptomycin group and three in the comparator group. By post-study, there were two additional deaths in the daptomycin group and three in the comparator group

The observed increased frequency of persistent and relapsing bacteremias in the daptomycin arm was paralleled by the development of increasing minimum inhibitory concentration (MIC) to daptomycin during treatment with the drug. Of the eight patients who developed daptomycin MICs ≥ 2, six had persisting/relapsing bacteremia.

The following table summarizes the patients who developed decreased susceptibility to daptomycin during the study and their clinical outcome:

Table 16: FDA Summary of Failures in the Daptomycin Group with Daptomycin MICs ≥ 2 mcg/ml

Case ID #	Study Group	Baseline Pathogen	Site	IEAC Final Diagnosis	IEAC Outcome at TOC	Study Day at which Daptomycin MIC ≥ 2 reported
004-193	Comparator	MRSA	Blood	Complicated RIE	Success	Day 11
009-212[#]	Daptomycin	MRSA	Blood	Complicated bacteremia	Failure	Day 09P
010-152[#]	Daptomycin	MSSA	Blood	Complicated RIE	Failure	Day 18
015-105[#]	Daptomycin	MRSA	Blood	Complicated bacteremia	Failure	Day 20P
017-037[#]*	Daptomycin	MRSA	Blood	LIE	Failure	Day 4
027-183[#]*	Daptomycin	MRSA	Blood	LIE	Failure	Day 7
088-172	Daptomycin	MSSA	Wound	Complicated bacteremia	Success	Day 13
324-136[#]	Daptomycin	MRSA	Blood	Complicated bacteremia	Failure	Day 7

*Patient death; [#]Subject with persistent or relapsing bacteremia
P denotes after completing treatment

Of the eight patients depicted in the table above, seven developed decreased susceptibility to daptomycin (MIC≥ 2) during or following treatment with the drug. Six of the patients had persistent or relapsing *S. aureus* bacteremia and there were two deaths (both had LIE). One patient who was successfully treated with daptomycin despite evidence of decreased susceptibility to daptomycin during therapy was a female patient with bacteremia and an MSSA-infected lumbar wound (following repair of a herniated disk) and osteomyelitis who was treated with 74 days of study medication. The time frame for development of daptomycin resistance was widely variable, ranging from day 4 of daptomycin therapy to 20 days post-treatment. One subject in the comparator group had bacteremia and the isolate (MRSA) had daptomycin MIC = 2.

VI. MICROBIOLOGY

Increasing daptomycin MICs have been documented both *in vitro* and *in vivo* and were also seen during the course of this clinical trial. Currently, *S. aureus* isolates with an MIC ≤ 1 μg/ml are considered susceptible to daptomycin; *S. aureus* isolates with an MIC >1 μg/ml are considered non-susceptible to daptomycin. Breakpoints for intermediate and resistant isolates have yet to be established. For purposes of the discussion below, *S. aureus* isolates with a MIC >1 μg/ml are considered resistant.

The primary question that arises is whether the increasing MICs raise concern regarding the use of daptomycin for the treatment of infective endocarditis. The answer to this question may be determined by the answers to the following questions:

1. *Does in vitro evidence suggest there is potential for daptomycin resistance to occur?*
2. *Do data from animal models suggest that there is potential for daptomycin resistance to occur?*
3. *Is there evidence in surveillance data that daptomycin resistance occurs in clinical isolates?*
4. *Do patients treated with daptomycin develop resistant organisms during therapy?*

5. *Do patients treated with daptomycin for* S. aureus *endocarditis or bacteremia develop resistant organisms during therapy?*

1. Does in vitro evidence suggest that there is potential for daptomycin resistance to occur?

In this application, the Sponsor has noted that spontaneous mutations leading to daptomycin resistance is rare in Gram-positive bacteria and that there are no known transferable elements that confer daptomycin resistance. In a recently published study, no spontaneously resistant mutants were obtained from any clinical or laboratory isolates after a single passage in daptomycin. However, stable resistant organisms have been isolated after multiple (n=20) passages in liquid media containing progressively increasing concentrations of daptomycin (initiated from sub-inhibitory MIC levels) and following chemical mutagenesis.[17] Daptomycin MICs for *S. aureus* isolates were 16-fold higher than the parental isolates. In another published study, daptomycin resistant mutants were not found to be resistant to vancomycin or ampicillin as would be expected because of the differences in their mechanisms of action. [18] However, cross resistance to nisin, an antimicrobial similar in structure to daptomycin was found.

2. Do data from animal models suggest there is potential for daptomycin resistance to occur?

The Sponsor has presented data from a number of animal models (rabbits, rats, and mice) that include bacteremia, endocarditis, fibrin clot, hematogenous pneumonia, and experimental meningitis. Daptomycin efficacy was measured by either a $\log_{10}$ reduction in bacterial burden in the target tissue or by increased survival. The daptomycin dose used produced $AUC_{0\text{-}24}$ exposures achievable at the human clinical dosage of 6 mg/kg q24h.

In published studies, daptomycin was shown to be more efficacious than comparators in the rabbit model of endocarditis. In one study, daptomycin was dosed at 8 mg/kg q8h for 4 days and compared to vancomycin treated rabbits. Daptomycin was more efficacious than vancomycin or teicoplanin against two strains of MSSA and one strain of MRSA as measured by percent sterile vegetations and by CFU/g per vegetation. Two of 16 animals yielded organisms resistant to daptomycin; one organism had a four-fold rise in MIC and another, an eight-fold rise in MIC. [19] *Thus, while daptomycin was more efficacious than either teicoplanin or vancomycin, diminished susceptibility developed during therapy*. The investigators theorized that resistant organisms were selected for by sub-inhibitory concentrations of daptomycin deep within the vegetations. The investigators warned that extensive clinical use will be required to establish whether resistance to daptomycin will be a major clinical problem, but their findings in the rabbit animal model raises concerns regarding this possibility.

