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APPLICATION NUMBER

21-572

Medical Review(s)

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

Clinical Review

NDA 21-572

Cubicin (daptomycin for injection)

Original New Drug Application for marketing approval for treatment of complicated skin and skin structure infections (cSSSI) due to Gram-positive bacteria including *Staphylococcus aureus* (methicillin-resistant and susceptible strains), *Streptococcus pyogenes*, *Enterococcus faecalis* (vancomycin-susceptible strains), *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subsp. *equisimilis*

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CLINICAL REVIEW

Integrated Review of Safety and Efficacy

Integrated Review of Safety and Efficacy

This document is the integrated review of safety and efficacy for NDA 21-572. Appendices describing the individual protocols, safety and efficacy, and a detailed analysis of CPK are appended to this review.

I. Recommendations

A. Recommendation on Approvability

Cubicin™ (daptomycin for injection; Cubist Pharmaceuticals) is the lead investigational antibiotic in a new class of drugs known as cyclic lipopeptides. Based on evidence from two randomized, active-controlled clinical trials submitted by the sponsor, there is adequate efficacy and safety data to recommend approval of daptomycin 4 mg/kg/day intravenously for 7-14 days, in patients 18-85 years of age, with complicated skin and skin structure infections (cSSSI) due to Gram-positive bacteria including *Staphylococcus aureus* (methicillin-resistant and susceptible strains), *Streptococcus pyogenes*, *Enterococcus faecalis* (vancomycin-susceptible strains), *Streptococcus agalactiae*, and *Streptococcus dysgalactiae*. In combined cSSSI studies, a total of 534 patients were treated with daptomycin. The safety database comprised data on 602 daptomycin-treated patients in Phase I studies, 349 daptomycin-treated patients in Phase II studies, and 989 patients in Phase III studies.

The two clinical studies conducted by Cubist in cSSSI were similar in trial design, but differed in certain baseline patient characteristics, such as underlying diabetes and peripheral vascular disease. Such differences in baseline characteristics may have had a significant effect on wound healing. Observed success rates were in fact quite different in the two studies. In both trials, daptomycin was demonstrated to be non-inferior to the comparator (vancomycin/semi-synthetic penicillins, including nafcillin, oxacillin, cloxacillin, or flucloxacillin), using a non-inferiority margin of 10%. Concomitant aztreonam or metronidazole could be used for Gram-negative/anaerobic coverage respectively. Concomitant surgical procedures such as debridement were also permitted during the study.

Sufficient numbers of patients with complicated skin and skin structure infections such as major abscesses, infected ulcers, wound infections, and cellulitis were included in the studies to justify inclusion in the label. Data were inadequate to include patients with infected diabetic ulcers. The number of patients enrolled with infected diabetic ulcers was small, errors in classification of diabetic ulcers occurred, and the clinical success rates observed in these limited data were low.

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

The safety profile of daptomycin is derived from 1755 subjects exposed to daptomycin in clinical studies conducted by Cubist and Lilly; limited 120-day safety data are available for an additional 52 patients enrolled in ongoing studies, most of whom received a higher dose of daptomycin at 6 mg/kg IV given once daily. Overall, the MedDRA system organ class (SOC) with the greatest percentages of reported adverse events was gastrointestinal disorders, most frequently nausea, constipation, diarrhea, and vomiting. The rates of overall adverse events, deaths, serious adverse events (SAEs) other than death, and adverse events (AEs) leading to discontinuation were similar in both treatment groups. Preclinical studies had predicted that the primary target of daptomycin toxicity was skeletal muscle. This prediction was confirmed in Phase I studies by the observed elevation of CPK with muscle-related symptoms in 2/5 subjects given 4 mg/kg IV q12h and 2/4 subjects administered daptomycin at 4 mg/kg IV q24h. In Phase III cSSSI trials, elevations in serum CPK were reported as clinical adverse events in 15/534 (2.8%) daptomycin-treated patients, compared to 10/58 (1.8%) comparator-treated patients. Symptoms consistent with muscle injury were observed in 1/534 (0.2%) of daptomycin-treated patients.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The Agency and Cubist have agreed that Cubist will conduct two Phase 4 studies.

- The first study will consist of a safety and efficacy study in patients with cSSSI. This study is scheduled to start in the first quarter of 2004 and has an estimated 18-month study duration. The study will be open-label, randomized, multicenter, non-comparative study. The patient population for this study will consist of 72 patients with renal insufficiency in the following categories: Clcr 30-50 mL/min and Clcr <30 mL/min. Patients in the latter category may be on hemodialysis, continuous ambulatory peritoneal dialysis, or may not be maintained on dialysis. Pharmacokinetic data will also be collected in this study.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Daptomycin [Cubicin®] is a cyclic lipopeptide antibiotic that is administered intravenously.

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

Phase I and II studies

The Cubist Phase I studies enrolled 240 subjects who received daptomycin. The Cubist human pharmacology studies included single- and repeat-dose pharmacokinetic studies in normal healthy subjects and in special populations. Repeat-dose studies were conducted in healthy subjects and in subjects with various degrees of renal impairment, including end-stage renal disease (ESRD). Single-dose studies were conducted in subjects with moderate hepatic impairment (Child-Pugh Classification B), in geriatric subjects, and in obese subjects, and in healthy subjects. Drug interaction studies with aztreonam, probenecid, warfarin, and simvastatin were conducted in healthy subjects. Studies on daptomycin protein binding were conducted in healthy subjects and in subjects with various degrees of renal impairment, including ESRD. A placebo-controlled study was conducted to examine the effect of daptomycin given to healthy subjects at 6 mg/kg q24h for 14 days on cardiac repolarization (QT interval) and peripheral nerve conduction. Cubist also studied the penetration of daptomycin into inflammatory exudate from cantharides-induced skin blisters. *In vitro* studies were conducted to assess the influence of daptomycin on induction or inhibition of cytochrome P450 enzymes in human hepatocytes.

The Lilly Phase I studies enrolled 362 subjects who received daptomycin. These human pharmacology studies included single- and multiple-dose safety and pharmacokinetic studies in healthy subjects. Multiple-dose studies examined various doses and regimens up to 4 mg/kg q 12h x 14 days. Also included are *in vivo* protein binding studies; a metabolism and excretion study using radiolabeled daptomycin, a study in subjects with various degrees of renal impairment and drug interaction studies with tobramycin and amikacin.

Cubist conducted two Phase II studies; a third study was discontinued due to slow enrollment. DAP-BAC-9803, is an open-label, Phase II, dose-ranging trial in subjects with culture-confirmed Gram-positive bacteremia or presumed bacteremia. The study compared three doses of daptomycin (4 mg/kg q24h, 6 mg/kg q24h, or 3 mg/kg q12h with a 6 mg/kg loading dose) with standard therapy (vancomycin 1 g every 12 hours or nafcillin or oxacillin 4-12 g daily in equally divided doses) and enrollment was 3:1 daptomycin:comparator. The second Phase II study, DAP-RRC-9804, is an open-label, non-comparative, multicenter study utilizing three dose regimens of daptomycin in hospitalized subjects with bacteremia (4 mg/kg q24h, 6 mg/kg q24h, 3 mg/kg q12h following a 6 mg/kg loading dose), complicated skin and skin structure infections (cSSSI) (4 mg/kg q24h), lower respiratory tract infections (LRTI) (6 mg/kg q24h), intra-abdominal infections (IAI) (6 mg/kg q24h), or complicated urinary tract infections (UTI) (4 mg/kg q24h potentially adjusted according to MIC level) caused by Gram-positive pathogens that were resistant to vancomycin or whose infection was otherwise refractory to currently available therapy or for whom currently available therapy was contraindicated. Study DAP-RRC-

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

9804 was terminated due to slow enrollment. Study DAP-00-03 was an open-label, microbiologist-blinded, Phase III study comparing daptomycin at a dosage of 4 mg/kg q24h with ciprofloxacin 400 mg in subjects with complicated urinary tract infections caused primarily by Gram-positive pathogens. Due to slow enrollment, this trial was terminated.

Three Phase II studies were conducted by Lilly during the years 1987 - 1990. Study B8B-MC-AVAE/B8B-EW-AVAG is described below, as it was submitted with the NDA as supportive of the cSSSI indication. The second Phase II study, B8B-MC-AVAM, was a randomized, open-label study in which subjects with endocarditis and bacteremia were given daptomycin (loading dose of 6 mg/kg followed by 3 mg/kg q 12h) for up to 42 days; pharmacodynamic data was collected in this study. The third Phase II study, B8B-EW-AVAH, was an open label, uncontrolled study to evaluate the efficacy of daptomycin in subjects with Gram-positive skin and skin structure infections. This study was terminated after only 4 of the planned 50 subjects were enrolled due to adverse events..

One controlled study, B8B-MC-AVAE/AVAG conducted by Lilly, was submitted as a supportive study. The dose of daptomycin used in this study was 2 mg/kg q 24 hours for a total duration of five days. As the dosing regimen of daptomycin used in this study is different from that used in the two Phase III cSSSI clinical trials, results of this study are not included in the overall efficacy analyses and will not be discussed in this review.

Phase III studies

Complicated skin and skin structure infections

Results of two Phase III studies, DAP-SST-9801 and DAP-SST-9901, were included in this NDA to support the indication of complicated skin and skin structure infections. The safety and efficacy of daptomycin was compared to that of vancomycin or a semi-synthetic penicillin (cloxacillin, flucloxacillin, oxacillin, or nafcillin) for the treatment of hospitalized patients with complicated skin and skin structure infections due to Gram-positive bacteria. The two studies were similar in design and conduct to a great extent. Both studies were randomized, active-controlled, and investigator-blinded. Study 9801 was conducted at 68 study sites, 63 in the United States and 5 in South Africa. Study 9901 was conducted at 67 study sites including Europe, South Africa, Australia, and Israel.

In the two pivotal studies, patients with complicated skin and skin structure infections including ulcers (diabetic and non-diabetic), wound infections, and major abscesses were randomized on a 1:1 basis to receive 7-14 days treatment with daptomycin 4 mg/kg intravenously as a single daily dose or a comparator agent. The comparator drug could be either

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

vancomycin or a semi-synthetic penicillin. Investigators could select the semi-synthetic penicillin based on local availability and treatment practice. Randomization was stratified based on the presence or absence of an infected diabetic ulcer as the primary site of infection. Adjunctive treatment with aztreonam or metronidazole could be given for Gram-negative or anaerobic organisms, respectively. Ancillary surgical treatment (e.g., debridement) was permitted.

In study 9801, a total of 547 patients were randomized and 530 received at least one dose of study medication. In study 9901, a total of 571 patients were randomized and 562 received at least one dose of study medication.

Community-acquired pneumonia

Cubist conducted two controlled clinical trials, DAP-CAP-00-05 and DAP-CAP-00-08, of essentially identical design to evaluate daptomycin in the treatment of moderate to severe community-acquired pneumonia (CAP) due to *S. 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. At the discretion of the investigator, adjunctive treatment with aztreonam could be given for suspected Gram-negative organisms. Therapy was to be administered 5 to 14 days, followed by Test-of-Cure and Post-Study visits conducted 7 to 14 and 21 to 28 days, respectively, after the last dose of study drug. Men and women who were 18 years of age or older and had pneumonia which required hospitalization and intravenous therapy for at least 5 days were eligible for the study. The infection must have been known or suspected to be due, at least in part, to Gram-positive bacteria. Subjects previously treated with potentially effective anti-infective agents for >24 hours (or one dosing day) within 72 hours of enrollment were excluded. Protocol DAP-CAP-00-05 enrolled patients in the U.S., Europe, Canada, Australia, South America, and New Zealand. Study DAP-CAP-00-05 enrolled 355 patients in the daptomycin arm and 359 in the comparator arm and was completed in October 2000.

Staphylococcus aureus infective endocarditis

In study B8B-MC-AVAM, 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). The Applicant postulated that this lower efficacy rate in the treatment of *S. aureus* endocarditis was due to low daptomycin peaks and troughs with q 12 hour dosing, and proposed a new trial DAP-IE-01-02 in infective endocarditis using daptomycin 6 mg/kg q 24 hours. Since patients with left-sided endocarditis might experience more severe consequences in terms of morbidity or mortality should daptomycin be inferior to comparator, given

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

the intrinsically more fulminant course of left-sided infective endocarditis, the Agency agreed to the proposed trial in patients with right-sided endocarditis only. A Data Management Committee will be convened following completion of the first 30 subjects (15 per arm) to review the safety and efficacy in these 30 subjects prior to enrollment of patients with left-sided endocarditis. This analysis as well as preliminary pharmacokinetic data will be submitted to the Agency.

B. Efficacy

DAP-SST-9801 and DAP-SST-9901: Complicated skin and skin structure infections

Cubist has provided sufficient data to support granting the indication of complicated skin and skin structure infections. Intravenous daptomycin 4 mg/kg/day as a single dose was demonstrated to be non-inferior to comparator (semi-synthetic penicillins or vancomycin). The 95% confidence intervals around the difference in clinical cure rates demonstrated that the two treatment regimens were equivalent using a non-inferiority margin of 10%.

