MO comments:
In the daptomycin arm, cure rates were higher in patients with abscesses while cure rates were lower in patients with infected ulcer (non-diabetic) compared to the comparator arm. In patients with abscesses, incision and drainage itself can be curative. Patients with non-diabetic ulcers included patients with venous ulcers, and decubitus ulcers, both of which are associated with decreased tissue perfusion. This may account for the lower cure rates seen in the daptomycin arm. Patients with history of diabetes had slightly lower cure rates compared to those without history of diabetes in the comparator arm; no difference was seen in the daptomycin arm.

F. Oral switch

Clinical success rates by treatment group were also compared for those patients who did and did not have oral switch therapy. Among patients in the MITT population who received only intravenous therapy, the clinical success rates were 67.0% (128/191) and 66.5% (125/188) for daptomycin and the comparator groups, respectively. Among the 46 patients in the MITT population who were switched to oral therapy, the clinical success rates were 66.7% (12/18) in the daptomycin group and 70.0% (17/24) in the comparator group.

Table 39: SDCO by oral switch status (Population: MITT)

Oral switch	Clinical Response	Daptomycin	Comparator	95% CI
No	No of patients	191	188	-10.0, 9.0
	Clinical Success	128 (67.0%)	125 (66.5%)	
	Cure	80 (41.9%)	71 (37.8%)	
	Clinical Improvement	48 (25.1%)	54 (28.7%)	
	Clinical Failure	63 (33.0%)	63 (33.5%)	
	Failure	43 (22.5%)	41 (21.8%)	
	Unable to Evaluate	20 (10.5%)	22 (11.7%)	
Yes	No of patients	18	24	
	Clinical Success	12 (66.7%)	17 (70.8%)	
	Cure	11 (61.1%)	14 (58.3%)	
	Clinical Improvement	1 (5.6%)	3 (12.5%)	
	Clinical Failure	6 (33.3%)	7 (29.2%)	
	Failure	4 (22.2%)	6 (25.0%)	
	Unable to Evaluate	2 (11.1%)	1 (4.2%)	

Source: Table 14.2.1.23

MO Comments:
Only a small number of patients were switched to oral therapy consistent with this primarily being an in-patient study. Review of a random sample of case report forms had identified that several investigators made errors in the timing of study visits relative to switch to oral antibiotics. However, for efficacy analyses the sponsor only utilized the appropriate visit window for TOC visit after oral medications were stopped. The overall efficacy analyses were thus not affected.

F. Concomitant procedures

Patients with surgical procedures (debridement, curettage, incision and drainage etc) were flagged. Results of an analysis separating patients into those who did and did not have these procedures are provided in table 40.

Table 40: SDCO by concomitant surgical procedures (Population: ITT)

Concomitant Procedures	Daptomycin (N=264)	Comparator (N=266)	95% C.I.
Yes	49/75 (65.3%)	57/78 (73.1%)	(-23.6%, 8.2%)
No	116/189 (61.4%)	105/188 (55.9%)	(-4.9%, 16.0%)

RESULTS (Study 9901)

Disposition of Patients

A total of 571 patients were randomized, 277 to receive daptomycin and 294 to receive comparator. Nine randomized patients discontinued prior to receiving any study treatment. Of the 562 patients who received at least one dose of study drug, 270 were randomized to the daptomycin arm and 292 to the comparator arm. One subject (0410100063) who was randomized to receive daptomycin but received comparator was considered misrandomized. In all efficacy analyses data for this subject are tabulated as randomized i.e., in the daptomycin arm and in all safety analyses as treated i.e. in the comparator arm.

Of the 293 patients treated with comparator drugs, 227 (77.5%) received semisynthetic penicillins (149 received cloxacillin, 59 received oxacillin, 19 received flucloxacillin), 64 (21.8%) received vancomycin and two received vancomycin in combination with flucloxacillin.

Comments:
Unlike in study 9801, semisynthetic penicillins were more commonly used as comparator agents rather than vancomycin, reflecting local antibiotic use patterns and prevalence of antibiotic resistant strains. For susceptible

organisms including methicillin-susceptible S. aureus, *bactericidal activity of semisynthetic penicillins is superior to that of vancomycin. This may have contributed to the lower cure rates in the comparator arm in study 9801 compared to 9901.*

Over 90% of patients in both treatment groups completed i.v. treatment as planned. The number of premature discontinuations were 18 (6.7%) and 13 (4.4%) in the daptomycin and comparator arms respectively. The most common reason for premature discontinuation in both treatment arms was adverse event (2.6% and 1.7% in the daptomycin and comparator arms, respectively). No patients discontinued study medication due to elevation in CPK. Table 39 presents a summary of subject disposition during the study.