3. Is there evidence in surveillance data that daptomycin resistance occurs in recent clinical isolates?

The Sponsor's data from surveillance studies in North America and Europe from 2000 to 2004 are shown in the following table:

Table 17: Activity of Daptomycin against Staphylococci

Species	Study/Year	N	Daptomycin MIC Distribution* n (%)				
			≤ 0.12	**0.25**	**0.5**	**1**	**2**
MSSA	2000-1	1601	304 (18.9%)	1165 (72.7%)	131 (8.2%)	1 (0.1%)	0 (0%
	2002	1547	83 (5.4%)	1140 (73.7%)	319 (20.6%)	3 (0.2%)	2 (0.1%
	2003	2894	229 (7.9%)	2371 (81.9%)	285 (9.9%)	8 (0.3%)	1 (<0.1%
	2003-4	3284	70 (2.1%)	1891 (57.6%	1297 (39.5%)	25 (0.8%)	1 (<0.1%
MRSA	2000-1	639	51 (7.9%)	396 (61.9%)	187 (29.3%)	5 (0.8%)	0 (0%)
	2002	1076	20 (1.9%)	655 (60.9%)	388 (36.1%)	13 (1.2%)	0 (0%)
	2003	1468	40 (2.7%)	963 (65.6%)	452 (30.8%)	13 (0.9%)	0 (0%)
	2003-4	1976	10 (0.5%)	878 (44.4%)	1047 (52.9%)	40 (2.0%)	1 (<0.1%)
	2000-1						

MIC_{90} is highlighted
Source: Table 2.7.2—24, NDA 21-572 SN008

When the percentages of isolates for each MIC dilution are calculated, the data show the percentage of isolates with MICs of ≤ 0.12 μg/ml and 0.25 μg/ml *decreasing* over time and the percentage of isolates with MICs of 0.5, 1, and 2 μg/ml *increasing* over time from studies performed in 2000-2001 to 2004. This trend is evident in both methicillin-susceptible and methicillin-resistant isolates of *S. aureus*. Thus, daptomycin MICs of clinical isolates of *S. aureus,* regardless of methicillin susceptibility, have increased over time.

4. Do patients treated with daptomycin develop resistant organisms during therapy?
The Sponsor had provided an overview of isolates with treatment associated decreases in daptomycin susceptibility following commercial availability.

These data are summarized in the Table 18:

Table 18: Overview of Isolates with Treatment Associated Decreases in Daptomycin Susceptibility Following Commercial Availability

		Daptomycin	MIC (µg/ml)
Isolate	**Source**	**Base**	**Final**
E. faecium	Blood	4	> 32
E. faecium	Urine/Blood	4	32
S. aureus	Blood	0.5	4
S. aureus	Blood	0.5	4
S. aureus	*	0.25	4
S. aureus	Blood	0.5	4
S. aureus	**	0.5	4
S. aureus	Blood	1	2--4
S. aureus	Blood	0.5	4
S. aureus	Blood	0.5	4
S. aureus		0.5	8
*VRE****			8
S. aureus	Blood	0.25	1
*VRE****	Blood		4
MRSA		0.25	1.5

Source: Table **2.7.2-29,** NDA 21-572 SN008
Note: one additional patient had a *S. aureus* isolate with baseline MIC= 0.5 µg/mL and non-susceptible isolate on treatment (MIC= 4.0 µg/mL) that were not related as determined by PFGE. Therefore emergence of resistance could not be confirmed.
*initial source was right tibial tubercle, final source was epidural fat tissue
**initial source was blood, final source was spine
*** not speciated

Table 18 shows that 15 patients developed MICs to daptomycin ≥ 1 µg/ml since daptomycin was approved by the Agency. (Isolates with a MIC ≤ 1 µg/ml are considered susceptible to daptomycin). Of these 15 patients, 9 patients had *S. aureus* isolated from blood. Of these 15 patients, 10 patients demonstrated a three step increase in daptomycin MIC.

5. Do patients treated with daptomycin for endocarditis or bacteremia due to* S. aureus *develop resistant organisms during therapy?

The Sponsor has provided patient report forms that contain MIC data for patients given daptomycin or comparators to treat endocarditis or bacteremia. Table 19 was constructed to show the numbers and percentages of patients in both study arms showing number of patients with increases in daptomycin and vancomycin MICs and those who developed daptomycin or vancomycin resistance.

Table 19: Frequency of Increased MICs and Resistance to Daptomycin and Vancomycin in Patients during Therapy

	N, % Increased daptomycin MIC from baseline***	N, % increased vancomycin MIC from baseline***	N, % developed daptomycin resistance	N, % developed vancomycin resistance
clinical successes				
daptomycin arm	***17/53 (32.1%)****	12/53 (22.6%)*	1/53 (1.9%)*	0/53 (0%)*
comparator arm	10/46 (21.7%)	11/46 (23.9%)	1/46 (2.2%)	0/46 (0%)
clinical failures				
daptomycin arm	***21/60 (35.0%)***	14/59 (23.7%)*	***6/60 (10.0%)***	0/59 (0.0%)*
comparator arm	11/50 (22.0%)*	14/51 (27.5%)*	0/50 (0.0%)**	0/50 (0.0%)**

*determination of MICs not done for one patient
**determination of MICs not done for two patients
*** one or more dilution increase

The data from Table 19 show that patients in the daptomycin arm, whether they were clinical successes or clinical failures, were *more likely* to demonstrate *increased MICs* to daptomycin than patients in the comparator arm. Also, patients in the daptomycin arm that were clinical failures were more likely to develop resistance to daptomycin (6/60, 10%) than clinical successes or patients treated with the comparator. The data also showed that increases in daptomycin MICs and daptomycin resistance are not correlated with increases in vancomycin MICs or vancomycin resistance.

Table 20 was constructed from the patient report forms and shows more detailed data from the patients in whom isolates developed at least a two dilution step increase with in daptomycin MIC.