Patients 18 years of age and older with complicated skin and skin structure infections including wound infections, major abscess, cellulitis, or infected ulcer (diabetic and non-diabetic) were enrolled in the studies. Patients with bacteremia, osteomyelitis, patients on hemodialysis or peritoneal dialysis, those receiving HMG-CoA reductase inhibitors, and those with creatinine clearance < 30 ml/min were excluded.

The primary efficacy endpoint was sponsor-defined clinical outcome at the test of cure (TOC) visit, 6-20 days after the end of therapy. The sponsor defined clinical outcome took into account the length of therapy in addition to the investigator's clinical response. The patient must have received ≥ 4 calendar days of study medication to be classified as a cure or > 2 days to be classified as a failure. Investigator response of either improved/cure at the TOC visit was considered a clinical success.

Study 9801 was conducted at sites in the United States and South Africa, while study 9901 was conducted entirely outside the United States, mainly in South Africa and Europe. Both studies were similar in design, but differed significantly in patient baseline characteristics that potentially impact the overall cure rates. Patients in study 9801 tended to be sicker, with more co-morbid conditions, required concomitant antibiotics for Gram-negative/anaerobic coverage more commonly, and needed concomitant surgical procedures more often. Patients in study 9901 were less sick, had fewer complicating medical illnesses, and the need for concomitant antibiotics for Gram-negative/anaerobic coverage or concomitant surgical procedures was also less frequent. Efficacy estimates

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

differed significantly in the two studies in both the daptomycin and comparator arms. Results of the two studies will thus be presented separately rather than in an integrated manner.

Sponsor-defined and FDA-defined populations differed in certain respects. Hence, re-analyses were performed using FDA-defined populations. In study 9801, the sponsor discontinued 13 patients from the study after they were randomized, and had received at least one dose of study medication; 12 of these patients had osteomyelitis, and one had an infected foreign body that was not removed. These patients were excluded from the sponsor-defined ITT population. All patients who are randomized and receive at least one dose of study medication should be included in the ITT population and hence they were included in the FDA-defined ITT population. The sponsor did not reject any patients in study 9901.

The sponsor-defined clinically evaluable (CE) population and the FDA-defined CE population differed in two respects.

- Patients who had received > 2 days of study medication, and had a missing test-of-cure (TOC) visit were classified as evaluable failures by the sponsor, and as non-evaluable in the FDA analyses.
- All patients who received concomitant antibiotics for > 2 days for reasons other than lack of efficacy were excluded by the sponsor. All patients who received concomitant antibiotics from day 2- TOC visit irrespective of the duration of such treatment were excluded from the FDA-defined CE population.

In the FDA analyses, 95% confidence intervals (CI) around the difference in success rates (daptomycin-comparator) were calculated, while the sponsor calculated the 95% CI for difference in success rates between comparator and daptomycin. Hence, using a non-inferiority margin of 10 %, non-inferiority is established if the value of the lower bound of the 95% CI is less than 10 % in the FDA analyses and a value of the upper bound of the 95% CI is less than 10 % in the sponsor's analyses.

The primary efficacy populations were the Intent To Treat (ITT) and Clinically Evaluable (CE) populations. Clinical success rates using the sponsor defined clinical outcome for the ITT and CE populations for both studies are presented below.

Study 9801

In study 9801, success rates in the ITT and CE populations (Tables 1, 2) were similar in the two treatment arms in analyses performed by the sponsor. Daptomycin was demonstrated to be non-inferior to the comparator using a non-inferiority margin of 10 %. This was evidenced by

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

the upper bound of the 95% CI around the difference in success rates being less than 10 % and the 95 % CI including the value of zero.

Sponsor's Results

Table 1: Sponsor-defined clinical outcome (Population: ITT)

Clinical Response	Daptomycin N = 256	Comparator N = 261	95% CI*
Clinical success	167 (65%)	166 (64%)	-9.9, 6.6
Cure	110 (43%)	100 (38%)	
Clinical improvement	57 (22%)	66 (25%)	
Clinical failure	89 (35%)	95 (36%)	
Failure	56 (22%)	56 (21.5%)	
Unable to evaluate	33 (13%)	39 (15%)	

Source: Table 14.2.1.1, final study report

*95% confidence interval around the difference in success rates (comparator-daptomycin)

Table 2: Sponsor-defined clinical outcome (Population: CE)

Clinical Response	Daptomycin N = 223	Comparator N = 222	95% CI*
Clinical success	167 (75%)	166 (75%)	-8.2, 8.0
Cure	110 (49%)	100 (45%)	
Clinical improvement	57 (26%)	66 (30%)	
Clinical failure	56 (25%)	56 (25%)	
Failure	56 (25%)	56 (25%)	

Source: Sponsor table 11-7, final study report

*95% confidence interval around the difference in success rates (comparator-daptomycin)

FDA Results

In study 9801, success rates in the ITT and CE populations (Tables 3, 4) were similar in the two treatment arms in analyses performed by the FDA. Daptomycin was demonstrated to be non-inferior to the comparator using a non-inferiority margin of 10 %. This was evidenced by the lower bound of the 95% CI around the difference in success rates being less than 10 % and the 95 % CI including the value of zero. Results of the FDA analyses were similar to those obtained by the sponsor.

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

Table 3: Sponsor-defined clinical outcome (Population: ITT)

Clinical Response	Daptomycin (N=264)	Comparator (N=266)
Clinical Success	165 (62.5%)	162 (61%)
Clinical Failure	99 (37.5%)	104 (39%)
Difference in Success Rate : Daptomycin vs. Comparator	1.6%, 95% C.I.: -7.1%, 10.3%	

Table 4: Sponsor-defined clinical outcome (Population: CE)

Clinical Response	Daptomycin (N=208)	Comparator (N=206)
Clinical Success	158 (76%)	158 (77%)
Clinical Failure	50 (24%)	48 (23%)
Difference in Success Rate: Daptomycin vs. Comparator	-0.7%, 95% C.I.: -9.4%, 7.9%	

Study 9901

Sponsor's Results

In study 9901, success rates in the ITT and CE populations (Tables 5, 6) were similar in the two treatment arms in analyses performed by the sponsor. Daptomycin was demonstrated to be non-inferior to the comparator using a non-inferiority margin of 10 %. This was evidenced by the upper bound of the 95% CI around the difference in success rates being less than 10 % and the 95 % CI including the value of zero.

Table 5: Sponsor-defined clinical outcome (Population: ITT)

Clinical Response	Daptomycin N = 270	Comparator N= 292	95% CI
Clinical Success	218 (81%)	237 (81%)	-6.1, 6.9
Cure	103 (38%)	123 (42%)	
Clinical Improvement	115 (43%)	114 (39%)	
Clinical Failure	52 (19%)	55 (19%)	
Failure	28 (10%)	27 (9%)	
Unable to Evaluate	24 (9%)	28 (10%)	

Source: Table 14.2.1.1, final study report

*95% confidence interval around the difference in success rates (comparator-daptomycin)

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

Table 6: Sponsor-defined clinical outcome (Population: CE)

Clinical Response	Daptomycin N = 245	Comparator N = 262	95% CI*
Clinical Success	217 (89%)	235 (90%)	-4.3, 6.5
Cure	103 (42%)	122 (47%)	
Clinical Improvement	114 (46.5%)	113 (43%)	
Clinical Failure	28 (11%)	27 (10%)	
Failure	28 (11%)	27 (10%)	

Source: Sponsor table 11-7, final study report

*95% confidence interval around the difference in success rates (comparator-daptomycin)

FDA Results

In study 9901, success rates in the ITT and CE populations (Tables 7, 8) were similar in the two treatment arms in analyses performed by the FDA. Daptomycin was demonstrated to be non-inferior to the comparator using a non-inferiority margin of 10 %. This was evidenced by the lower bound of the 95% CI around the difference in success rates being less than 10 % and the 95 % CI including the value of zero. Results of the FDA analyses were similar to those obtained by the sponsor.

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CLINICAL REVIEW

Integrated Review of Safety and Efficacy

Table 7: Sponsor-defined clinical outcome (Population: ITT)

Clinical Response	Daptomycin (N=270)	Comparator (N=292)
Clinical Success	217 (80%)	235 (80.5%)
Clinical Failure	53 (20%)	57 (19.5%)
Difference in Success Rate: Daptomycin vs. Comparator	-0.1%, 95% C.I.: -7.0%, 6.8%	

Table 8: Sponsor-defined clinical outcome (Population: CE)

Clinical Response	Daptomycin (N=238)	Comparator (N=250)
Clinical Success	214 (90%)	226 (90%)
Clinical Failure	24 (10%)	24 (10%)
Difference in Success Rate: Daptomycin vs. Comparator	-0.5%, 95% C.I.: -6.2%, 5.2%	

Efficacy Summary:

Based on the results of these two randomized, active-controlled, Phase III clinical trials there is sufficient evidence to support the efficacy of intravenous daptomycin in the treatment of complicated skin and skin structure infections. Intravenous daptomycin 4 mg/kg/day as a single daily dose for 7-14 days was demonstrated to be non-inferior to comparator drug (semi-synthetic penicillin or vancomycin). The 95% confidence intervals around the difference in clinical cure rates demonstrated that the two treatment regimens were equivalent using a non-inferiority margin of 10%.

Demographic Characteristics

The number of male patients enrolled in both studies was slightly higher (~55%) than that of female patients (~45%). Distribution of patients by gender was comparable between the two treatment arms.

The protocol specified age groups to be enrolled in the two cSSSI studies were patients from 18-85 years of age, except in South Africa, where the upper age limit for enrollment was 65 years. A few patients < 18 years/ >85 years were also enrolled. Overall, patients in study 9801 were slightly older, with a mean age ~55 years versus ~48 years in study 9901. The majority of patients in both studies were between 40-64 years of age. In both studies, distribution of patients by age group was comparable in the two treatment arms.

In study 9801, over 60 % of patients were Caucasian, ~ 20% were blacks and the remainder were Asian/others. In study 9901 ~50% of patients were

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

Caucasian, over a third were blacks, and the remainder were Asian/others. In both studies, distribution of patients by race was comparable in the two treatment arms.

The demographic characteristics of patients in study 9801 and 9901 are summarized in Tables 9 and 10 respectively.

Study 9801

Table 9: Demographic characteristics (Population: ITT)

Characteristic	Daptomycin (N=264)	Comparator (N=266)	P-Value
Age (yrs.)			
Range (Min, Max)	(18, 91)	(18, 94)	
Mean \pm SD	55.2 \pm 17.6	55.5 \pm 17.7	*0.8455
Distribution			
< 65 years	173 (65.5%)	183 (68.8%)	0.4233
\geq 65 years	91 (34.5%)	83 (31.2%)	
Gender			
Male	143 (54.2%)	148 (55.6%)	0.7334
Female	121 (45.8%)	118 (44.4%)	
Race			
White	177 (67.1%)	167 (62.8%)	0.5366
Black	50 (18.9%)	60 (22.6%)	
Other	37 (14.0%)	39 (14.7%)	
Weight (kg)			
Range (Min, Max)	(36, 274)	(44, 193)	
Mean \pm SD	87.6 \pm 33.5	87.0 \pm 27.7	*0.8417

* Using t-test; others using chi-square test

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

Study 9901

Table 10: Demographic characteristics (Population: ITT)

Characteristic	Daptomycin (N=270)	Comparator (N=292)	P-Value
Age (yrs.)			
Range (Min, Max)	(18, 87)	(17, 85)	*0.6284
Mean ± SD	47.9 ± 17.2	48.6 ± 16.7	
Distribution			
< 65 years	216 (80.0%)	236 (80.8%)	0.8062
≥ 65 years	54 (20.0%)	56 (19.2%)	
Gender			
Male	150 (55.6%)	160 (54.8%)	0.8562
Female	120 (44.4%)	132 (45.2%)	
Race			
White	136 (50.4%)	146 (50.0%)	0.3156
Black	95 (35.2%)	91 (31.2%)	
Other	39 (14.4%)	55 (18.8%)	
Weight (kg)			
Range (Min, Max)	(40, 165)	(40, 130)	*0.6244
Mean ± SD	73.5 ± 19.8	72.7 ± 17.4	

* Using t-test; others using chi-square test

Efficacy

Study 9801

In study 9801, clinical success rates were slightly higher in females in both treatment arms. In the daptomycin arm, success rates were lower in patients ≥ 65 years of age. In the comparator arm, success rates were comparable in the two age group categories. In study 9801, higher success rates were seen in black patients compared to Caucasian and others. Clinical success rates by demographic characteristics in the ITT population in study 9801 are presented in table 15.