Table 41 (Sponsor Table 10-1): Subject Disposition

Population	Daptomycin	Comparator
Randomized	277	294
Randomized But Not Treated	7	2
Intent-to-Treat Population	270	292
Misrandomized	1	0
Safety Population	269 (100.0%)	293 (100.0%)
Completed Therapy	251 (93.3%)	280 (95.6%)
Prematurely Discontinued Therapy	18 (6.7%)[2]	13 (4.4%)
Adverse Event	7 (2.6%)	5 (1.7%)
Clinical Failure	4 (1.5%)	3 (1.0%)
Subject's Decision	3 (1.1%)	4 (1.4%)
Protocol Violation	2 (0.7%)	0 (0.0%)
Lost to Follow-up	0 (0.0%)	1 (0.3%)
Death	2 (0.7%)	0 (0.0%)

Protocol Deviations

Eligibility Deviations

One or more eligibility deviations were reported for 32 (11.9%) patients in the daptomycin arm and 47 (16.1%) in the comparator arm. The most commonly reported deviation was serum CPK >50% above upper limit of normal (ULN) at baseline and was reported in 7.0% and 7.5% of patients in the daptomycin and comparator arms respectively. Elevations in CPK were generally considered to reflect prior trauma to the tissue at the primary site of infection, surgical incision and debridement, and intramuscular injections. All other deviations were reported in ≤2% of patients in either treatment group. Table 42 tabulates deviations that were reported in two or more patients.

Table 42 (Sponsor Table 10-2): Eligibility deviations reported in ≥ 2 patients (Intent-to-Treat)

Deviation	Daptomycin N = 270	Comparator N = 292
CPK >50% above ULN	19 (7.0%)	22 (7.5%)
X-rays not obtained at baseline for infections proximal to bone	3 (1.1%)	6 (2.1%)
Specimen available for Gram stain, culture and susceptibility test within 48 hr	3 (1.1%)	5 (1.7%)
Did not have diagnosis of Gram positive skin infection with complicating factor	4 (1.5%)	3 (1.0%)
Two sets of blood cultures not obtained within 48 hours prior to first dose	3 (1.1%)	2 (0.7%)
Calculated creatinine clearance < 30 mL/min or serum creatinine >1.9 mg/dL (170 µmol/L)	1 (0.4%)	4 (1.4%)
Age <18 or > 85 years (18 to 65 for South African sites)	1 (0.4%)	2 (0.7%)
Multiple infected ulcers at distant sites	2 (0.7%)	0 (0.0%)

Two patients were discontinued from the study due to protocol violations. Subject 0310100054 was discontinued after receiving 4 doses of daptomycin when the baseline wound culture was reported as yielding only Gram-negative rods. Subject 0401100061 was discontinued after receiving one dose of daptomycin when it was noted that the subject was also receiving flucloxacillin in error.

MO Comments:

Most protocol violations were of a minor nature and were similar in the two arms. They are unlikely to impact assessment of drug efficacy. Enrollment of patients with elevated CPK could impact safety assessments.

Data Sets Analyzed

The ITT population includes all patients who received at least one dose of study treatment. The MITT population represents all ITT patients who had an infecting Gram positive pathogen isolated at baseline. In the comparator arm, 87.3% of patients were included in the MITT population compared to 78.9% in the daptomycin arm.

The CE population includes approximately 90% of patients in both treatment arms. Fourteen (5.2%) patients in the daptomycin arm and 20 (6.8%) in the comparator arm were excluded from the CE population by the sponsor as no evaluation was conducted during the TOC window. Twelve (4.4%) patients in the daptomycin arm and 10 (3.4%) in the comparator arm were excluded from the CE population because they received potentially effective non-study antibiotics either prior to treatment or post-baseline for reasons other than therapeutic failure. Seven

patients in the daptomycin arm and eight patients in the comparator arm were excluded from the CE population as they received an inadequate duration of treatment or < 80% of expected dose.

The ME population comprises all patients in the CE population who had an infecting Gram positive pathogen isolated at baseline, ~73% and ~79% of ITT patients in the daptomycin and comparator arms respectively were included in the ME population. Table 43 presents the patient populations used for efficacy analysis.