Table 20: Clinical Failures in Daptomycin Arm with Increased Daptomycin MICs

Case #	Final Diagnosis	Organism	Baseline MIC	High MIC	MIC Step Increase
009-212	complicated bacteremia	MRSA	0.25	2	3
010-152	complicated RIE	MSSA	0.25	4	4
015-105	complicated bacteremia	Both	0.25	2	3
017-037	left IE	Both	0.25	2	3
027-183	left IE	MRSA	0.5	2	2
324-136	complicated bacteremia	MRSA	0.5	2	2
300-111	left IE	MRSA	0.25	1	2
300-246	left IE	MRSA	0.25	1	2

Note: Data is not limited to baseline MICs. At baseline, case# 015-105 had only MRSA in the blood and MSSA was not isolated until Day 20P. The baseline pathogen was MRSA for case #017-037 and MSSA was not isolated from blood until Day 04.

Data from patient report forms were used to construct the following table. Table 21 presents the MIC distributions (by dilution) for patients with bacteremia or endocarditis in the ITT population.

Table 21: Distribution of MICs for Daptomycin Treated Patients (ITT)

Clinical success (N=53)	**0.12**	**0.25**	**MIC (µg/ml) 0.5**	**1**	**2**	**4**
	1/53 (1.9%)	36/53 (67.9%)	14/53 (26.4%)	2/53 (3.8%)	1/53 (1.9%)	0/53 (0%)
bacteremia						
uncomplicated	1/53 (1.9%)	11/53 (20.7%)	3/53 (5.7%)			
complicated		18/53 (33.9%)	9/53 (16.9%)	2/53 (3.8%)		
RIE						
uncomplicated		3/53 (5.7%)	1/53 (1.9%)			
complicated		3/53 (5.7%)	1/53 (1.9%)			
LIE		1/53 (1.9%)				
Clinical failure (N=59)	**0.12**	**0.25**	**MIC (µg/ml) 0.5**	**1**	**2**	**4**
	1/59 (1.7%)	34/59 (57.6%)	15/59 (25.4%)	3/59 (5.1%)	***5/59 (8.5%)***	***1/59 (1.7%)***
bacteremia						
uncomplicated		9/59 (15.3%)	4/59 (6.8%)			
complicated	1/59 (1.7%)	19/59 (32.2%)	6/59 (10.2%)	1/59 (1.7%)	3/59 (5.1%)	
RIE						
uncomplicated		1/59 (1.7%)	2/59 (3.4%)			
complicated		3/59 (5.1%)	2/59 (3.4%)			1/59 (1.7%)
LIE		2/59 (3.4%)	1/59 (1.7%)	2/59 (3.4%)	2/59 (3.4%)	
total	**2/112 (1.8%)**	**70/112 (62.5%)**	**29/112 (25.9%)**	**5/112 (4.4%)**	**5/112 (4.5%)**	**1/112 (0.9%)**

Data from Table 21 indicate there were more patients with daptomycin MICs of ≥ 1 µg/ml among clinical failures than among clinical successes. Six patients with complicated bacteremia, one patient with complicated RIE, and four patients with LIE had pathogens demonstrating MICs ≥ 1 µg/ml. Six patients who were clinical failures developed resistance (MIC >1µg/ml) during treatment with daptomycin.

Table 22 shows data from patients with relapsing or persistent bacteremia. The table shows clinical failures associated with MSSA, MRSA, MICs equal to or greater than 1 µg/ml, and MICs that increased by ≥ 2-fold dilutions.

Table 22: Changes in MICs for Relapsing or Persistent Bacteremia Patients

	MIC ≥ 1	≥ 2 steps	MRSA	MSSA
daptomycin arm (N=20)	***9/20 (45.0%)***	***9/20 (45.0%)***	12/20 (60.0%)*	11/20 (55.0%)*
comparator arm (N=11)	1/11 (9.1%)	0/11 (0%)	8/11 (72.7%)	2/11 (18.2%)
Total (N=31)	10/31 (32.2%)	9/31 (29.0%)	20/31 (64.5%)	13/31 (41.9%)

*3 patients had both MSSA and MRSA

Data from Table 22 indicate that patients with relapsing or persistent bacteremia in daptomycin arm were more likely to have pathogens with a MIC ≥ 1 μg/ml and demonstrate a two or more increase in MIC dilution steps than relapsing or persistent bacteremia patients treated with comparator.

Summary

In vitro studies have demonstrated that bacteria develop resistance to daptomycin when subjected to sub-inhibitory concentrations of daptomycin, such as may be found in endocarditis vegetations. Daptomycin did not exhibit cross-resistance to vancomycin or ampicillin but did exhibit cross-resistance to nisin. In a rabbit model of *S. aureus* endocarditis, daptomycin was more efficacious than vancomycin but diminished susceptibility developed during therapy. Patients treated with daptomycin for endocarditis or bacteremia caused by *S. aureus* who were clinical failures are more likely to exhibit isolates with increased daptomycin MICs and resistance to daptomycin. Patients with relapsing or persistent bacteremia were more likely to have increased MICs if treated with daptomycin rather than comparator. This was irrespective of whether *S. aureus* demonstrated oxacillin susceptibility or resistance.

VII. SAFETY

The safety analyses presented in this portion of the document were generated from the pivotal study, Study DAP-IE-01-02, supporting this application. Only selected safety analyses are presented in this briefing document.

Overall Adverse Events

Adverse Event (AE) rates were relatively similar in the two treatment arms, with more non-serious gastrointestinal events in the comparator arm. There was also a higher rate of renal events in the comparator arm compared to the daptomycin arm.

Serious Adverse Events (SAE's) by Treatment Group

Figure 3 shows all SAE's reported in the study by preferred term and treatment arm. Rates for specific SAE's were generally similar between treatment arms, however, there was a trend towards more cases of renal SAEs in the comparator arm and infection-related SAEs in the daptomycin arm. It should be noted that osteomyelitis and other possible metastatic complications were not evaluated in every patient in a systematic

manner. Anyone identified with an abnormal diagnostic imaging scan possibly indicative of a metastatic site was classified as having had an adverse event.