Table 15: FDA efficacy analyses by demographic characteristics (Population: ITT)

Subgroup	Daptomycin (N=264)	Comparator (N=266)	95% C.I.
Age			
< 65 years	119/173 (69%)	112/183 (61%)	(-2.9%, 18.0%)
≥ 65 years	46/91 (50.5%)	50/83 (60%)	(-25.6%, 6.2%)
Gender			
Male	86/143 (60%)	87/148 (59%)	(-10.6%, 13.3%)
Female	79/121 (65%)	75/118 (64%)	(-11.2%, 14.7%)
Race			
White	101/177 (57%)	93/167 (56%)	(-9.7%, 12.4%)
Black	42/50 (84%)	47/60 (78%)	(-10.7%, 22.1%)
Other	22/37 (59.5%)	22/39 (56%)	(-21.8%, 27.9%)

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

Study 9901

In study 9901, slightly higher success rates were seen in females in the comparator arm, and in males in the daptomycin arm. Success rates were lower in patients ≥ 65 years of age in both arms. However, the reduction in success rates in patients ≥ 65 years was more pronounced in the daptomycin arm. Higher success rates were seen in patients of black/other races compared to Caucasian. Clinical success rates by demographic characteristics in the ITT population in study 9801 are presented in table 16.

Table 16: FDA efficacy analyses by demographic characteristics (Population: ITT)

Subgroup	Daptomycin (N=270)	Comparator (N=292)	95% C.I.
Age			
< 65	181/216 (83.8%)	194/236 (82.3%)	(-5.8%, 9.0%)
≥ 65	36/54 (66.7%)	41/56 (73.2%)	(-25.5%, 12.4%)
Gender			
Male	122/150 (81.3%)	125/160 (78.1%)	(-6.4%, 12.8%)
Female	95/120 (79.2%)	110/132 (83.3%)	(-14.6%, 6.3%)
Race			
White	107/136 (78.7%)	111/146 (76.0%)	(-7.8%, 13.1%)
Black	78/95 (82.1%)	75/91 (82.4%)	(-12.4%, 11.7%)
Other	32/39 (82.1%)	49/55 (89.1%)	(-23.8%, 9.7%)

Summary

Success rates in patients ≥ 65 years of age were lower in the daptomycin arm in both studies. In the comparator arm, reduction in success rate in patients ≥ 65 years of age was seen only in study 9901. The reason for a more pronounced reduction in success in older patients treated with daptomycin is unclear. Success rates were higher in patients of black race in both studies. No specific gender differences in efficacy were noted in either study.

C. Safety

The safety database comprised data on 602 daptomycin-treated patients in Phase I studies, 349 daptomycin-treated patients in Phase II studies, and 989 patients in Phase III studies.

Adverse events in Phase I studies

A total of 240 subjects received daptomycin in the Phase I studies: 19 human pharmacology studies were conducted by Lilly (9 single-dose Phase I in the U.S., 3 repeat-dose in the U.S., 3 single dose in Japan, and 4 repeat dose in Japan). Cubist conducted 22 human pharmacology studies (7 single dose and 5 repeat dose). In Lilly-sponsored Phase I studies, 102 subjects were administered single-dose daptomycin at doses ranging from 5 mg to 6.0 mg/kg; Phase I repeat-dose studies assessed doses of 1 mg/kg q 24h in a total of 25 subjects. In the Cubist-sponsored Phase I studies there were 240 daptomycin-treated patients and 109 comparator treated patients. The greatest number of subjects in the Cubist-sponsored Phase I trials were exposed to daptomycin for less than or equal to one day, or to a single dose and received a dose of daptomycin <1g. Eighty-six subjects received a total dose of daptomycin >4g in multiple dose studies.

No deaths occurred in clinical pharmacology studies conducted by either sponsor. Three serious adverse events (SAEs) in daptomycin-treated subjects were reported in the Cubist-sponsored Phase I studies. Two subjects had gastrointestinal symptoms considered "probably related" to study drug, and one subject had Bell's palsy considered by the investigator to be unrelated to study drug. One subject in the Lilly-sponsored Phase I trials developed the SAE of anemia, described as unrelated to study drug.

In the Cubist-sponsored clinical pharmacology studies, seven subjects discontinued study medication due to adverse events (AEs): 5 of 240 (2.1%) in the daptomycin group and 2 of 109 (1.8%) in the comparator group. The most common reason for discontinuation was elevation of CPK, with three subjects in the daptomycin group and one in the comparator group being discontinued for this reason. The three subjects with elevation in CPK (maximum of 1940/1593/4490 with MM isoenzymes, all asymptomatic) were considered to have a drug-related AE; AEs of facial palsy and diarrhea were also considered drug related in the daptomycin group. In the comparator group 1/2 AEs was drug-related, a rash with pruritis. In the Lilly-sponsored Phase I studies, 2/5 subjects in one study given 4 mg/kg IV q12h discontinued daptomycin due to symptomatic CPK elevations to a maximum of 20,812 and >10,000 with a MM isoenzyme pattern. CPK returned to normal in both subjects.

During the Cubist-sponsored Phase I studies, similar proportions of subjects in the daptomycin and comparator arms experienced at least one adverse event (daptomycin, 62/240 (25.8%); comparator, 32/109 (29.4%)).

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

In Cubist-sponsored multiple dose studies, 37% (44/119) of subjects experienced one or more adverse events; the most commonly occurring adverse events (>5%) were injection site pain (5.9%, 7/119), injection site edema (5%, 6/119), increased blood creatine phosphokinase (5%, 6/119), and headache (5%, 6/119). In single-dose Cubist-sponsored Phase I trials, no adverse event occurred in more than 5% of subjects. Adverse events seen in 19/102 (18.6%) of subjects in the Lilly-sponsored Phase I studies included headache, abdominal pain, and pain and bruising at the venipuncture site.

The frequency of probably or possibly drug-related AEs in daptomycin-treated subjects was 12.1% (29/240) in the Cubist-sponsored Phase I studies.

Summary of daptomycin risk profile in Phase I studies

General

- In the Cubist-sponsored Phase I studies, similar proportions of subjects in the daptomycin and comparator arms experienced at least one AE (daptomycin, 62/240 [25.8%]; comparator, 32/109 [29.4%]).
- In the Lilly-sponsored Phase I trials, adverse events were seen in 40/102 (39.2%) of subjects, most commonly headache, abdominal pain, and pain and bruising at the venipuncture site.

CPK Elevation/Myopathy

- In the Cubist-sponsored Phase I studies, 7/240 (2.9%) of daptomycin-treated subjects had elevation of CPK reported as an AE. In subjects receiving comparator, 2/109 (1.8%) had elevation of CPK reported as an AE.
- In the Lilly-sponsored Phase I studies, 2/102 (2.0%) of subjects had elevation of CPK reported as an AE.
- In the Cubist-sponsored Phase I studies, 3/240 subjects in the daptomycin group discontinued study medication due to elevation of CPK; 1/109 subjects in the comparator group discontinued due to elevation of CPK.
- In the Lilly-sponsored Phase I studies, 2/102 subjects discontinued daptomycin due to symptomatic serum CPK elevations (20,812 and >10,000 IU/L)
- No SAEs of elevated CPK or myopathy were reported in any Phase I study.
- Patients with symptoms had resolution after discontinuation of daptomycin, and elevations of CPK either resolved or were improved at the last follow-up.

Neuropathy

- A randomized, double-blind, placebo-controlled study in 60 subjects at a dose of 6 mg/kg q24h for 14 days did not demonstrate any significant neurophysiologic effect of daptomycin on peripheral nerve function

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

- 2/240 subjects had a Bell's palsy reported in the Cubist-sponsored Phase I studies, one as an SAE and one as an AE resulting in drug discontinuation; there were no such neuropathies reported in the Lilly-sponsored Phase I studies.

Cardiac

- A randomized, double-blind, placebo-controlled study in 60 subjects at a dose of 6 mg/kg q24h for 14 days did not demonstrate any significant changes in ECG results.
- No SAEs or discontinuations due to cardiac AEs were reported in Phase I trials.
- No cardiac AEs were reported in Lilly-sponsored Phase I studies; one case of tachycardia was reported in Cubist Phase I studies.

The safety data derived from the Phase I trials demonstrating elevations in serum CPK, sometimes with symptoms of myopathy is consistent with preclinical data predicting skeletal muscle as a target organ of daptomycin toxicity. There is not a strong signal of neuropathy in Phase I, supporting the findings from animal studies showing peripheral neuropathy as an AE occurring at higher doses than myopathy. Preclinical animal studies including histopathological examination of cardiac muscle were not predictive of cardiac toxicity and none was identified in Phase I.

Adverse events in Phase II studies

Three Phase II studies were conducted by Lilly. In study B8B-MC-AVAE/B8B-EW-AVAG, daptomycin was given at 2 mg/kg q24h for up to 25 days in 81 patients with various Gram-positive infections. The groups were well matched with respect to age; there were more males than females. In the daptomycin group, 7 subjects (8.7%) died and 6 subjects (7.4%) in the comparator group died. Causes of death included cardiac arrest, cerebral hemorrhage, lung cancer, renal failure, respiratory failure, sepsis, shock and sudden death. None of these deaths were attributed to study drug by the investigator or reviewing Medical Officer.

SAEs were reported in 6/80 (7.5%) of daptomycin-treated subjects and 6/81 (7.4%) of subjects in the comparator group. These SAEs included angina, urinary tract infection, cerebral hemorrhage, pancreatitis, decreased nerve conduction velocity (NCV), renal failure, aortic valve replacement, myocardial infarction, pulmonary embolism, edema, labial pain and neutropenia. None of these SAEs were attributed to study drug by the investigator or reviewing Medical Officer.

Overall, 166 adverse events were reported in this study by 53 of 80 (66.3%) patients treated with daptomycin and 53 of 81 (65.4%) treated with comparator. The most commonly occurring AEs across both treatment groups were (daptomycin/comparator) nausea (4%/9%), vomiting ((0/2%),

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

pruritis (1%/5%), diarrhea (6%/5%), headache (2%/4%), rash (4%/3%), and phlebitis (6%/8%).

In the second Phase II study, B8B-MC-AVAM, 89 patients with endocarditis and bacteremia were given daptomycin (loading dose of 6 mg/kg followed by 3 mg/kg q12h) for up to 42 days and 35 patients received comparator. The groups were well matched with respect to age; there were more males than females.

In this study, 13 daptomycin-treated patients (14.6%) and 6 comparator-treated patients (17.1%) died. Causes of death included abscess, cardiac arrest, cirrhosis of the liver, congestive heart failure, end-stage pulmonary disease, gastrointestinal hemorrhage, gastric aspiration, metastatic carcinoma, multi organ system failure, peritonitis, post-operative complications, respiratory failure and sepsis. None of the patient deaths were attributed by the investigator or reviewing Medical Officer to daptomycin administration. The relatively high death rate in this study is due to the severity of the presenting illnesses and underlying conditions.

SAEs were reported in 6/89 (6.7%) of patients in the daptomycin group including candida endocarditis, epidural abscess, acute renal failure, mitral valve vegetation, vasovagal episode, and mediastinal emphysema. There were no reported SAEs for patients in the comparator group. None of these SAEs were attributed to daptomycin administration by the reviewing Medical Officer.

Overall AEs occurred in 52/89 (58.4%) of the daptomycin-treated patients (6 mg/kg loading dose followed by 3 mg/kg q12h for up to 44 days) and 20/35 (57.1%) comparator-treated patients had at least one treatment-emergent adverse event. The most commonly reported adverse events occurring in >10% of subjects across both treatment groups included cardiovascular disorder, constipation, nausea, edema, pain, insomnia, vaginitis, rash and surgical procedure.

The third Lilly-sponsored Phase II study, B8B-EW-AVAH, was an open label, uncontrolled study to evaluate the efficacy of daptomycin in subjects with Gram-positive skin and skin structure infections. This study was terminated after only 4 of the planned 50 patients were enrolled. One of the four patients enrolled in study B8B-EW-AVAH was discontinued due to the SAE of a 50% decrease in NCV amplitude after a 1 mg dose of daptomycin. The study was put on hold due to the SAE, and no further enrollment occurred.

Cubist-sponsored Phase II studies

Cubist conducted two Phase II studies; a third study was discontinued due to slow enrollment, and is included here for purposes of this safety review. DAP-BAC-9803 included 74 daptomycin patients and 24 comparator patients with culture-confirmed Gram-positive bacteremia or presumed

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

bacteremia. The study compared three doses of daptomycin (4 mg/kg q24h, 6 mg/kg q24h, or 3 mg/kg q12h with a 6 mg/kg loading dose) with standard therapy. The majority of patients were treated for at least 14 days.

Ten daptomycin patients and two comparator patients died. Death occurred in patients as follows: three of 24 (12.5%) in the daptomycin 4 mg/kg q24h group, four of 26 (15.4%) in the daptomycin 6 mg/kg q24h group, three of 24 (12.5%) in the daptomycin 3 mg/kg q12h group, and in two of 24 (8.3%) in the comparator group. The death of one patient- with a history of cardiac dysrhythmias and congestive heart failure who received daptomycin 3 mg/kg q 12 h for a complicated UTI who developed complete heart block on day 3 and died- was considered possibly related to study drug. This death appears unlikely to be related to the study drug, in the reviewing Medical Officer's opinion.