Table 43 (Sponsor Table 11-1): Patient populations for efficacy analyses

Population	Daptomycin	Comparator
Intent-to-Treat	270 (100.0%)	292 (100.0%)
Modified Intent-to-Treat	213 (78.9%)	255 (87.3%)
No Baseline Pathogen	57 (21.1%)	37 (12.7%)
Clinically Evaluable	245 (90.7%)	262 (89.7%)
Not Clinically Evaluable	25 (9.3%)	30 (10.3%)
No Evaluation in the Test-of-Cure Window	14 (5.2%)	20 (6.8%)
Dosing Compliance	7 (2.6%)	8 (2.7%)
Post-baseline Effective Antibiotic	5 (1.9%)	4 (1.4%)
Prior Effective Antibiotic	4 (1.5%)	3 (1.0%)
Sponsor Override	3 (1.1%)	3 (1.0%)
Misrandomized	1 (0.4%)	0 (0.0%)
Microbiologically Evaluable	196 (72.6%)	231 (79.1%)
Not Microbiologically Evaluable	74 (27.4%)	61 (20.9%)

Demographic and Other Baseline Characteristics

Demographic Characteristics

The two treatment groups were well balanced with regard to all demographic characteristics. Majority of patients was male and Caucasian. Mean age of patients was 47.9 years in the daptomycin group and 48.6 years in the comparator group. Approximately 20% of patients in both treatment groups were ≥65 years of age at study entry. Table 44 presents a summary of the demographic characteristics.

Table 44 (Sponsor Table 11-2): Demographic Characteristics

Characteristic	Daptomycin N = 270	Comparator N = 292	p-value
Age (years)			0.628
Mean ± SEM	47.9 ± 1.05	48.6 ± 0.98	
Minimum, Maximum	18, 87	17, 85	
Weight (kg)			0.623
Mean ± SEM	73.5 ± 1.20	72.7 ± 1.02	
Minimum, Maximum	40, 165	40, 130	
Gender (N, %)			0.856
Female	120 (44.4%)	132 (45.2%)	
Male	150 (55.6%)	160 (54.8%)	
Race (N, %)			0.489
Caucasian	136 (50.4%)	146 (50.0%)	
Black	95 (35.2%)	91 (31.2%)	
Asian	2 (0.7%)	2 (0.7%)	
Other	37 (13.7%)	53 (18.2%)	

MO Comments:

Patients in this study were younger, with a mean age of ~48 years compared to ~55 years in study 9801. This is partly due to the fact that the upper limit for enrollment was 65 years in South Africa. Only 110/562 (19.6%) patients were ≥ 65 years in this study compared to 168/517(32.5%) in study 9801. The percentage of blacks was higher in this study reflecting differences in the study population.

Of the 562 treated patients, 303 (53.9%) were enrolled in South Africa, 237 (42.2 %) in Europe/Asia, and 22 (3.9 %) in Australia. The distribution of patients by country and by treatment group is displayed in the following table.

Table 45: Patient enrollment by country (Population: ITT)

Country	No. of sites	Daptomycin	Comparator	Total
Austria	2	5	3	8
Australia	5	10	12	22
Czech Republic	6	29	27	56
France	7	10	10	20
Germany	9	13	20	33
Hungary	4	15	18	33
Israel	3	3	5	8
Russia	3	29	29	58
Slovak Republic	3	3	5	8
S. Africa	20	149	154	303
Spain	2	1	4	5
United Kingdom	3	3	5	8
Total	67	270	292	562

Source: Table 14.1.2

MO Comments:

Sites in South Africa enrolled more than half the patients in this study. Five of these South African study sites had also enrolled ~18% of patients in study 9801. No patients, however, participated in both studies. The sponsor performed sensitivity analyses to evaluate the impact of these centers on the overall outcome. Results of those analyses and that of the FDA will be discussed later in the review.

Baseline Disease Characteristics

Primary Diagnosis

The distribution of diagnoses was similar in both treatment arms. Wound infection was the most common diagnosis reported; 102 (37.8%) in the daptomycin arm and 108 (37.0%) in the comparator arm. Sponsor reviewed the 107 patients designated as having "other" infections, 67 had specific diagnoses, primarily wound infections or abscesses. All of the remaining 40 infections had complicating factors; 10 required adjunctive surgery, 11 were in patients with significant co-morbidity (e.g., diabetes), and 19 were assessed as complicated by the investigator (e.g., involved deeper tissues). Table 46 summarizes the primary diagnoses reported by the investigators at study entry. The sponsor-determined final diagnosis is shown in Table 47.