Figure 3: SAEs by Treatment Group

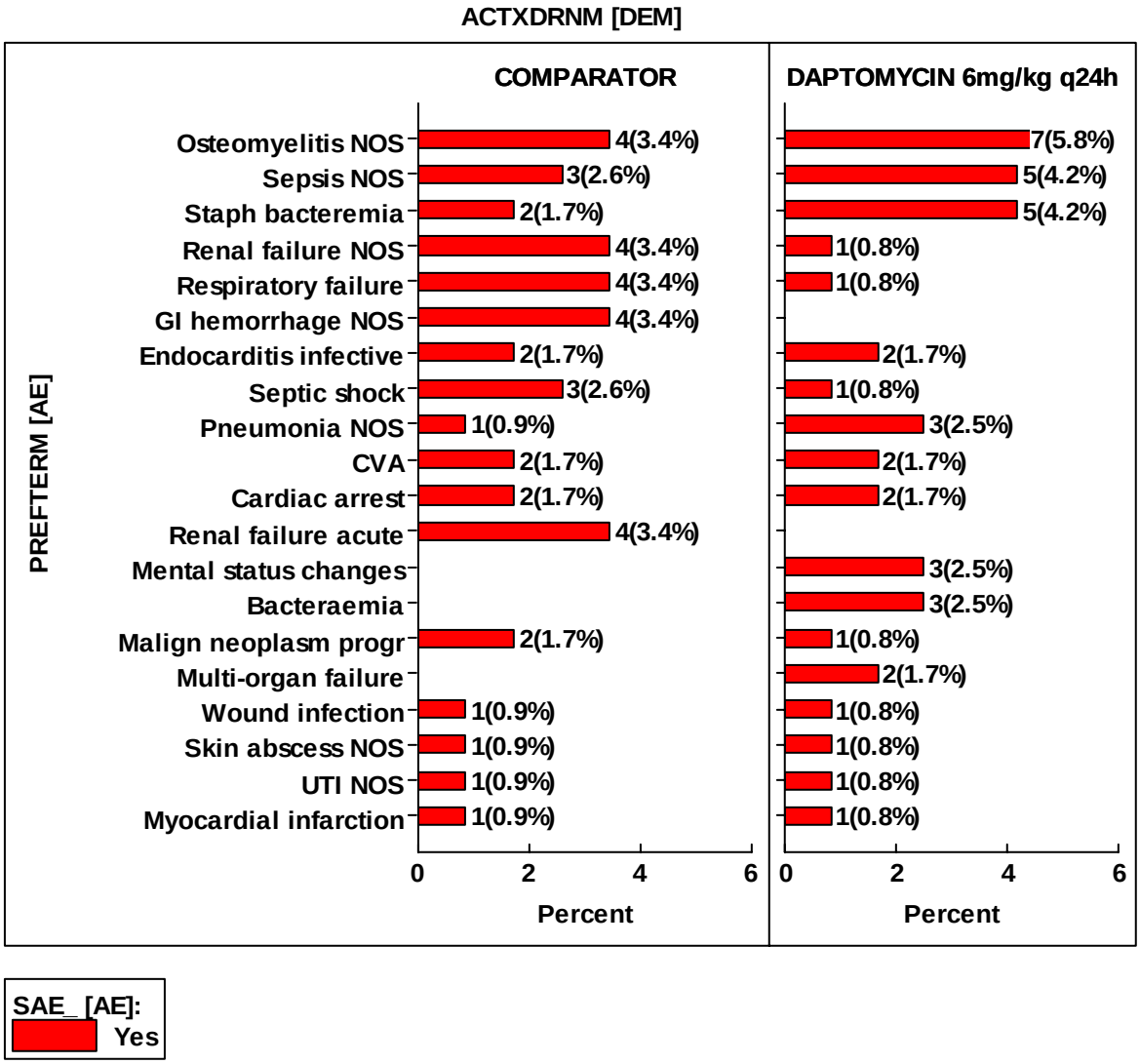


Figure 4 shows the overall rate of infection-related SAEs by treatment arm. The rates of infection-related SAEs were higher in the daptomycin arm compared to the comparator arm.