A total of 66 (89.2%) patients in the daptomycin group and 19 (79.2%) in the comparator group reported at least one AE during the study. The most frequently reported AEs were nausea, reported in 14 patients (18.9%) in the daptomycin group and constipation, reported in seven patients (29.2%) in the comparator group. A total of 32 subjects experienced one or more SAEs, including 25 of 74 (33.8%) in the daptomycin group and seven of 24 (29.2%) in the comparator group. There was a higher incidence of SAEs reported in the 6 mg/kg q24h daptomycin group (46.2%, 12/26) than in the 4 mg/kg q24h (20.8%, 5/24) or the 3 mg/kg q12h (33.3%, 8/24) groups; however, no system organ class was represented disproportionately in the 6 mg/kg q24h group.

The second Phase II study, DAP-RRC-9804, used three dose regimens of daptomycin in 72 hospitalized subjects with bacteremia (4 mg/kg q24h, 6 mg/kg q24h, 3 mg/kg q12h following a 6 mg/kg loading dose), complicated skin and skin structure infections (cSSSI) (4 mg/kg q24h), lower respiratory tract infections (LRTI) (6 mg/kg q24h), intra-abdominal infections (IAI) (6 mg/kg q24h), or complicated urinary tract infections (UTI) (4 mg/kg q24h potentially adjusted according to MIC level) caused by Gram-positive pathogens. This study also included a "dialysis group" consisting of six patients on hemodialysis with dose modification based on decreased creatinine clearance. Note that six patients received seven "treatment periods" in this hemodialysis group. This study was terminated due to slow enrollment. The majority of patients received daptomycin treatment for at least fourteen days.

Death occurred in six of 23 (26.1%) in the 4 mg/kg q24h group, 10 of 33 (30.3%) in the 6 mg/kg q24h group, five of 10 (50.0%) in the 3 mg/kg q12h group, and four of six (66.7%) in the dialysis group. None of the deaths in this study were considered by the investigator to be related to study drug; the Medical Officer agrees with this assessment. The relatively high mortality rate in study DAP-RRC-9804 reflects the serious underlying

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

illnesses in this patient population; there was no comparator arm in this study.

AEs were most commonly reported in the system organ class of gastrointestinal disorders. The most frequently reported AEs were nausea (16.7%), diarrhea (15.3%), and vomiting (15.3%). A total of 45/72 (62.5%) patients experienced a total of 86 SAEs including 13/23 (56.5%) in the 4 mg/kg q24h group, 19/33 (54.3%) in the 6 mg/kg q24h group, 7/10 (63.6%) in the 3 mg/kg q12h group, and 6/7 (85.7%) in the dialysis group.

Study DAP-00-03 was an open-label Phase III study comparing daptomycin at a dosage of 4 mg/kg q24h (34 patients) with ciprofloxacin 400 mg (34 patients) in patients with complicated urinary tract infections caused primarily by Gram-positive pathogens. Due to slow enrollment, this trial was terminated early. The majority of patients were treated for 2 to 14 days. No deaths occurred in study DAP-00-03. In Study DAP-00-03, 2/68 (2.9%) patients (1/34 daptomycin - 2.9%, 1/34 comparator - 2.9%) experienced a total of 3 SAEs: arrhythmia and paralytic ileus in a daptomycin subject, and deep venous thrombosis in a comparator patient. A total of 4 (11.8%) patients in the daptomycin group and 13 (38.2%) in the ciprofloxacin group reported at least one AE during the study. The most frequently reported AE was diarrhea occurring in 5 patients (14.7%) in the ciprofloxacin group and no patients in the daptomycin group.

Overall, in the three Cubist-sponsored Phase II/3 studies, six subjects in the daptomycin group had a total of six SAEs assessed as possibly or probably related to study treatment. These SAEs included cholecystitis, leucopenia, pericardial effusion, complete atrioventricular block, acute renal failure, and thrombocytopenia. The patients in studies DAP-BAC-9803 and DAP-RRC-9804 had severe presenting illness and underlying medical conditions, and the relatively high mortality rate reflects these factors. There was not a disproportionate mortality rate in the daptomycin arm in the comparative study, and the deaths did not appear to be related to study drug. The death rate appeared to be unrelated to dose, although the high dose group in study DAP-RRC-9804 had a somewhat higher mortality rate; the small numbers preclude definitive conclusions.

Summary of daptomycin risk profile in Phase II studies

General

- In the Cubist-sponsored Phase II studies a high rate of adverse events occurred in study DAP-BAC-9803 66/74 (89%) and study DAP-RRC-9804 (95.8%) in the daptomycin arms, reflective of the critical nature of the patient's illnesses. The comparator arm in study 9804 had a similar high rate of AEs. The most common AEs in both studies were gastrointestinal.
- In the Lilly-sponsored Phase II trials, 166 AEs were reported in study B8B-MC-AVAE/B8B-EW-AVAG by 53 of 80 (66.3%) patients treated with daptomycin

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

and 53 of 81 (65.4%) treated with comparator and in study B8B-MC-AVAM, 58% of daptomycin-treated subjects and 57% of those treated with conventional therapy experienced at least one adverse event.. The most commonly occurring AEs across both treatment groups in study AVAE/B8B-EW-AVAG were nausea, vomiting, pruritis, diarrhea, headache, rash, and phlebitis. The most commonly reported adverse events occurring across both treatment groups in study B8B-MC-AVAM included cardiovascular disorder, constipation, nausea, edema, pain, insomnia, vaginitis, rash and surgical procedure.

CPK Elevation/Myopathy

- In the Cubist-sponsored Phase II studies, 4/74 (5.4%) of daptomycin-treated subjects had elevation of CPK reported as an AE in DAP-BAC-9803 and 4/72 (5.6%) in study DAP-RRC-9804 had elevation of CPK reported as an AE. In subjects receiving comparator in DAP-BAC-9803, 1/24 (4.2%) had elevation of CPK reported as an AE.
- In the Lilly-sponsored Phase II studies B8B-MC-AVAE/B8B-EW-AVAG and B8B-MC-AVAM, 1 patient treated with daptomycin and 1 patient treated with comparator in each studies had elevated CPK.
- In the Cubist-sponsored Phase II studies, one subject in study DAP-RRC-9804 receiving daptomycin discontinued study medication due to elevation of CPK.
- In the Lilly-sponsored Phase II studies, 2 subjects in study B8B-MC-AVAM and no patients in study B8B-MC-AVAE/B8B-EW-AVAG discontinued daptomycin due to serum CPK elevations.
- No SAEs of elevated CPK or myopathy were reported in any Phase II study.
- Patients with symptoms had resolution after discontinuation of daptomycin, and elevations of CPK either resolved or were improved at the last follow-up.

Neuropathy

- One case of decreased NCV was reported as an SAE in the Lilly-sponsored study B8B-MC-AVAE/B8B-EW-AVAG; no other cases of neuropathy were reported in Phase II as an SAE.
- In the Lilly-sponsored Phase II studies, one patient in study B8B-MC-AVAM discontinued study drug due to neuropathy; no patient discontinued study for this reason in Cubist-sponsored Phase II studies.
- 2 patients had a Bell's palsy reported in study DAP-RRC-9804.

Cardiac

- In the Cubist-sponsored Phase II studies cardiopulmonary SAEs, deaths, and discontinuations occurred at similar rates in the daptomycin and comparator arms in study DAP-BAC-9803. None of the cardiopulmonary adverse events in the noncomparative study DAP-RRC-9804 were considered to be due to study drug.

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

- In the Lilly-sponsored Phase II study B8B-MC-AVAE/B8B-EW AVAG, there were no cardiac AEs resulting in discontinuation thought to be secondary to daptomycin. Cardiac SAEs and deaths reported in daptomycin treated patients did not appear to be related to study drug, but rather the serious nature of the underlying illnesses. In Study B8B-MC-AVAM, there were similar percentages of patients who developed treatment emergent cardiac SAEs and cardiac related deaths in each group

The safety data derived from the Phase II trials conducted by Cubist and Lilly again demonstrate elevations in serum CPK, consistent with preclinical and Phase I data demonstrating skeletal muscle toxicity of daptomycin. The occurrence of neuropathy, cranial neuropathy, and decreases in NCV raise concern about neuropathy as an additional AE of daptomycin. However, the small number of cases involving neurological AEs, the similarity between daptomycin and comparator in the occurrence of AEs related to neuropathy, as well as the disparate nature of the neurological AEs make a causative relationship between daptomycin and neuropathy tenuous. As was seen in Phase I, the cardiac events described in Phase II do not seem to be related to daptomycin, supporting the conclusion that daptomycin is not cardiotoxic.

Adverse events in Phase III studies

Complicated Skin and Skin Structure Infections - Studies 9801 and 9901

For details of the study protocols, please see the Appendix A. A total of 1092 patients were treated during the cSSSI studies; 534 received daptomycin 4 mg/kg q24 hours for 7-14 days and 558 received comparator: vancomycin, nafcillin, oxacillin, flucloxacillin or cloxacillin, as designated by the investigator prior to randomization. There were no apparent differences between the treatment groups in either study or in the pooled results in the proportion of patients who discontinued I.V. drug therapy prematurely or in the reasons for discontinuation. One patient in the daptomycin arm and no patients in the comparator arm of study 9801, and no patients in either arm in study 9901 discontinued therapy due to an elevated CPK. The treatment groups were well-balanced in terms of demographic characteristics. Overall, 381 of 534 patients (71.3%) in the daptomycin group and 401 of 558 patients (71.9%) in the comparator group received 7 to 14 days of I.V. study therapy.

A total of 16 patients (8 (1.5%) daptomycin, 8 (1.4%) comparator) died during the cSSSI studies. All of the deaths appeared to be directly related to pre-existing underlying conditions and were assessed by the investigator as unrelated to study treatment; the MO reviewed these cases and agrees with this assessment.

A total of 107 patients, 58/534 (10.9%) in the daptomycin group and 49/558 (8.8%) in the comparator group, experienced one or more SAEs. There was little difference between the drug exposure groups for the overall incidence of any individual SAE. The only SAEs with a reported incidence of $\geq 1\%$ of patients in either arm of the two studies were

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

cellulitis and urosepsis, occurring in 7 (1.3%) patients and 3 (0.6%) patients, respectively, in the daptomycin group of the combined studies. All other serious events were reported in <1% of subjects in both drug exposure groups. Five patients, including 3 in the daptomycin group and one in the comparator group, experienced serious drug-related events. These included a hypersensitivity reaction, diarrhea (aggravated) and eosinophil count increased in the daptomycin group; and hypersensitivity reaction and pruritic rash in the comparator group.

The proportions of patients in the daptomycin and comparator treatment groups that experienced at least one AE in the cSSSI studies (51.3% daptomycin, 52.5% comparator) were similar. There was no statistically significant difference between the treatment groups in the number of AEs in any SOC with the exception of Diagnostic Investigations where 15 daptomycin patients (12.2%) and ten comparator patients (9.0%) reported AEs (95% CI, -6.3, 0.0). The rates of the most common reported AEs, organized by MedDRA System Organ Class (SOC), are shown in Table 17. The MedDRA SOC with the greatest numbers of reported AEs was gastrointestinal disorders; 103 of 534 daptomycin patients (19.3%) and 123 of 558 comparator patients (22.0%) reported AEs in this SOC. The most commonly reported AEs in this SOC included nausea and constipation.

The majority of events were assessed as unrelated to treatment by the investigators. A somewhat higher percentage of patients in comparator group than in the daptomycin group experienced at least one AE that was considered possibly or probably related to study treatment (17.6% of daptomycin patients, 21.1% of comparator patients). For the daptomycin group the Diagnostic Investigations SOC had the most drug-related AEs (36 patients), and for the comparator group, Gastrointestinal Disorders SOC had the most drug-related AEs (41 patients). The most frequently reported drug-related AEs were nausea (12 daptomycin, 19 comparator) and blood creatine phosphokinase increased (11 daptomycin, 8 comparator).

Because of the preclinical data suggesting skeletal muscle and peripheral nerves as target organs for daptomycin toxicity, adverse events involving these systems were analyzed in further detail. Increased blood CPK (as a clinical adverse event, as opposed to a laboratory change) was seen in 15 of 534 (2.8%) patients in the daptomycin group and 10 of 558 (1.8%) patients in the comparator group. The MedDRA SOC of Musculoskeletal, Connective Tissue, and Bone Disorders (comprised of the SOC terms reported in >1% of patients, of pain in limb, arthralgia, back pain, myalgia, muscle cramps) were reported in 7 of 534 (2.6%) daptomycin treated and 5/558 (0.9%) comparator-treated patients. Paresthesias were reported in 1 of 534 (0.2%) and 2 of 558 patients (0.4%).

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

Eleven patients in the daptomycin arm (2.1%) and 8 patients in the comparator arm (1.4%) had an increase in CPK considered to be drug-related. Drug-related AEs in the MedDRA SOC of Musculoskeletal, Connective Tissue, and Bone Disorders were reported in 3 of 534 (0.6%) daptomycin-treated and 0/558 (0.0%) comparator-treated patients. Drug-related paresthesias were reported in 0 of 534 and 1 of 558 comparator-treated patients (0.2%).