Table 46 (Sponsor Table 11-3): Investigator's Primary Diagnosis (Population: ITT)

Primary Diagnosis	Daptomycin N = 270	Comparator N = 292	P-value
Wound Infection	102 (37.8%)	108 (37.0%)	0.781
Major Abscess	59 (21.9%)	65 (22.3%)	
Infected Ulcer (non-diabetic)	30 (11.1%)	37 (12.7%)	
Infected Diabetic Ulcer	23 (8.5%)	31 (10.6%)	
Other Infection	56 (20.7%)	51 (17.5%)	

Table 47 (Sponsor Table 11-4): Sponsor-Determined Final Diagnosis (Population: ITT)

Primary Diagnosis	Daptomycin N = 270	Comparator N = 292
Wound Infection	115 (42.6%)	122 (41.8%)
Major Abscess	78 (28.9%)	79 (27.1%)
Infected Ulcer (non-diabetic)	34 (12.6%)	40 (13.7%)
Infected Diabetic Ulcer	23 (8.5%)	31 (10.6%)
Other Infection	20 (7.4%)	20 (6.8%)

MO Comments:
Compared to study 9801, proportion of patients with abscesses was higher in this study and the proportion of patients with diabetic ulcers was smaller. Patients with abscesses will have higher cure rates compared to patients with other complicated skin infections as an incision and drainage procedure in of itself can be curative thus skewing the overall cure rates.

Stratification by diagnosis of infected diabetic ulcer
At the time of randomization, 28 (10.4%) patients in the daptomycin arm were assigned to the diabetic ulcer stratum by the investigator compared to 39 patients (13.4%) in the comparator arm. The sponsor reviewed the primary diagnosis and the description of the infection for each patient and compared these data with the stratum assigned by the study site at the time of randomization. In the daptomycin arm five patients stratified as having diabetic ulcer had a primary diagnosis other than diabetic ulcer. In the comparator group, 10 patients stratified as having diabetic ulcer had other infections and two patients with a primary diagnosis of diabetic ulcer were not assigned to that stratum. The sponsor performed analyses using either stratum or final diagnosis and found no difference in the efficacy results.

MO Comments:
Similar to study 9801, few patients with infected diabetic ulcers were enrolled and errors in classification of diabetic ulcer infection also occurred in this study. Sponsor and FDA analyses based on randomization strata will be presented in this review.

Baseline pathogens

The distribution of pathogens was similar in both treatment groups. The most common pathogen was *S. aureus*, which was isolated from 70% and 67.8% of patients in the daptomycin and comparator arms respectively. *S.pyogenes* and *S.agalactiae* were isolated from ~35% of patients in both groups. Dual infection with both *S. aureus* and β -hemolytic streptococci was present in 20.7% of the MITT population. Table 48 presents the infecting Gram positive pathogens isolated from the primary site of infection at the baseline evaluation.

Table 48 (Sponsor Table 11-5): Infecting Gram positive pathogens at baseline (MITT)

Pathogen	Daptomycin N = 213	Comparator N = 255
Staphylococcus aureus	149 (70.0%)	173 (67.8%)
Streptococcus pyogenes	59 (27.7%)	68 (26.7%)
Streptococcus agalactiae	13 (6.1%)	18 (7.1%)
Other streptococcus species	20 (9.4%)	28 (11.0%)
Enterococcus faecalis	20 (9.4%)	28 (11.0%)
Other enterococci	4 (1.9%)	6 (2.4%)
Gram positive anaerobes	2 (0.9%)	8 (3.1%)

Signs and symptoms of infection

At the baseline visit, moderate to severe tenderness, erythema, edema and purulent drainage were present in the majority of patients in both treatment groups. Localized pain, swelling, and redness were present in 97% or more of all patients. The proportion of patients reported to have fever at baseline was higher in the comparator group than in the daptomycin group (57% vs. 45%, respectively, p = 0.004). The recorded mean oral temperatures at baseline, however, were similar between the two arms (37.4°C, daptomycin, 37.5°C, comparator).

Severity of infection

Patients were characterized as having severe infection at baseline if they met one or more of the following criteria:

- fulfilled the definition for Systemic Inflammatory Response Syndrome (SIRS) by having 2 or more of the following findings: temperature >38° C or < 36° C; heart rate >90 beats/minute; respiration rate >20 breaths /minute; or WBC >12 x 10^3 /L or < 4 x 10^3 /L or >10% bands)
- had positive blood cultures at baseline;
- were evaluated as having severe tenderness or severe erythema.

A total of 181 (67%) patients in the daptomycin treatment group and 177 (60.6%) in the comparator group were classified as having severe infection. Approximately one third of the patients in each treatment group had SIRS. Bacteremia was diagnosed at baseline in six patients in each treatment group.

Comments:
In study 9801, patients were considered to have severe infections if they fulfilled definition of SIRS or had a positive blood culture at baseline, or if the investigator assessed at least 3 of 8 physical signs at the primary site of infection as severe. In this study however, presence of severe tenderness or severe erythema was sufficient to classify an infection as severe. So, it is not surprising that although patients in study 9801 were sicker, the proportion of patients with severe infections was slightly lower than in study 9901. The number of bacteremic patients was similar to that seen in study 9801.