Figure 4: Infection Related SAEs by Treatment Group

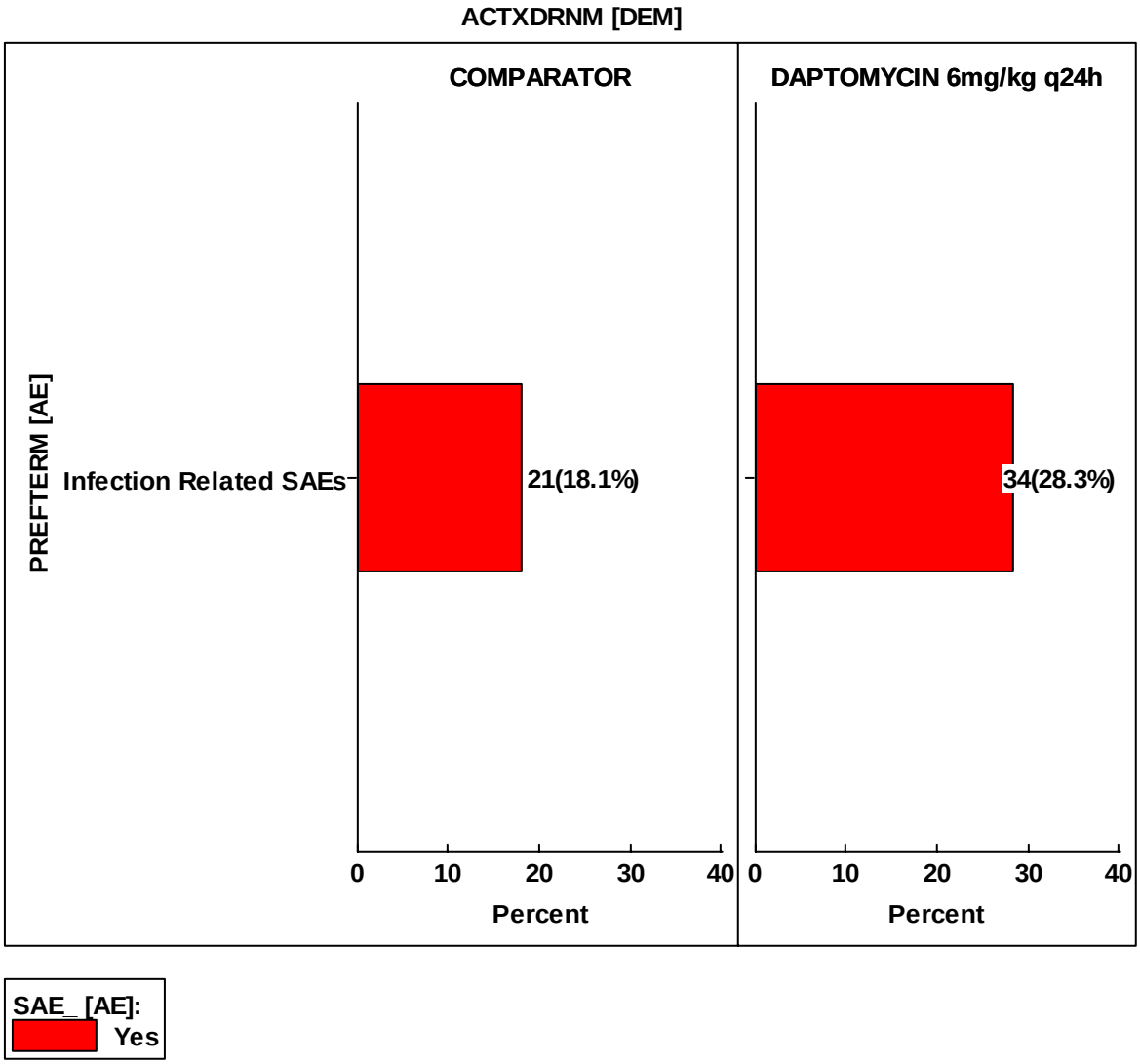
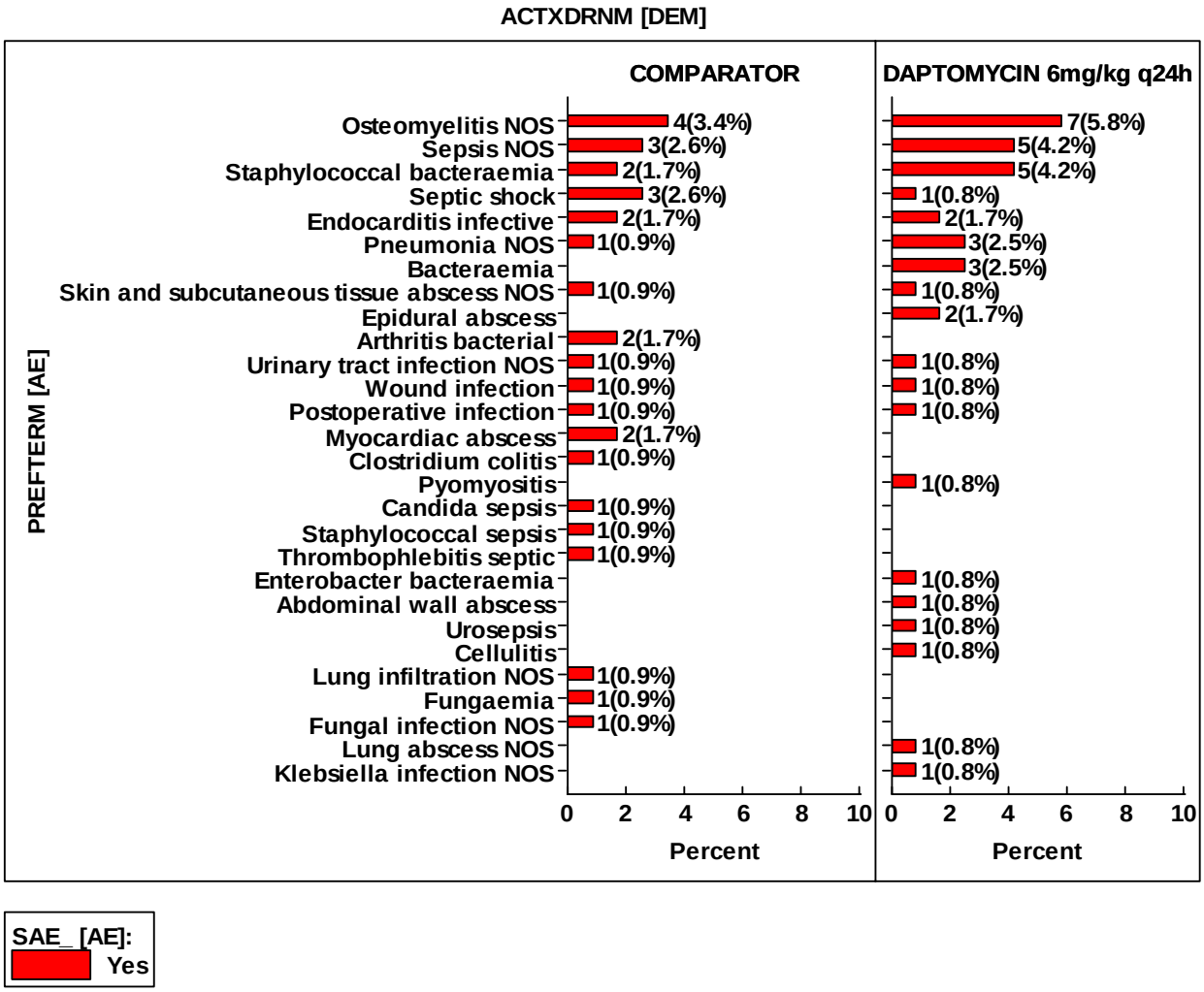


Figure 5 shows a breakdown of the specific preferred terms for all infection-related SAEs by preferred term and treatment arm.