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CLINICAL REVIEW

Integrated Review of Safety and Efficacy

Table 17. Incidence of Adverse Events that Occurred in $\geq 2\%$ of Patients in Phase III cSSSI Studies

Adverse Event	Daptomycin (N=534)	Comparator* (N=558)
Any adverse event	51.3%	52.5%
Gastrointestinal disorders	19.3%	22.0%
Constipation	6.2%	6.8%
Nausea	5.8%	9.5%
Diarrhea	5.2%	4.3%
Vomiting	3.2%	3.8%
Dyspepsia	0.9%	2.5%
General disorders	13.9%	15.1%
Injection site reactions	5.8%	7.7%
Fever	1.9%	2.5%
Nervous system disorders	13.9%	13.4%
Headache	5.4%	5.4%
Insomnia	4.5%	5.4%
Dizziness	2.2%	2.0%
Skin/subcutaneous disorders	11.2%	11.8%
Rash	4.3%	3.8%
Pruritus	2.8%	3.8%
Diagnostic investigations	12.2%	9.0%
Abnormal liver function tests	3.0%	1.6%
Elevated CPK	2.8%	1.8%
Infections	12.4%	13.4%
Fungal Infections	2.6%	3.2%
Urinary Tract Infections	2.4%	0.5%
Vascular disorders	5.4%	5.6%
Hypotension	2.4%	1.4%
Hypertension	1.1%	2.0%
Renal/urinary disorders	3.2%	3.2%
Renal failure	2.2%	2.7%
Blood/lymphatic disorders	2.8%	3.2%
Anemia	2.1%	2.3%
Respiratory disorders	6.7%	5.6%
Dyspnea	2.1%	1.6%
Musculoskeletal disorders	6.2%	6.3%
Limb pain	1.5%	2.0%
Arthralgia	0.9%	2.2%

* vancomycin/semi-synthetic penicillin

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

Summary of daptomycin risk profile in Phase III cSSSI trials

In the 534 daptomycin-treated patients in cSSSI trials, daptomycin was not related to any deaths. Serious adverse events attributed to daptomycin included a hypersensitivity reaction, diarrhea, and eosinophilia. The most common adverse events observed in daptomycin-treated patients were constipation, nausea, injection site reactions, and headache. Symptoms consistent with myopathy occurred in 7/534 of daptomycin-treated patients, while those consistent with neuropathy occurred in 1/534 (0.2%) of daptomycin patients. CPK elevations were reported in 2.8% of daptomycin patients; one daptomycin patient (0.2%) had both clinical and biochemical evidence of myopathy. There was no signal suggestive of daptomycin-associated cardiotoxicity.

Community-acquired pneumonia – Studies DAP-CAP-00-05 and DAP-CAP-00-08

For details of the clinical protocols of these studies, see section IIA of this review (Brief overview of Clinical Program). Cubist conducted two controlled clinical trials (DAP-CAP-00-05 and DAP-CAP-00-08) of essentially identical design to evaluate daptomycin at a dosage of 4 mg/kg q24h versus ceftriaxone 2 g q24h in the treatment of moderate to severe CAP due to *S. pneumoniae*, including penicillin-resistant strains. Study DAP-CAP-00-05 enrolled 355 patients in the daptomycin arm and 359 in the comparator arm and was completed in October, 2000. After completion of the study, the sponsor's analysis indicated that daptomycin did not meet the predetermined criteria for non-inferiority (which specified that the upper bound of the 95% CI for the difference in clinical success between the comparator, ceftriaxone, and daptomycin be <10%) in any of the populations analyzed. At that time the second study DAP-CAP-00-08 (which had enrolled 100 patients in the daptomycin arm and 101 patients in the comparator arm) was discontinued. Safety data from these two studies was submitted to the NDA, and a summary of the data from the combined studies is presented here.

Overall, the treatment groups were well-balanced in terms of demographic characteristics. A total of 177 subjects in the daptomycin group and 168 subjects in the comparator group were age 65 or older. In study DAP-CAP-00-08, there were more 18-39 and >65-year-old patients in the daptomycin arm than in the comparator arm; conversely, there were fewer 40-65-year-old patients in the daptomycin arm than in the comparator arm. These differences are evened out somewhat when the two studies are combined. However, since differences in daptomycin adverse event rates were found by age group (≥ 65 years of age versus <65 years; see below) these differences between study arms are worthy of note.

Overall, 265 of 455 patients (58.2%) in the daptomycin group and 279 of 460 patients (60.7%) in the comparator group received 7 to 14 days of intravenous study therapy. It is of interest that when the combined CAP

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

studies are examined, more patients in the daptomycin arm (14/455; 3.1%) than in the comparator arm (7/460; 1.5%) received more than 14 days of therapy. Although the numbers are small, it may be that longer durations of therapy in these patients were necessary due to slow clinical response. Most subjects in both treatment groups completed the planned treatment course of intravenous treatment; however, more daptomycin-treated patients (23.3%) than comparator patients (14.1%) prematurely discontinued therapy. The most common reason for premature discontinuation in both treatment groups was "Clinical Failure" (9.7% and 5.0% of patients in the daptomycin and comparator groups, respectively).

Table 18 shows the incidence of death, serious adverse events, and common adverse events in the CAP studies. A total of 33 patients (21 daptomycin - 4.6%, 12 comparator - 2.6%) died during the CAP studies. All of the deaths appeared to be directly related to pre-existing underlying conditions and/or the presenting condition of CAP, and all were assessed by the investigator as unrelated to study treatment. Among the 33 patients who died, 18 were male and 15 were female; 21 were \geq 65 years of age and 12 were <65 years of age. Twenty-two (16 daptomycin, 6 comparator) of the 33 deaths occurred while patients were on study drug or up to three days after study drug had been stopped. The other 11 (5 daptomycin, 6 comparator) deaths occurred four to 51 days after treatment with study drug had stopped. According to the sponsor's assessment, in study DAP-CAP-00-05, in 10 (67%) of the 15 deaths in the daptomycin group, the cause of death was potentially related to lack of efficacy; in study DAP-CAP-00-08, 2 of the 6 deaths in the daptomycin group were potentially related to lack of efficacy. The MO reviewed these cases in detail, and agrees with these assessments. In study DAP-CAP-00-05, 60% of patients who died had severe underlying cardiac or respiratory conditions; all except one of the remaining patients had other serious preexisting underlying conditions. The patients who died also tended to enter the study with more serious CAP: 10 (67%) of the daptomycin patients who died and 4 (40%) of ceftriaxone patients entered the study with Fine Score Grades IV or V. In study DAP-CAP-00-08, all 6 of the patients who died entered the study with Fine Score Grade IV. Four of these six patients had serious underlying cardiac or respiratory preexisting conditions.

A total of 100 patients, 62 (13.6%) in the daptomycin group and 38 (8.3%) in the comparator group, experienced one or more SAEs in CAP studies DAP-CAP-00-05 or DAP-CAP-00-08. The only SAEs by preferred term with a reported incidence of \geq 1% of patients in either of the two studies were pneumonia aggravated, chronic obstructive airways disease exacerbated, and respiratory failure, occurring in 6 (1.3%), 5 (1.1%) and 7 (1.5%) of patients, respectively, in the daptomycin group, and 2 (0.4%), 1 (0.2%) and 1 (0.2%) of patients, respectively in the comparator group. All

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

other serious events were reported in <1% of patients in both drug exposure groups. When SAEs were examined by SOC, differences between the daptomycin arm and the comparator arm were seen in Cardiac Disorders (16/455; 3.5% versus 6/460; 1.3%, respectively) and Respiratory, Thoracic and Mediastinal disorders (15/455; 3.3% versus 3/460; 0.7%). In four of the 100 patients with serious adverse events, three in the daptomycin group and one in the comparator group, the serious adverse events were considered drug-related. These included coma, tachyarrhythmia, and respiratory failure in the daptomycin group, and neutropenia in the comparator group. Review by the MO of the narratives and case report forms for these four patients indicated agreement with each assessment except that of respiratory failure, which in the opinion of the Medical Officer was not related to study drug. No SAE appeared to be reflective of myopathy or neuropathy.

The differences between daptomycin and comparator arms in the occurrence of the SAEs pneumonia, exacerbation of chronic obstructive airways disease, and respiratory failure, as well as Cardiac Disorders, is most likely attributable to the inferior efficacy of daptomycin relative to ceftriaxone in this population with significant co-morbidity and/or severe baseline infections.

Significantly more patients in the daptomycin arm than in the comparator arm experienced at least one AE (reported in $\geq 2\%$ of patients within a study and in either study arm) in the CAP studies (57.4% of daptomycin patients, 49.8% of comparator patients). SOCs where significantly more daptomycin patients reported AEs were General Disorders and Administration Site Conditions and Infections and Infestations. In the Nervous System Disorders SOC, significantly more comparator patients than daptomycin patients reported AEs. The MedDRA SOC with the greatest numbers of reported AEs was Gastrointestinal Disorders; 86 of 455 daptomycin patients (18.9%) and 86 of 460 comparator patients (18.7%) reported AEs in this SOC. Increased blood CPK was seen in 6 of 455 (1.3%) patients in the daptomycin group and 6 of 460 (1.3%) patients in the comparator group. The MedDRA SOC of Musculoskeletal, Connective Tissue, and Bone Disorders (comprised of the SOC term reported in >1% of patients of arthralgia) was reported in 21 of 455 (4.6%) daptomycin-treated and 32/460 (7.0%) comparator-treated patients; the corresponding rates in all treated patients were 4.6% and 7.1%, respectively. Paresthesias were reported in 2 of 455 (0.4%) of daptomycin-treated patients and 2 of 460 comparator-treated patients (0.4%); neuritis was reported in 1 of 455 (0.2%) daptomycin-treated patients and none of 460 comparator treated patients.

The majority of AEs in the two CAP studies were assessed as unrelated to study drug by the investigators. A higher percentage of patients in the comparator groups than in the daptomycin groups experienced at least one

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

AE that was considered possibly or probably related to study treatment (20.2% daptomycin, 18.3% comparator). The Gastrointestinal Disorders SOC had the most drug-related AEs (27 daptomycin and 30 comparator patients). Blood creatine phosphokinase assessed as drug-related was increased in 6 (1.3%) daptomycin-treated patients and 2 (0.4%) comparator-treated patients. Drug-related Musculoskeletal, Connective Tissue and Bone Disorders were seen in 7 (1.5%) daptomycin-treated and 4 (0.9%) comparator-treated patients. Drug-related paresthesias were seen in 2 (0.4%) of daptomycin-treated patients and no comparator-treated patients.

In the two CAP studies a total of 34 patients, 19 (4.2%) of 455 in the daptomycin group and 15 (3.3%) of 460 in the comparator group, were discontinued from study drug due to AEs. The events leading to discontinuation were reported as possibly or probably related to study treatment for three of the 19 daptomycin-treated and three of the 15 comparator-treated patients. In study DAP-CAP-00-05, four patients (2 daptomycin, 2 comparator) discontinued due to adverse events reported as possibly or probably related to study treatment. The AEs in the daptomycin arm were acute respiratory insufficiency leading to coma in one patient and increased cardiac enzymes in a second patient. The drug-related AEs resulting in study discontinuation in the comparator group were neutropenia in one patient and a drug-related allergic reaction in the second. In study DAP-CAP-00-08, a daptomycin-treated patient discontinued study drug due to severe respiratory failure assessed as possibly related to treatment. In the comparator group of that study, one patient discontinued from treatment due to drug-related severe urticaria. Case report forms and narratives from the three patients in the daptomycin arm who had AEs resulting in discontinuation either possibly or probably attributable to daptomycin were reviewed. In the opinion of the MO, these three events are unrelated to daptomycin administration.

Table 18. Incidence of Death, Serious Adverse Events, and Cardiac and Respiratory SOC Adverse Events in CAP Studies		
	Daptomycin (N=455)	Comparator* (N=460)
Death	4.6%	2.6%
Any Serious Adverse Event	13.6%	8.3
Cardiac SOC SAE	3.5%	1.3%
Respiratory SOC SAE	3.3%	0.7%

* Ceftriaxone 2 g q 24 hr

Summary of daptomycin risk profile in Phase III CAP trials

In the 455 daptomycin-treated patients in CAP trials, no deaths were directly attributed to daptomycin; however, the mortality rate was 4.6% in daptomycin-treated patients and 2.6% in comparator-treated patients. SAEs were also more frequent in daptomycin-treated patients, particularly cardiac SAEs (3.5% vs. 1.3%) and respiratory SAEs (3.3% vs 0.7%). These differences were attributable to the lower efficacy of daptomycin in the treatment of CAP, rather than toxicity; suboptimal alveolar penetration by daptomycin is the most likely explanation for this phenomenon, based on data from animal models. This is reflected in the failure of daptomycin to show noninferiority to comparator in these trials. Serious adverse events attributed to daptomycin included coma, respiratory failure, and tachyarrhythmia. The most common nonserious adverse events noted in daptomycin-treated patients in CAP studies included nausea, diarrhea, and headache. Symptoms consistent with myopathy occurred in 10/455 (2.2%) of daptomycin-treated patients, while those consistent with neuropathy in 4/455 (0.9%) of daptomycin-treated patients. CPK elevations were reported in 1.3% of daptomycin-treated patients in CAP studies; there were no daptomycin-treated patients with both clinical and biochemical evidence of myopathy. There was no signal suggestive of daptomycin-associated cardiotoxicity.