Baseline medical history, vital signs, and physical examination
There were no statistically significant differences between the treatment groups in the history of co-morbid illnesses, including diabetes, peripheral vascular disease, or immunocompromise. A history of diabetes was reported in 18.5% and 23.3% of patients and a history of peripheral vascular disease was reported in 11.9% and 15.8%, in the daptomycin and comparator arms respectively. Most patients in both treatment groups (~97%) were not immunocompromised. More patients in the daptomycin arm were chronically bedridden compared to the comparator arm (2.6% vs. 0.3%, p = 0.024). There were no statistically significant differences between the treatment groups for any vital signs assessments at baseline.

MO comments:
In study 9801, a history of diabetes was reported by >40% of subjects in both treatment arms which is much higher than that reported in this study. Similarly, a history of peripheral vascular disease was also more common in study 9801. Both these conditions can have a significant effect on wound healing and hence affect clinical success rates.

Baseline laboratory evaluations
Mean white blood cell count was 11.4 x 10^3 /μL in the daptomycin arm and 12.1 x 10^3 /μL in the comparator arm. Mean neutrophil percentage was 70.2% in the daptomycin arm and 72.4% in the comparator arm (p = 0.031). There was no difference between treatment groups in absolute neutrophil count or other hematology parameters. There were no statistically significant differences between the treatment groups for any clinical chemistry assessments at baseline. Mean CPK at baseline was 172.5 U/L (SEM 25.14) and 158.9 U/L (SEM 15.57) in the daptomycin

and comparator groups, respectively (p = 0.638), with a range of 18- 3702 U/L in the daptomycin arm and 19-2410 in the comparator arm.

Measurements of treatment compliance
Study Treatment
Majority of patients received study treatment for 7 to 14 days, including 230 (78.8%) patients in the comparator arm and 214 (79.3%) in the daptomycin arm. Only 8 patients, including one in the daptomycin treatment group and 7 in the comparator group, received treatment for >14 days.

Table 49 (Sponsor Table 12-1): Summary of duration of exposure (Safety population)

Duration of IV therapy	Daptomycin N = 269	Comparator N = 293
Mean ± SD	7.2 ± 2.0	7.9 ± 2.5
Median	7.0	8.0
Minimum, Maximum	1, 15	1, 21
< 7 days	54 (20.1%)	56 (19.1%)
7 to 14 days	214 (79.6%)	230 (78.5%)
>14 days	1 (0.4%)	7 (2.4%)

Seven patients (4 in the daptomycin arm and 3 in the comparator arm) were < 80% compliant with expected dosing. Switch to oral therapy was significantly more frequent among patients in the comparator arm (37/292; 12.7%) than in the daptomycin arm (20/270; 7.4%). The primary reasons for switch to oral therapy were clinical improvement and patient request.

MO Comments:
In comparison to study 9801 where ~ 15% of patients in each treatment arm received treatment for greater than 14 days, only eight patients in this study received treatment for > 14 days. The need for prolonged therapy in a greater proportion of patients in study 9801 is consistent with the differences in patient characteristics in the two studies.

Dosing regimens
Patients with creatinine clearance between 30-70 ml/min were to receive a modified dosing regimen for daptomycin (loading dose 4mg/kg, followed by 3mg/kg q 36 hrs). However, based on data subsequently submitted by the sponsor, it was noted that, only 9/35 (25.7%) patients with creatinine clearance between 30-70 ml/min actually received a modified regimen. These results are summarized in the table 50.

Table 50: Dosing in renal insufficiency

Creatinine Clearance ml/min	Dose Adjusted	No Dose Adjustment	Total
30-50*	9	7	16
50-70	0	19	19
Total	9	26	35

*includes 1 patient with CrCL < 30ml/min

Concomitant antibiotic therapy and concurrent procedures

Fifteen patients (5.6%) in the daptomycin group and 12 (4.1%) in the comparator group received effective non-study antibiotic for lack of effficacy and were considered clinical failures. Twelve patients (4.4%) in the daptomycin group and 10 (3.4%) in the comparator group were excluded from the CE population as they were administered potentially effective antibiotics for >2 days either prior to enrollment or post-baseline for reasons other than lack of efficacy.

Overall, 46 patients (17%) in the daptomycin arm and 65 (22.3%) in the comparator arm received either aztreonam or metronidazole or both during the study.

A total of 53 (19.6%) patients in the daptomycin arm and 58 (19.9%) in the comparator group underwent a surgical procedure during study treatment. The most commonly performed procedures were incision and drainage, and wound debridement. Two patients were designated clinical failure on the basis of surgical removal of the primary site of infection; one patient in the daptomycin group had an above knee amputation on Day 4 and one patient in the comparator group had a below knee amputation on Day 4.