Figure 5: Infection-related SAEs



Review of all infection related SAEs revealed an increase in the rate of patients in the daptomycin arm who developed gram-negative SAE's compared to the comparator arm. These infections included Klebsiella infection and Enterobacter bacteremia as well as gram-negative sepsis.

Creatine Phosphokinase (CPK) Analysis

The protocol was designed such that all patients were to have CPK measurements done at each study visit. Abnormal results were to be followed until normalization. Table 23 shows distribution of CPK results for all measurements by treatment arm.

Table 23: CPK values for all measurements by treatment arm

Range for CPK	COMPARATOR	DAPTOMYCIN 6mg/kg q24h	Total
0 to 100	108	109	217.00
101 to 200	43	49	92.00
201 to 300	15	18	33.00
301 to 400	6	10	16.00
401 to 500	8	6	14.00
501 to 600	1	5	6.00
601 to 700		4	4.00
701 to 800	1	2	3.00
801 and up	1	9	10.00
missing	9	6	15.00
Total	192.00	218.00	410.00

For patients with CPK measurements between 100 and 500, the two treatment arms were relatively similar (72 for comparator vs. 83 for the daptomycin arm). However, there were greater numbers of CPK measurements over 500 in the daptomycin arm (21 measurements from 16 different patients) compared to the comparator arm (3 measurements from 3 different patients). There was only one specific report of rhabdomyolysis (patient 070) who developed an increase in CPK to 847 while on daptomycin therapy and required discontinuation of therapy. This event was not considered to be serious by the investigator. No specific criteria were specified in the protocol regarding the definition of rhabdomyolysis.

Prior or Concomitant Therapy with a HMG-CoA reductase inhibitors

A review of patients with high level CPK elevations revealed several who had been pre-treated or concomitantly treated with a HMG-CoA reductase inhibitors. Because of this, an analysis was done looking at rates of increased CPK levels in the presence or absence of a HMG-CoA reductase inhibitors. A total of 44 patients were identified who had concomitantly or previously been treated with HMG-CoA reductase inhibitors. Among those study patients who had been previously or concomitantly treated with HMG-CoA reductase inhibitors, there were 24 daptomycin-treated patients who had a total of 49 CPK measurements and 20 comparator treated patients who had a total of 33 CPK measurements.

Table 24 below shows all CPK measurements done for HMG-CoA reductase inhibitor-treated patients without regard to baseline CPK measurements.

Table 24: CPK measurements in HMG-CoA reductase inhibitor-treated patients without regard to baseline CPK

	COMPARATOR	DAPTOMYCIN 6mg/kg q24h	Total
Range for CPK	HMG COA REDUCTASE INHIBITORS		
0 to 100	17	21	38.00
101 to 200	9	9	18.00
201 to 300	3	5	8.00
301 to 400		3	3.00
401 to 500	2	2	4.00
501 to 600	1	3	4.00
801 and up		5	5.00
missing	1	1	2.00
Total	33.00	49.00	82.00

Some of these patients were enrolled with very elevated baseline CPK measurements which then normalized during the course of the study. Therefore, individual patients with CPK measurements over 500 were reviewed and the following analysis is limited to those patients with a normal or near normal baseline who then went on to develop a CPK level above 500 and patients with abnormal baseline CPK levels whose CPK level increased to such a degree that therapy with study drug had to be discontinued.

Table 25 shows the rates of CPK elevations above 500 by treatment group and presence or absence of prior/concomitant treatment with a HMG-CoA reductase inhibitors.

Table 25: CPK elevations > 500 by treatment group and prior/concomitant treatment with a HMG-CoA reductase inhibitors

Rates of CPK Elevations > 500 by Treatment Group		
	Comparator n/N (%)	Daptomycin n/N (%)
Overall Study	1/116 (0.95)	11/120 (9.2)
Prior or Concomitant treatment with a HMG-CoA reductase inhibitor	0/20 (0.0)	4/24 (16.7)
Patients with CPK > 500 who received prior or concomitant treatment with a HMG-CoA reductase inhibitor	0/1 (0.0)	4/11 (36.4)

Review of comparator-treated patients who had prior or concomitant treatment with HMG-CoA reductase inhibitors revealed that no patient (0 out of 20) went on to develop a CPK level above 500. However, in the daptomycin-treated patients who had received either prior or concomitant therapy with a HMG-CoA reductase inhibitors, 4/24 (patients 149 and 183 – Simvastatin pre-treatment, patient 229 – Simvastatin concomitant treatment, patient 079 – Atorvastatin pre-treatment) went on to develop CPK levels greater than 500. Of the 11 daptomycin treated patients who developed worsening CPK abnormalities of a high level, 4 (36.4%) received prior or concomitant therapy with a HMG-CoA reductase inhibitor. Because overall numbers of patients who received a

HMG-CoA reductase inhibitor was small, definite conclusions cannot be reached, however, the association of HMG-CoA reductase inhibitor exposure and daptomycin with increased CPK levels is noted.

Of the 11 patients in the daptomycin arm who had CPK elevations above 500, six required discontinuation of therapy, two in whom the CPK elevation was first recognized after the last dose of therapy, and three in whom CPK levels normalized while on continued therapy.

Renal Toxicity

Figure 6 compares the preferred terms and rates of renal adverse events for comparator and daptomycin-treated patients. Overall, reported renal AEs were more common in the comparator treated arm than in the daptomycin treated arm (31 for comparator-treated patients vs. 18). The majority of the renal AEs in comparator-treated patients were in patients reported to have had an event coded as either Renal Failure NOS or Renal Failure Acute.