Cardiac safety

Correlation of preclinical cardiac effects with cardiac toxicity in clinical trials

Preclinical Studies of Cardiac Muscle Function and Cardiac Conduction

In vivo and *in vitro* data demonstrated that daptomycin had no adverse effect on the cardiovascular system. No effect on cardiac muscle function was seen *in vitro* at concentrations 20-25-fold higher than peak plasma concentrations of unbound drug at the intended clinical dose of 4 mg/kg q 24h. Daptomycin also had no effect on hERG channel exposed to concentrations of unbound drug up to 100 times the clinical plasma concentration of daptomycin.

Exposure of dogs to daptomycin for periods of up to 6 months did not show any histopathologic effect of daptomycin on cardiac muscle. A study in anesthetized dogs did not reveal any effect of daptomycin on cardiac repolarization at a dose of 50 mg/kg.

Phase I Studies

Cubist conducted a study of the effects of daptomycin on cardiac repolarization. Study DAP-QTNC-01-06 included 120 healthy volunteers: 60 in the daptomycin group and 60 in the placebo group. No clinically significant changes in ECG results were seen in either treatment group.

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

The mean values for QTcB and the associated standard deviations were similar across all time points and both treatment groups. For the daptomycin group, the mean values of QTcB ranged from 417.1 to 431.5 msec; for the normal saline group the range was 415.4 to 430.0 msec. Standard deviations were all between 19 and 27 msec. There were no statistically significant or clinically meaningful differences in the mean QTcB values at any time point. There were no statistically significant differences in mean QTcB changes from baseline between the treatment groups. On Day 1 and Day 7, the proportion of subjects with increases of 30 to 60 msec was low in both treatment groups (5.9% in the daptomycin group, $\leq 10.5\%$ in the NS group), with no statistically significant differences between the treatment groups at any time point on Day 1 and Day 7. On Day 14, 2 subjects in the daptomycin group (3.9%) and eleven subjects in the NS group (19.3%) had an increase in QTcB of 30 to 60 msec. This difference was statistically significant ($p < 0.037$). There were only 3 increases in QTcB > 60 msec observed during the study, one in the daptomycin group (Day 1, 2 hrs) and two in the NS group (Day 7, pre-dose and Day 7, 12 hrs). QTcB values classified as prolonged (males > 450 msec, females > 470 msec) occurred in both treatment groups (0 to 9.8% in the daptomycin group; 0 to 10.5% in the NS group). The highest value among daptomycin treated subjects was QTcB of 493 msec on Day 1 (2 hrs post dose) and among normal saline treated subjects was QTcB of 499 msec on Day 1 (30 minutes post dose). No values in either group exceeded 500 msec. There was no apparent temporal relationship between the frequency of prolonged QTcB and the time or study day of the measurement.

In other Cubist Phase I studies, one daptomycin-treated subject experienced a cardiac AE of tachycardia, which was assessed as unrelated to study drug. No cardiac adverse events were reported in any Lilly Phase I single dose clinical study.

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CLINICAL REVIEW

Integrated Review of Safety and Efficacy

Phase II Studies

Cubist studies

Cubist conducted two Phase II studies (DAP-BAC-9803 – a controlled trial of daptomycin in bacteremia, and DAP-RRC-9804, an uncontrolled study of daptomycin in the treatment of infections due to resistant Gram-positive pathogens) which enrolled 146 daptomycin-treated subjects and 24 comparator-treated subjects. Daptomycin was dosed in these studies at 4 mg/kg q24h, 6 mg/kg q24h, or 3 mg/kg q12h. Subjects in both studies generally had serious bacterial infections such as pneumonia or intra-abdominal infection and had multiple co-morbidities.

In these studies, which enrolled seriously ill patients, the mortality rate was 35/146 (24.0%) in daptomycin patients and 2/24 (12.5%). The majority of deaths occurred in the uncontrolled study (DAP-RRC-9804). Most fatal events were due to the underlying infection or co-morbid conditions. One death, in Study DAP-BAC-9803, was caused by a third degree heart block and was considered by the investigator to be possibly related to daptomycin treatment. However, the reviewing Medical Officer did not feel that this death was causally related to daptomycin.

In Cubist Phase II studies, the incidence of serious cardiac AEs was 8.2% in daptomycin-treated subjects and 12.5% in comparator-treated subjects. There were no serious arrhythmic events in these studies.

In these two studies, the rate of cardiac AEs was 32/146 (21.9%) in the daptomycin group and 8/24 (33.3%) in the comparator group. In daptomycin treated patients, 9/146 (6.2%) had a dysrhythmia versus 2/24 (8.3%) in the comparator group; five of the events in the daptomycin group were tachycardias. There were no reports of torsades de pointes. The rates of congestive heart failure were 2/146 (1.4%) for daptomycin-treated patients and 3/24 (12.5%) for comparator patients. None of these were assessed as related to study drug by the investigator or reviewing Medical Officer.

Lilly Studies

In the Phase II studies B8B-MC-AVAE/B8B-EW AVAG, causation was not assessed. There were no cardiac AEs resulting in discontinuation thought to be secondary to daptomycin. SAEs reported in daptomycin treated patients included angina, aortic valve replacement, and myocardial infarction; from the information available, these do not appear to be related to study drug. The seven deaths in this study do not appear to be related to daptomycin, and were not attributed to cardiac events.

In Study B8B-MC-AVAM, there were 9 daptomycin treated subjects (9/89, 10.1%) and 3 (3/35, 8.6%) comparator treated subjects who developed treatment emergent cardiac SAEs and one cardiac related death in each group (1.1% and 2.9%, respectively). Of the three cardiac deaths

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

that occurred in all the studies combined, 2 occurred in comparator treated subjects and one in a daptomycin treated subject (attributed to mechanical failure of a prosthetic aortic valve).

Phase III Studies

In the comparative studies of cSSSI (Study 9801 and Study 9901), there were two cardiac deaths in the daptomycin group (one due to cardiopulmonary insufficiency and one to myocardial infarction) and one in the comparator group (heart failure). None of these was assessed as being drug-related. The incidence of cardiac AEs was 18/534 (3.4%) in daptomycin treated patients and 18/558 (3.2%) in comparator-treated subjects. The incidence of serious cardiac AEs was 5/534 (0.9%) daptomycin-treated patients and 6/558 (1.1%) in comparator-treated patients. The incidence of cardiac AEs that represented dysrhythmic events was 12/534 (2.2%) in daptomycin-treated subjects and 10/558 (1.8%) in comparator-treated subjects. Two events in the daptomycin group (atrial flutter and nodal arrhythmia) and one in the comparator group (tachycardia NOS) were assessed as being related to study drug.

In the CAP studies (DAP-CAP-00-05 and DAP-CAP-00-08), the mortality rates were 21/455 (4.6%) for daptomycin-treated patients and 12/460 (2.6%) for comparator-treated patients. There were six cardiac deaths in daptomycin-treated patients and two in comparator-treated patients. No death was attributed to study drug by either the investigator or the reviewing Medical Officer. The difference in mortality rates between treatment arms is attributable to the differences in efficacy in the treatment of CAP between treatment arms. The rates of serious cardiac adverse events were 3.5% in the daptomycin arm and 1.3% in the comparator arm.

Overall, in the CAP studies, the rates of cardiac adverse events were 8.8% in daptomycin-treated patients and 5.4% in comparator-treated patients; of note, this difference has a nominal p-value <0.05. The rates of dysrhythmias were 2.9% in daptomycin patients and 2.3% in comparator patients. The rates of congestive heart failure were 0.4% in the daptomycin group and 0.6% in the comparator group. The rates of drug-related cardiac adverse events were 1.3% in daptomycin-treated patients and 0.2% in comparator-treated patients; however, none of these included congestive heart failure or ventricular tachycardia. There were no reports of torsades de pointes in these studies.

In general, the differences in cardiac deaths, serious cardiac AEs, and cardiac AEs in these studies reflected complications resulting from the lower efficacy of daptomycin relative to comparator in the treatment of CAP.

In a Phase III study of daptomycin in the treatment of complicated urinary tract infections at a dose of 4 mg/kg q24h, which enrolled 34 daptomycin-

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

treated patients and 34 comparator-treated patients (DAP-00-03), there were no deaths. There was one cardiac adverse event in a daptomycin-treated patient, designated as serious and described as arrhythmia NOS; this event was not attributed to daptomycin.

Summary of Cardiac Safety

In conclusion, in vivo and in vivo preclinical data suggest that myocardial tissue and conductive systems are not targets for daptomycin toxicity. The safety database from Phase I, II, and III trials do not show clinical evidence for a cardiotoxic effect of daptomycin, manifested either as dysrhythmias or congestive heart failure. This consistent body of scientific data supports the conclusion that daptomycin is not cardiotoxic.

Laboratory Analyses in Phase III Studies

Measures of central tendency

Complicated skin/skin structure (cSSSI) studies

In the pooled safety database for the two cSSSI studies (9801 and 9901) measures of central tendency (mean, standard deviation, median, and interquartile range) were similar between daptomycin and comparator at baseline and for all on-therapy and post-therapy hematologic parameters (hematocrit, white blood cell count, and platelets), chemistry parameters (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, and calcium), hepatobiliary function tests (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin).

CPK analyses

Analysis of creatinine phosphokinase (CPK, a marker for muscle injury) showed an on-therapy mean of 120.3 ± 410.8 U/L for daptomycin-treated patients and 93.2 ± 130.9 U/L for comparator-treated patients, reflecting the presence of a number of daptomycin-treated patients with significant elevations in CPK on-therapy (see below under Outlier Analysis). Although not statistically significant, this difference persisted for post-therapy CPK values (124.0 ± 289.2 U/L for daptomycin-treated patients and 98.9 ± 112.6 U/L for comparator-treated patients). Stratification of these analyses by demographic subgroups (age ≥ 65 , sex, race) gave similar results. On-therapy differences in mean CPK, although not statistically significant, occurred primarily in individuals younger than 65 years (140.1 ± 484.9 U/L for daptomycin-treated patients and 104.6 ± 148.0 U/L for comparator-treated patients) and women (109.3 ± 579.3 U/L for daptomycin-treated patients and 66.0 ± 78.8 U/L for comparator-treated patients).

Community-acquired pneumonia studies

In the pooled safety database for the two CAP studies (DAP-05 and DAP-08), measures of central tendency (mean, standard deviation, median, and

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

interquartile range) were similar between daptomycin and comparator at baseline and for all on-therapy and post-therapy hematologic parameters (hematocrit, white blood cell count, and platelets), chemistry parameters (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, and calcium), hepatobiliary function tests (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin), and myopathy markers (creatinine phosphokinase and lactate dehydrogenase). Stratification of these analyses by demographic subgroup did not reveal any differences.

CPK outlier analysis

In the cSSSI studies, there were similar proportions of patients with on-therapy outlier values and similar on-therapy maximum values for all laboratory parameters between treatment arms except for CPK. Figure 1 shows the distribution of CPK values obtained on therapy in daptomycin and comparator patients in cSSSI trials. Table 19 shows an analysis by the FDA medical reviewer of the incidence of CPK elevations from baseline values for patients in the pooled cSSSI database. Although there were 534 daptomycin-treated patients and 558 comparator-treated patients in cSSSI trials, not all patients had valid baseline or on-therapy CPK assessments. For purposes of these analyses, the upper limit of normal for CPK was 200 U/L.