MO Comments:

In study 9801, ~ 40% of patients had concomitant surgical procedures and ~30% received concomitant antibiotics for Gram negative and or anaerobic coverage which again points to the differences in the patient population enrolled in the two studies. It may also represent differences in treatment practices between US and non-US sites.

Analysis of Efficacy

Primary Efficacy Analysis

The sponsor has presented clinical outcomes in the MITT and CE populations in the main body of the final study report. Results for the ITT and ME populations were provided in the additional tables included in the study report. Sponsor's analyses of the ITT, MITT, CE, and ME populations using the SDCO are included in this review.

As discussed for study 9801, the ITT and CE populations are considered the primary efficacy populations. The sponsor's results for the ITT and CE populations, and the results for the FDA-defined ITT and CE populations for sponsor-defined clinical outcomes are presented in the following tables:

Sponsor's Results

Clinical success rates in the ITT population were 80.7% in the daptomycin arm and 81.2% in the comparator arm (95% CI: -6.1, 6.9). In the CE population, clinical success rates were 88.6% (217/245) and 89.7% (235/262) in the daptomycin and comparator arms, respectively (95% CI: -4.3, 6.5).

Table 51: Sponsor-defined clinical outcome (Population: ITT)

Clinical Response	Daptomycin N = 270	Comparator N= 292	95% CI
Clinical Success	218 (80.7%)	237 (81.2%)	-6.1, 6.9
Cure	103 (38.1%)	123 (42.1%)	
Clinical Improvement	115 (42.6%)	114 (39.0%)	
Clinical Failure	52 (19.3%)	55 (18.8%)	
Failure	28 (10.4%)	27 (9.2%)	
Unable to Evaluate	24 (8.9%)	28 (9.6%)	

Source: Table 14.2.1.1, Section 14.2

Table 52 (Sponsor table 11-7): Sponsor-defined clinical outcome (Population: CE)

Clinical Response	Daptomycin N = 245	Comparator N = 262	95% CI
Clinical Success	217 (88.6%)	235 (89.7%)	-4.3, 6.5
Cure	103 (42.0%)	122 (46.6%)	
Clinical Improvement	114 (46.5%)	113 (43.1%)	
Clinical Failure	28 (11.4%)	27 (10.3%)	
Failure	28 (11.4%)	27 (10.3%)	

FDA Results

Table 53: Sponsor-defined clinical outcome (Population: ITT)

Clinical Response	Daptomycin (N=270)	Comparator (N=292)
Clinical Success	217 (80.4%)	235 (80.5%)
Clinical Failure	53 (19.6%)	57 (19.5%)
Difference in Success Rate Daptomycin vs. Comparator:	-0.1%, 95% C.I.: -7.0%, 6.8%	

Table 54: Sponsor-defined clinical outcome (Population: CE)

Clinical Response	Daptomycin (N=238)	Comparator (N=250)
Clinical Success	214 (89.9%)	226 (90.4%)
Clinical Failure	24 (10.1%)	24 (9.6%)
Difference in Success Rate Daptomycin vs. Comparator:	-0.5%, 95% C.I.: -6.2%, 5.2%	

MO Comments:
Point estimates for cure rates in the FDA defined populations were similar to those of the sponsor. Cure rates were comparable in the two treatment groups using a non-inferiority margin of 10 %. The lower bound of the 95% CI around the difference in success rates was less than 10 % in the FDA analysis and the upper bound of the 95% CI was less than 10 % in the sponsor's analysis. Also, the 95% CI include the value of zero consistent with non-inferiority.

The sponsor's results in the MITT and ME populations, and the results in the FDA defined MITT and ME populations for sponsor-defined clinical outcomes are presented in the following tables:

Sponsor's Results

Table 55 (Sponsor table 11-6): Sponsor-defined clinical outcome (Population: MITT)

Clinical Response	Daptomycin N = 213	Comparator N = 255	95% CI
Clinical Success	180 (84.5%)	214 (83.9%)	-7.2, 6.0
Cure	82 (38.5%)	110 (43.1%)	
Clinical Improvement	98 (46.0%)	104 (40.8%)	
Clinical Failure	33 (15.5%)	41 (16.1%)	
Failure	17 (8.0%)	19 (7.5%)	
Unable to Evaluate	16 (7.5%)	22 (8.6%)	

As per the statistical analysis plan, patients who were judged cured or improved by the investigator at the TOC evaluation and were assigned a SDCO of non-evaluable only because of compliance <80% were considered as success in the ITT and MITT populations. Three patients (one in the daptomycin arm, two in the comparator arm) met these criteria. Thus, the number of successes in the ITT and MITT populations is higher than in the CE and ME populations respectively.