Figure 6: Renal adverse events by treatment arm

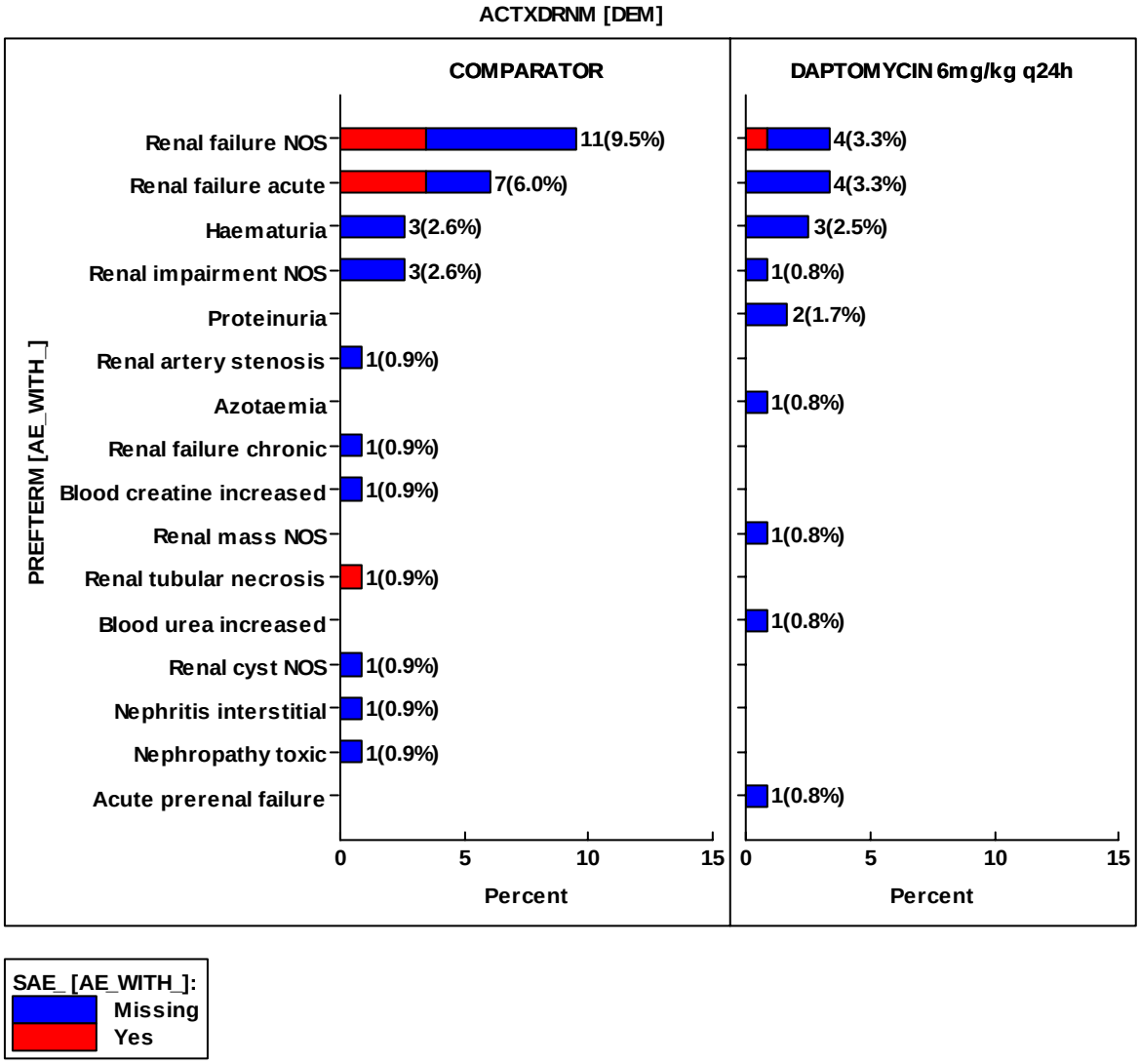
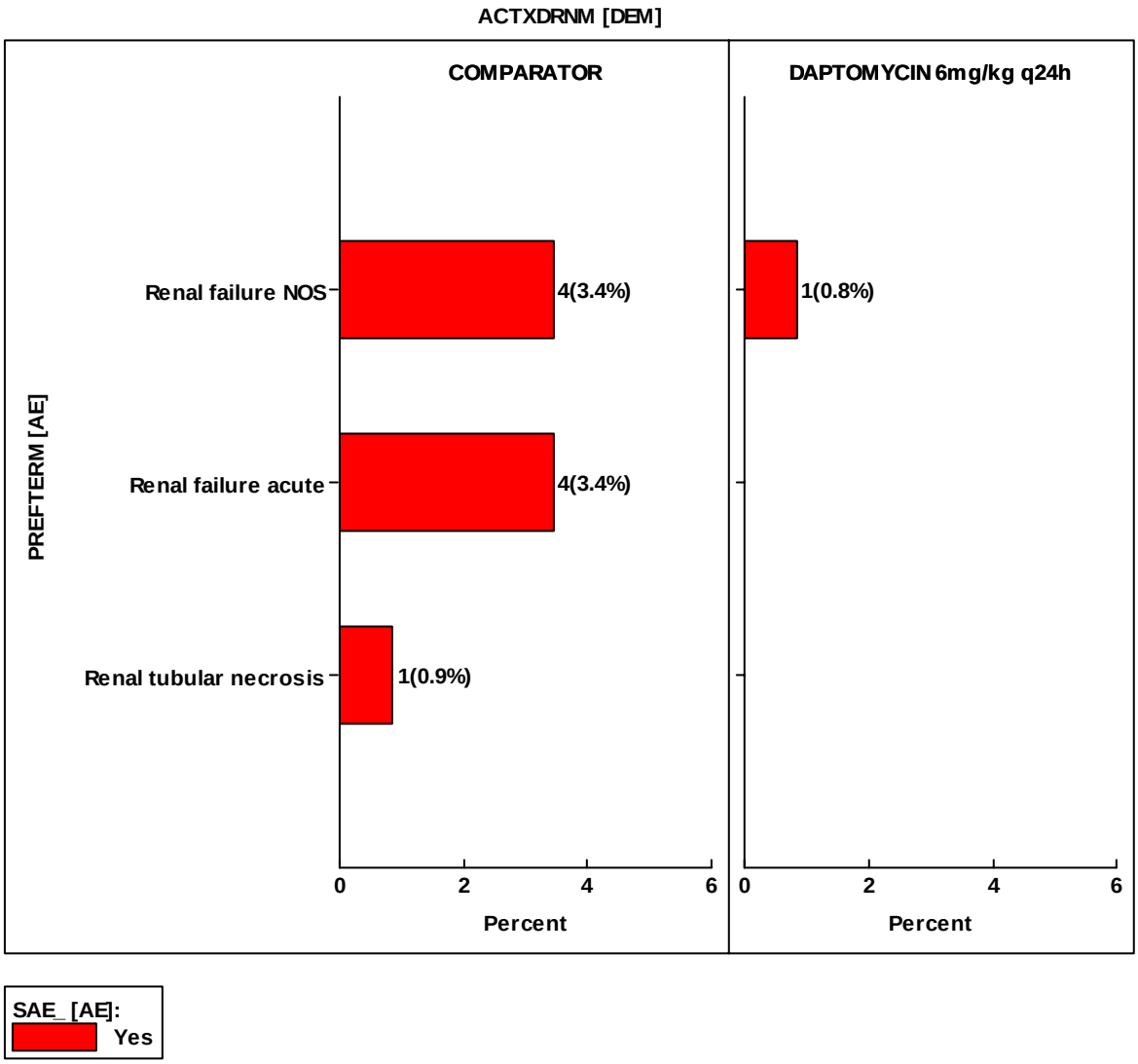