Increase in CPK	All patients		Patients with normal CPK at baseline	
	Daptomycin (N=430)	Comparator (N=459)	Daptomycin (N=374)	Comparator (N=392)
>1x ULN	40 (9.3%)	41 (8.9%)	33 (8.8%)	35 (8.9%)
>2x ULN	21 (4.9%)	22 (4.8%)	14 (3.7%)	12 (3.1%)
>4x ULN	6 (1.4%)	7 (1.5%)	4 (1.1%)	4 (1.0%)
>5x ULN	6 (1.4%)	2 (0.4%)	4 (1.1%)	0 (0.0%)
>10x ULN	2 (0.5%)	1 (0.2%)	1 (0.2%)	0 (0.0%)

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

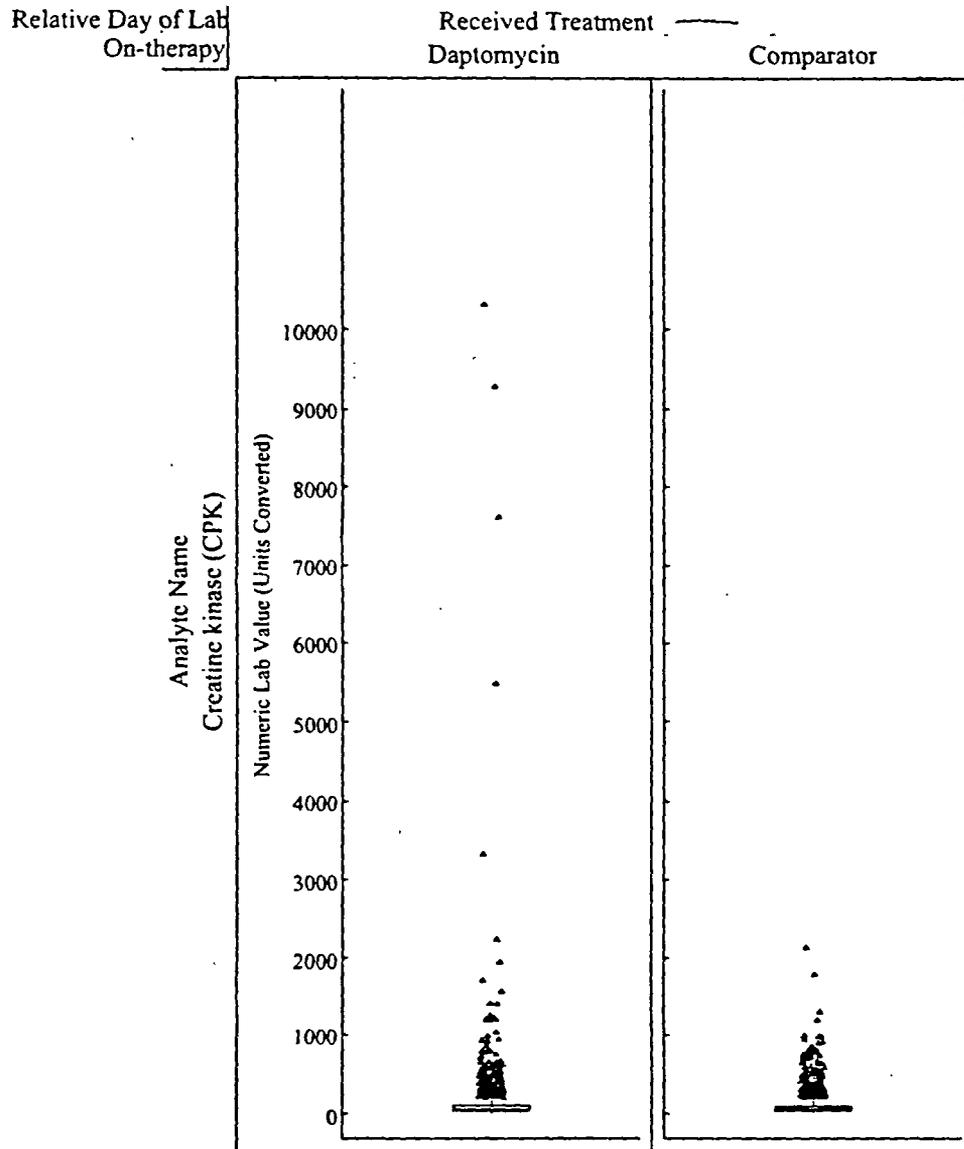


Figure 1. Distribution of creatine phosphokinase values in daptomycin and comparator-treated patients in cSSSI trials. Analyses were performed and graphs generated by FDA medical reviewer using data provided by sponsor. Values are expressed in U/L. The narrow boxes at the bottom of each panel represent the interquartile range, with the median shown as a horizontal line within the box; red triangles represent outlier values. Multiple lab values were obtained for each patient; therefore, the number of outliers may exceed the number of corresponding patients. Analyses were conducted using the maximum on-therapy value for each patient.

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

The maximum on-therapy CPK value for the daptomycin-treated group was 10,320 U/L; the maximum on-therapy CPK value for the comparator-treated group was 2,130 U/L. For patients with normal CPK values at baseline, the maximum on-therapy CPK value for the daptomycin-treated group was 10,320 U/L; the maximum on-therapy CPK value for the comparator-treated group was 977 U/L.

Three daptomycin-treated patients with CPK elevations had clinical events described by terms relevant to the musculoskeletal system. All of these events resolved after discontinuation of therapy. One patient, described below, had a clinical and laboratory course consistent with myopathy induced by daptomycin.

CPK values can be elevated by a variety of nonspecific factors that should be roughly balanced between treatment groups in a properly randomized trial; thus, CPK elevations in the daptomycin group greater than those in the comparator group may represent a toxic effect attributable specifically to the study drug. Thus, the medical reviewer examined those daptomycin-treated patients whose on-therapy CPK values were in excess of the maximum value in the comparator group. In order to avoid confounding factors that might lead to elevation of CPK, only patients with normal CPK values at baseline were included in this analysis. Of patients with normal CPK values at baseline, there were 4/374 (1.1%) daptomycin-treated patients with maximum on-therapy CPK values greater than the maximum on-therapy CPK value in the comparator group. The range of maximum CPK values for these patients was 1,420 U/L (7x ULN) – 10,320 U/L (51x ULN). The ages of these patients ranged from 41 to 72 years. Two were men and two were women; there were three white patients and one black patient. Of these patients, 2/4 had a history of diabetes, and 1/4 had a history of peripheral vascular disease. Three were in study 9801, and one, in study 9901. The day of the maximum value ranged from 5-11 days after the start of study medication.

Of these patients, one had associated symptoms consistent with muscle injury. The daptomycin-treated patient with the highest CPK elevation had associated muscle symptoms which did not appear to be associated with any other co-morbid event that might account for the CPK elevation.

CPK elevations occurring during daptomycin therapy appeared to resolve or show a trend towards resolution during follow-up after discontinuation of drug. However, of daptomycin-treated patients who had elevations in CPK while on-therapy, 6/40 ((15%) did not show complete resolution during therapy. However, the last observed CPK value in these cases was only modestly elevated (maximum follow-up value of 418 U/L).

The FDA medical reviewer performed a similar analysis for the CAP studies (Table 20). CPK elevations in the CAP studies did not show significant differences between daptomycin and comparator-treated

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

patients overall; however, there was a slight excess of higher CPK elevations in daptomycin-treated patients.

Table 20. Incidence of patients with elevations of CPK from baseline in CAP studies

Increase in CPK	All patients		Patients with normal CPK at baseline	
	Daptomycin (N=344)	Comparator (N=358)	Daptomycin (N=277)	Comparator (N=305)
>1x ULN	32 (9.3%)	27 (7.5%)	20 (7.2%)	26 (8.5%)
>2x ULN	15 (4.4%)	12 (3.4%)	7 (2.5%)	8 (2.6%)
>4x ULN	7 (2.0%)	5 (1.4%)	3 (1.1%)	2 (0.7%)
>5x ULN	6 (1.7%)	3 (0.8%)	3 (1.1%)	1 (0.3%)
>10x ULN	2 (0.6%)	1 (0.2%)	1 (0.3%)	0 (0.0%)

Liver function test outlier analyses

Preclinical studies did not show the liver to be a target organ for daptomycin toxicity, and clinical adverse events in Phase I, II, and III studies did not show a signal suggestive of hepatotoxicity. However, because other antimicrobials have shown clinically significant hepatotoxicity, the effects of daptomycin on biochemical markers of hepatobiliary injury were examined. The distribution of values for serum levels of alanine aminotransferase (ALT), aspartate aminotransferase, alkaline phosphatase, and total bilirubin in cSSSI studies are shown in Figures 2 and 3. There was no difference in the distribution of increases from baseline or maximum values between daptomycin and comparator-treated patients for any of these markers. Only one daptomycin-treated patient had an increase on-therapy in total bilirubin to >1.5x ULN; this patient, who had an increase to 2x ULN but did not have any clinical adverse events, did not have a concomitant increase in ALT or AST values, arguing against hepatocellular injury as the source of the increase in bilirubin. In daptomycin-treated patients in cSSSI studies, the maximum ALT value noted was 280 U/L; the maximum AST values was 386 U/L. Of note, the patients with these modest transaminase elevations also had elevation of CPK, suggesting that the source of the elevated transaminases was muscle, not liver. Similar results were obtained in analyses of liver function test results in the CAP studies.

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

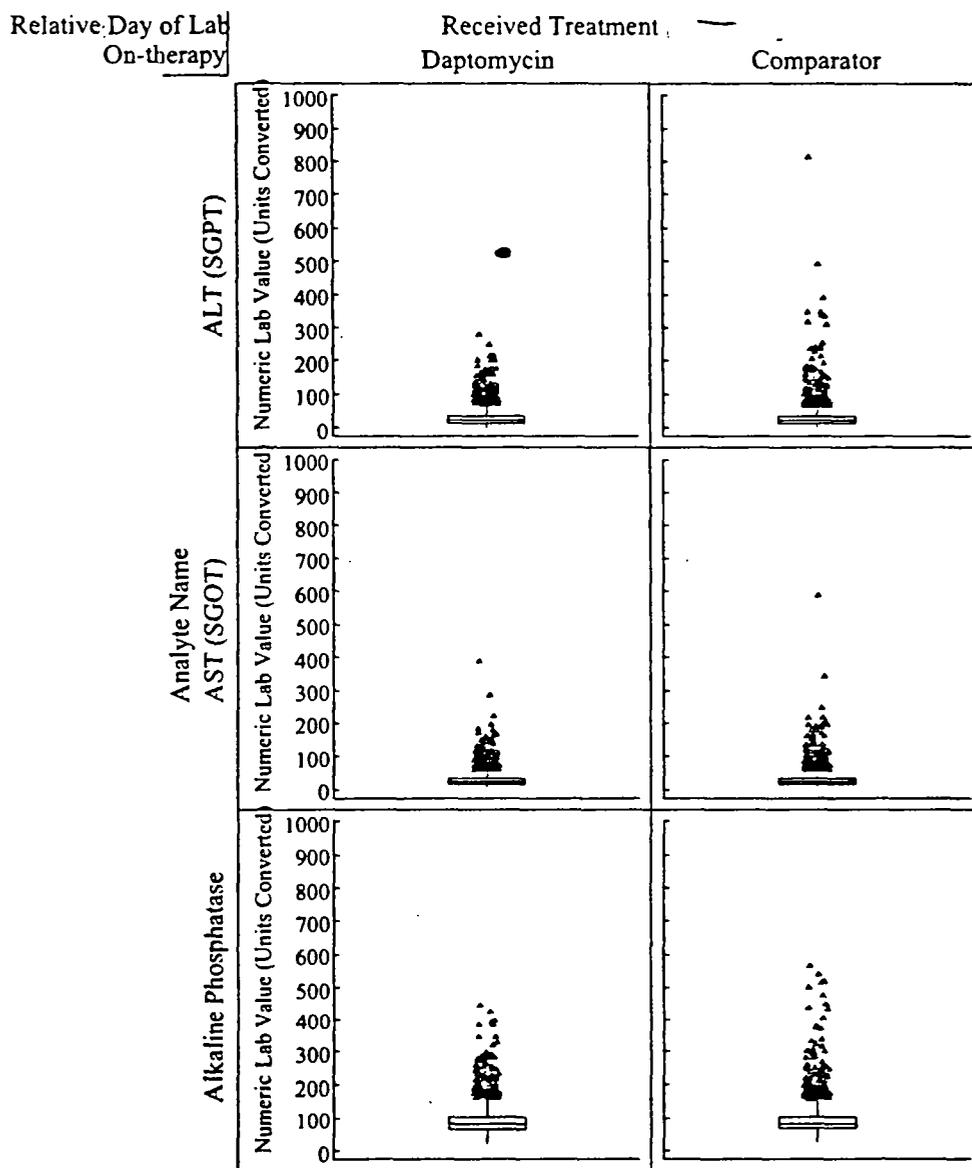


Figure 2. Distribution of ALT, AST, and alkaline phosphatase values in daptomycin and comparator-treated patients in cSSSI trials. Analyses were performed and graphs generated by FDA medical reviewer using data provided by sponsor. Values are expressed in U/L. The narrow boxes at the bottom of each panel represent the interquartile range, with the median shown as a horizontal line within the box; red triangles represent outlier values. Multiple lab values were obtained for each patient; therefore, the number of outliers may exceed the number of corresponding patients. Analyses were conducted using the maximum on-therapy value for each patient.