Table 56: Sponsor-defined clinical outcome (Population: ME)

Clinical Response	Daptomycin N = 196	Comparator N = 231	95% CI
Clinical Success	179 (91.3%)	212 (91.8%)	-4.9, 5.7
Cure	82 (41.8%)	109 (47.2%)	
Clinical Improvement	97 (49.5%)	103 (44.6%)	
Clinical Failure	17 (8.7%)	19 (8.2%)	

Source: Table 14.2.1.4, Section 14.2

FDA Results

Table 57: Sponsor-defined clinical outcome (Population: MITT)

Clinical Response	Daptomycin (N=213)	Comparator (N=255)
Clinical Success	179 (84.0%)	212 (83.1%)
Clinical Failure	34 (16.0%)	43 (16.9%)
Difference in Success Rate Daptomycin vs. Comparator:	0.9%, 95% C.I.: -6.3%, 8.1%	

Table 58: Sponsor-defined clinical outcome (ME population)

Clinical Response	Daptomycin (N=191)	Comparator (N=220)
Clinical Success	176 (92.1%)	203 (92.3%)
Clinical Failure	15 (7.9%)	17 (7.7%)
Difference in Success Rate Daptomycin vs. Comparator:	-0.1%, 95% C.I.: -5.8%, 5.6%	

MO comments:

Point estimates for cure rates in the FDA defined populations were similar to those of the sponsor. Cure rates were comparable in the two treatment groups using a non-inferiority margin of 10 %. The lower bound of the 95% CI around the difference in success rates was less than 10 % in the FDA analysis and the upper bound of the 95% CI was less than 10 % in the sponsor's analysis. Also, the 95% CI include the value of zero consistent with non-inferiority.

Secondary efficacy analyses

Sponsor's Results

Sponsor-Defined Clinical Outcome by Infecting Pathogen

In the MITT population, clinical success rates using the SDCO were comparable for both treatment groups for patients infected with *S. aureus* and *S. pyogenes*, the pathogens isolated most frequently at baseline.

Clinical success rates for patients infected with less commonly represented pathogens (e.g., *S. agalactiae* and *E. faecalis*) were also clinically comparable, but the number of isolates were smaller. Similar results were observed in the ME population. Sponsor's results in the MITT population are summarized in table 59.

Table 59 (Sponsor table 11-9): SDCO by infecting pathogen (Population: MITT)

Infecting Pathogen	Daptomycin N = 213	Comparator N = 255	95% CI
Staphylococcus aureus	123/149 (82.6%)	145/173 (83.8%)	-6.9, 9.5
Streptococcus pyogenes	54/ 59 (91.5%)	57/ 68 (83.8%)	-19.0, 3.6
Streptococcus agalactiae	11/ 13 (84.6%)	9/ 18 (50.0%)	--
Other streptococcus sp.	14/ 20 (70.0%)	24/ 28 (85.7%)	--
Enterococcus faecalis	14/ 20 (70.0%)	23/ 28 (82.1%)	--

For patients infected with *S. aureus*, the clinical success rates were also evaluated by the oxacillin susceptibility of the baseline isolate for patients in the MITT and the ME populations. These analyses were restricted to isolates that were tested by the central laboratory. Only 16 isolates were reported as oxacillin-resistant. Clinical success rates for patients with oxacillin-resistant *S. aureus* in the MITT population were 80.0% (4/5) in the daptomycin and 81.8% (9/11) in the comparator arm respectively.

Table 60: Sponsor defined clinical success rates by oxacillin susceptibility*

Oxacillin susceptibility	Daptomycin	Comparator
MITT	**N = 129**	**N = 151**
Susceptible	104/124 (83.9%)	119/140 (85.0%)
Resistant	4/5 (80%)	9/11 (81.8%)
ME	**N= 118**	**N= 137**
Susceptible	103/114 (90.4%)	119/128 (93.0%)
Resistant	4/4 (100%)	9/9 (100%)

Source: Appendix 2 and Appendix 3, ISE

* Only isolates tested at central laboratory

MO Comments:

The number of MRSA isolates was far less than that seen in study 9901, reflecting the epidemiologic factors associated with antimicrobial resistance. A greater proportion of patients in study 9801 had other co-morbidities, hence they were more likely to have been exposed to MRSA in healthcare settings. They were also more likely to have other risk factors for MRSA acquisition such as prolonged hospitalization, prior antibiotic exposure, and admission to intensive care units.

Three patients in the comparator arm were treated with semi-synthetic penicillin and not vancomycin. Two of these patients were classified as clinical success, again raising the question of whether these MRSA isolates represent colonization or true infection.