Figure 7 shows the rates of renal SAEs by study treatment arm. There were more instances of renal SAEs in the comparator arm vs. the study drug arm (9 vs. 1) with all but one occurring as either Renal Failure NOS or Renal Failure Acute.

Figure 7: Renal SAEs by study treatment arm



Of the 9 daptomycin-associated renal SAE's, three did not have a strong temporal relationship having occurred 21, 28 and 30 days after the final dose of study drug. These patients had alternative explanations for their SAE and the investigators did not believe that their renal toxicity was related to study drug. There were 2 additional patients (143, and 201) who also had possible alternative explanations and were categorized as being "not related" by the investigator, although their events did have a stronger temporal relationship, one having occurred on therapy and the other only seven days after the last dose of study drug. The remaining four patients (120, 237, 034, and 029) had strong temporal relationships to study drug administration and were felt by investigators to be possibly related to study drug exposure. The single case of a daptomycin-associated renal SAE occurred 1 day after the final day of treatment and was felt to be possibly related to study drug by the investigator.

VIII. CLINICAL PHARMACOLOGY IN RENAL IMPAIRMENT

All patients with CL_{CR} ≥30 mL/min received daptomycin 6 mg/kg q24h. Patients with a CL_{CR} <30 mL/min were to be excluded from the study. However, two patients in the daptomycin arm and three patients in the comparator arm with CL_{CR} <30 mL/min were enrolled.

Sparse sampling and a population pharmacokinetic (PK) analysis was performed for the Phase 3 clinical trial to assess the impact of renal function on the pharmacokinetics of daptomycin 6 mg/kg q24h in this study. The results are shown in Table 26.

The exposure of daptomycin (AUC) among patients with normal renal function receiving daptomycin 6 mg/kg q24h is 545 μg*hr/mL. In comparison, the exposure of daptomycin among patients with moderate renal impairment receiving is 868 μg*hr/mL. Thus, the exposure of daptomycin in patients with moderate renal impairment was approximately 1.59-fold the exposure of daptomycin in patients with normal renal function.

Table 26: IEAC outcome at TOC by degree of renal impairment (ITT population)

Baseline renal function	Daptomycin (n=120)	Comparator (n=115)	Difference in success rates (C.I.)
Overall			
Success	44.2% (53/120)	41.7% (48/115)	2.4%
Failure	48.3% (58/120)	46.1% (53/115)	(-10.2 to 15.1)
Non-evaluable	7.5% (9/120)	12.2% (14/115)	
Severe renal impairment			
Success	0% (0/2)	0% (0/3)	0.0%
Failure	100% (2/2)	100% (3/3)	(0.0 to 0.0)
Non-evaluable	0% (0/0)	0% (0/3)	
Moderate renal impairment			
Success			-35.6%
Failure	11.8% (2/17)	47.4% (9/19)	(-62.8 to -8.4)
Non-evaluable	88.2% (15/17)	36.8% (7/19)	
	0% (0/17)	15.8% (3/19)	
Mild renal impairment			
Success	38.2% (13/34)	41.2% (14/34)	-2.9%
Failure	52.9% (18/34)	44.1% (15/34)	(-26.2 to 20.3)
Non-evaluable	8.8% (3/34)	14.7% (5/34)	

Although patients with moderate renal impairment have an increased exposure of daptomycin, the efficacy of daptomycin based on the IEAC outcome at TOC (ITT population) was lower among patients with moderate renal impairment compared to all patients receiving daptomycin and patients receiving daptomycin with mild renal impairment as shown in Table 26. The efficacy of daptomycin was also lower than comparator among patients with moderate renal impairment. An analysis of the adverse events for daptomycin and comparator stratified by renal function is in progress.

IX. ISSUES FOR DISCUSSION

We will be asking your advice on the following topics at the Advisory Committee meeting:

1. Performance of daptomycin in the overall population and in subgroups including infective endocarditis:

   The study demonstrated non-inferiority of daptomycin to the comparator in the overall population with at least one positive blood culture for *S. aureus*. Certain caveats, however, are noteworthy. These include heterogeneity of the study population, small number of patients with infective endocarditis, and in overall failures, a higher proportion of persisting or relapsing bacteremias in patients treated with daptomycin.

2. Implications of development of increasing MICs to daptomycin during treatment with daptomycin:

   In some patients, *S. aureus* demonstrated increasing MICs (> 1 mcg/ml) to daptomycin during or after therapy with the drug. Most of these patients had persistent or relapsing bacteremia.

3. Advice on study design for clinical trials in patients with infective endocarditis:

   Clinical studies that enroll patients based solely upon a positive blood culture for *S. aureus* may not achieve a substantial clinical experience in infective endocarditis.

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