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

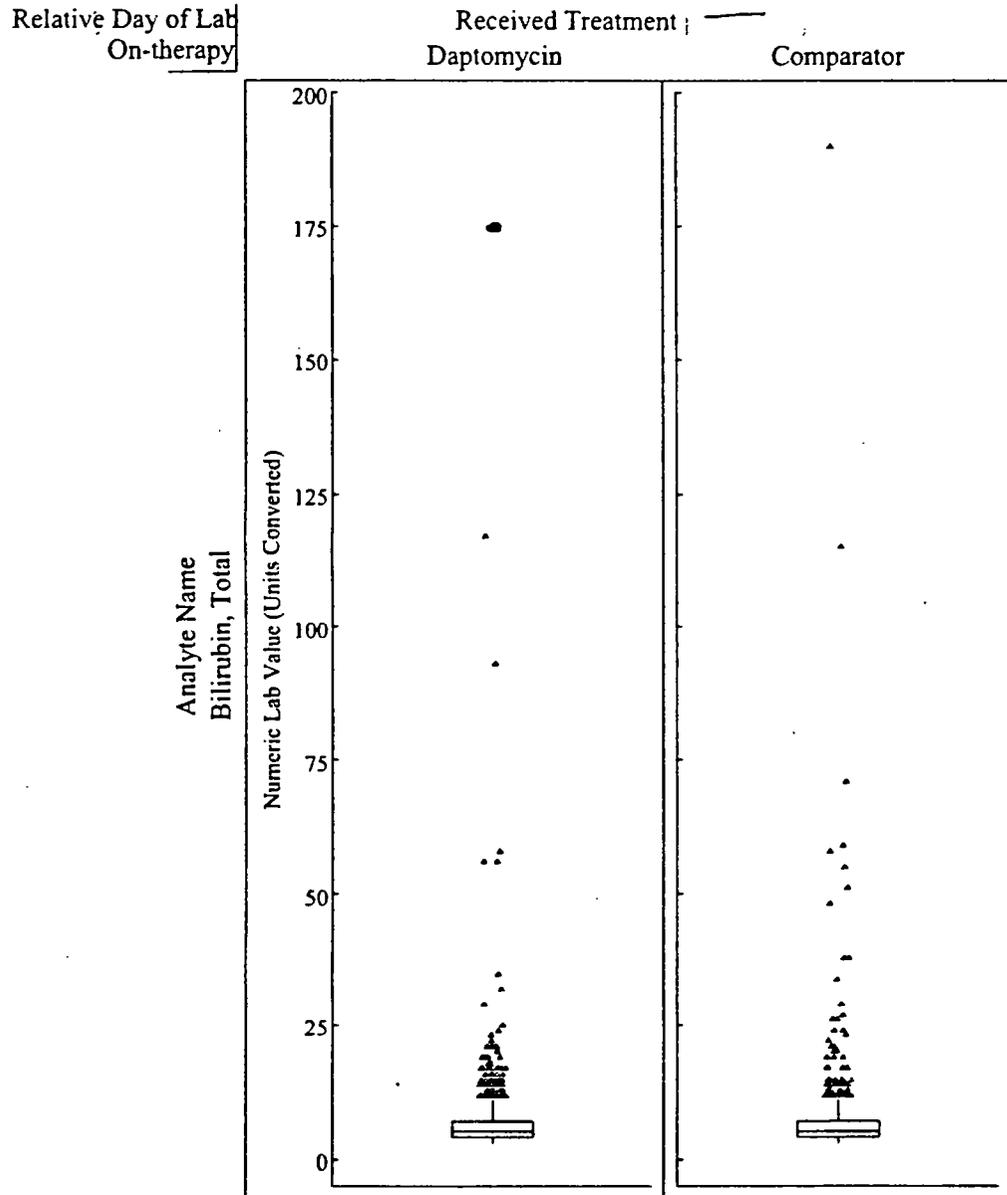


Figure 3. Distribution of total bilirubin values in daptomycin and comparator-treated patients in cSSSI trials. Analyses were performed and graphs generated by FDA medical reviewer using data provided by sponsor. Values are expressed in $\mu\text{mol/L}$. The narrow boxes at the bottom of each panel represent the interquartile range, with the median shown as a horizontal line within the box; red triangles represent outlier values. Multiple lab values were obtained for each patient; therefore, the number of outliers may exceed the number of corresponding patients. Analyses were conducted using the maximum on-therapy value for each patient.

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

Summary of laboratory analyses

In summary, the incidence of daptomycin-associated on-therapy CPK elevations beyond those seen in the comparator group was approximately 1.1% in patients with normal values at baseline. The maximum elevation in this group was approximately 51.5x ULN. Given the relatively few cases of extreme elevations, it is difficult to draw definitive conclusions regarding risk factors for CPK elevations. The latency of CPK elevation appeared to range from 5-11 days in those daptomycin-treated patients with values greater than those in the comparator group. In most but not all cases, elevations of CPK completely resolved following daptomycin discontinuation. In the daptomycin-treated patient with the most extreme elevation of CPK value, the laboratory event was associated with clinically evident signs of muscle injury and led to drug discontinuation. There were no significant sequelae noted as a result of CPK elevations in the NDA patient population. Many of the cases were asymptomatic and symptoms resolved after drug discontinuation after daptomycin discontinuation. When follow-up information was available, elevated CPK had either returned to normal after daptomycin discontinuation or was declining. No patient had further complications due to elevated CPK.

There was no evidence from Phase III laboratory data that daptomycin is associated with clinically significant hepatotoxicity, consistent with the absence of a significant effect of daptomycin on the liver in animal toxicology studies.

Drug-drug interactions

Because of the concern over possible additive myotoxicity, concomitant administration of HMG CoA-reductase inhibitors to patients receiving daptomycin was not allowed in the protocols for the cSSSI studies. However, 34/534 (6.4%) daptomycin-treated patients did receive a statin or fibrate during these studies. There was no difference in the incidence of adverse events, particularly CPK elevations in daptomycin-treated patients who received a statin or fibrate versus those who did not, relative to comparator. The incidence of CPK elevations was, however, increased in the CAP studies in daptomycin-treated patients who received a statin, although the small numbers involved make any conclusions difficult (Table 21). A placebo-controlled pharmacokinetic study in which 10 subjects received concomitant daptomycin and simvastatin did not show any increase in adverse events in these subjects; however, the power of this study to detect a difference in specific adverse event rates was quite limited.

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

Table 21. Adverse events stratified by statin/fibrate use in cSSSI and CAP studies				
	Daptomycin		Comparator	
	Concomitant statin or fibrate		Concomitant statin or fibrate	
cSSSI Studies	Present (N=34)	Absent (N=500)	Present (N=40)	Absent (N=518)
	n (%)	n (%)	n (%)	n (%)
Any AE	23 (67.6%)	251 (50.5%)	26 (65.0%)	267 (51.5%)
CPK Increased	1 (2.9%)	14 (2.8%)	1 (2.5%)	9 (1.7%)
Musculoskeletal SOC	1 (2.9%)	32 (6.4%)	3 (7.5%)	32 (6.2%)
CAP Studies	Present (N=16)	Absent (N=439)	Present (N=11)	Absent (N=449)
	n (%)	n (%)	n (%)	n (%)
Any AE	10 (62.5%)	252 (57.4%)	10 (90.9%)	220 (49.0%)
CPK Increased	1 (6.3%)	5 (1.1%)	0	6 (1.3%)
Musculoskeletal SOC	1 (6.3%)	21 (4.8%)	1 (9.1%)	31 (6.9%)

Risk profile of daptomycin analyzed by demographic group

Adverse events by demographic group in the Phase III studies are shown in Table 22.

Community acquired pneumonia

The incidence of adverse events in CAP patients was higher in all age groups in the daptomycin arm than in the comparator arm; this difference was largest in the <65 year old age group (54.3% versus 45.4%, daptomycin versus comparator, respectively). There was no difference in adverse events reported by gender in the daptomycin arm; in the comparator arm, AE's were more frequent in females (278/522; 53.3%) than in males (309/663; 46.6%). In both arms, patients in the racial group described as "Other" had higher rates than other racial groups; the difference between arms, however, was small.

Complicated skin and skin structure infections

Adverse event rates were similar between treatment groups when stratified by gender and race; however, overall adverse event rates were higher in daptomycin-treated patients than in comparator-treated patients in patients 65 years of age and older. The higher adverse event rates in the ≥65 years age group likely reflects the higher rate of underlying medical conditions in this age group, since this same differential in adverse events by age is also present in the comparator group. Pharmacokinetic data in the geriatric population do not support a need for a change in dose in this age group.

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

Table 22. Adverse event rates by demographic groups in Phase III (cSSSI and CAP) studies

Demographic Characteristic	Daptomycin			Comparator		
	cSSSI	CAP	All Studies	cSSSI	CAP	All Studies
	(N=534) n/N (%)	(N=455) n/N (%)	(N=1409) n/N (%)	(N=558) n/N (%)	(N=460) n/N (%)	(N=1185) n/N (%)
Gender						
Male	148/294 (50.3)	153/262 (58.4)	417/793 (52.6)	151/307 (49.2)	126/266 (47.4)	309/663 (46.6)
Female	126/240 (52.5)	108/193 (56.5)	320/616 (51.9)	142/251 (56.6)	104/194 (53.6)	278/522 (53.3)
Age						
< 65 years	176/390 (45.1)	152/278 (54.3)	472/991 (47.6)	208/418 (49.8)	132/291 (45.4)	389/846 (46.0)
≥ 65 years	98/144 (68.1)	111/177 (62.7)	261/411 (63.5)	85/140 (60.7)	98/168 (58.3)	198/338 (58.6)
≥ 75 years	46/66 (69.7)	49/75 (65.3)	117/180 (65.0)	43/67 (64.2)	54/86 (62.8)	103/166 (62.0)
Race						
Caucasian	196/313 (62.6)	211/378 (55.8)	540/938 (57.6)	184/313 (58.8)	177/375 (47.2)	407/811 (50.2)
Black	45/145 (31.0)	21/35 (60.0)	102/254 (40.2)	59/151 (39.1)	19/40 (47.5)	83/205 (40.5)
Other*	33/76 (43.4)	30/42 (71.4)	95/217 (43.8)	50/94 (53.2)	34/45 (75.6)	97/169 (57.4)

*includes Other + Asian

Label Modifications

The following section addresses modification of the product label negotiated with the sponsor based on the safety review, together with justification of the modifications. These descriptions reflect labeling changes as of **9/9/03**

INDICATIONS AND USAGE

- Add "Daptomycin is not indicated for the treatment of pneumonia". The review of the safety data from studies DAP-CAP-00-05 and DAP-CAP-00-08 demonstrated a higher mortality rate as well as higher cardiorespiratory complications in the daptomycin arm than in the comparator arm. These differences appear to be due to the lower efficacy of daptomycin in the treatment of CAP, demonstrated in both clinical trials. The postulated mechanism to account for the lower efficacy of daptomycin in the treatment of CAP is poor penetration of daptomycin into the alveolar space. Therefore, daptomycin would not be expected to be effective in the treatment of pneumonia.

WARNINGS

- The phrase "including daptomycin" was appended to the sentence "Pseudomembranous colitis has been reported with nearly all antibacterial agents, . . ." since cases of pseudomembranous colitis were reported in this NDA.

PRECAUTIONS

- The FDA-proposed changes in the Precaution section, under Skeletal Muscle, include the addition of rates of CPK elevations (as clinical adverse events) among patients in cSSSI trials, a recommendation to monitor CPK values weekly in patients

CLINICAL REVIEW

Integrated Review of Safety and Efficacy

receiving daptomycin, and recommendations to discontinue Cubicin in patients with CPK elevations to >5x ULN who have symptoms, or in asymptomatic patients with elevations to >10x ULN.

The addition of rates is intended to provide information to prescribers about the risk of CPK elevation, a marker for muscle injury which may provide early warning of myopathy, in the population of patients for whom this drug is indicated. Elevations in CPK may precede overt clinical symptoms; thus, information on the rates of CPK elevations that may serve as harbingers of frank myopathy should be useful to practitioners.

The recommendation to monitor CPK values weekly is based on the potential value of CPK as a signal for muscle injury; the recommended frequency is based on the latency of CPK elevations observed in Phase III clinical trials. The recommendation to discontinue Cubicin in symptomatic patients with CPK elevations >5x ULN is based on need to mitigate potential daptomycin-associated myopathy in patients experiencing the early stages of such an event; the threshold is based on the observed frequencies of outliers in the Phase III clinical trial population for daptomycin relative to comparator (Tables 19 and 20). The recommendation to discontinue Cubicin in asymptomatic patients with CPK elevations >10x ULN is based on the potential risk of CPK elevations reflecting serious injury in patients who are intubated, who have altered mental status, or who otherwise may be unable to report symptoms of muscle injury. The threshold of 10x ULN is based on the recommendations contained in labeling for another class of myotoxic agents, HMG-CoA reductase inhibitors.

- Second paragraph: The sentence "In addition, concomitant administration of agents associated with rhabdomyolysis such as HMG-CoA reductase inhibitors should be avoided in patients receiving Cubicin" was added. Although drug interaction studies with daptomycin and simvastatin in 10 patients showed no higher incidence of AEs than 10 subjects receiving placebo, the pathophysiologic mechanism of CPK elevation and myopathy remained undefined, as do predisposing factors. Therefore, a caution was added to this section, such that coadministration should be avoided if at all possible.
- Addition of 3rd paragraph regarding neuropathy: " In a small number of patients in Phase I and Phase II studies, administration of Cubicin was associated with decreases in nerve conduction velocity and with adverse events (e.g. paresthesias, Bell's palsy) possibly reflective of peripheral or cranial neuropathy. Nerve conduction deficits were also detected in a — number of