Microbiologic response by pathogen

Pathogen specific microbiologic response rates for those Gram positive pathogens most commonly isolated at baseline are summarized in Table 61 for the ME population.

Table 61: Microbiologic response rates by pathogen (Population: ME)

Pathogen	Daptomycin n/N (%)	Comparator n/N (%)
Staphylococcus aureus (all)	101/133 (75.9)	127/155 (81.9)
Staphylococcus aureus (MSSA)	84/114 (73.7)	103/128 (80.5)
Staphylococcus aureus (MRSA)	3 /4 (75.0)	8/9 (88.9)
Streptococcus pyogenes	51/55 (92.7)	52/63 (82.5)
Streptococcus agalactiae	10/12 (83.3)	7/13 (53.8)
Streptococcus dysgalactiae equisimilis	2/3 (66.7)	6/6 (100)
Viridans Streptococci Group	13/14 (92.9)	15/18 (83.3)
Enterococcus faecalis (all)	13/18 (72.2)	18/25 (72.0)

Source: Appendix 5, ISE

Microbiologic response by patient

Microbiologic success rates in the MITT population were 73.2% for the daptomycin and 74.9% for the comparator arm, and in the ME population, 79.6% and 82.3%, respectively.

Table 62: Microbiologic response by patient (ME population)

Response	Daptomycin N =196	Comparator N =231	95% CI
Microbiologic Success	156 (79.6%)	190 (82.3%)	-4.8, 10.2
Microbiologic Failure	40 (20.4%)	41 (17.7%)	

Modified from sponsor table 11-8

FDA Results

Results of FDA analyses are presented in the following tables. Viridans group streptococci were not considered significant pathogens and hence are not included in the following tables.

Table 63:Clinical success by pathogen (Population: MITT)

Baseline Pathogen	Daptomycin	Comparator
MSSA	103/124 (83.1%)	119/140 (85.0%)
MRSA	4/5 (80.0%)	9/11 (81.8%)
Streptococcus pyogenes	53/59 (89.8%)	57/68 (83.8%)
Streptococcus agalactiae	11/13 (84.6%)	8/18 (44.4%)
Enterococcus faecalis	14/20 (70.0%)	22/28 (78.6%)
Streptococcus dysgalactiae	2/4 (100%)	7/9 (77.8%)

Table 64: Microbiologic success by pathogen (Population: ME)

Baseline Pathogen	Daptomycin N (%)	Comparator N (%)
MSSA	83/111 (74.8%)	99/123 (80.5%)
MRSA	3/4 (75.0%)	8/9 (88.9%)
Streptococcus pyogenes	52/55 (94.5%)	50/59 (84.7%)
Streptococcus agalactiae	10/12 (83.3%)	7/13 (53.8%)
Enterococcus faecalis	13/16 (81.3%)	17/24 (70.8%)
Streptococcus dysgalactiae	2/2 (100%)	7/9 (77.8%)

Table 65: Microbiologic success by subject (Population: ME)

Microbiologic Response	Daptomycin (N=191)	Comparator (N=220)
Microbiologic Success	153 (80.1%)	182 (82.7%)
Microbiologic Failure	38 (19.9%)	38 (17.3%)
Difference in Success Rate Daptomycin vs. Comparator:	-2.6%, 95% C.I.: -10.7%, 5.4%	

MO Comments:
Microbiologic eradication rates by pathogen and by subject and clinical success rate by pathogen were essentially similar in the two treatment arms in both the FDA and sponsor's analyses.

Analyses by diabetic ulcer stratification

At the time of randomization, patients were stratified based on the presence or absence of diabetic ulcer. Sponsor's results for the SDCO based on stratification by diabetic ulcer are summarized in table 66, followed by the FDA results in table 67.

Table 66: Sponsor-defined clinical outcome by randomization stratification (MITT)

Randomization stratum	Clinical Response	Daptomycin	Comparator	95% CI
Diabetic Ulcer	No of patients	24	34	-6.7, 6.4
	Clinical Success	14 (58.3%)	25 (73.5%)	
	Cure	3 (12.5%)	11 (32.4%)	
	Clinical Improvement	11 (45.8%)	14 (41.2%)	
	Clinical Failure	10 (41.7%)	9 (26.5%)	
	Failure	8 (33.3%)	6 (17.6%)	
	Unable to Evaluate	2 (8.3%)	3 (8.8%)	
Other stratum				
	No of patients	189	221	
	Clinical Success	166 (87.8%)	189 (85.5%)	
	Cure	79 (41.8%)	99 (44.8%)	
	Clinical Improvement	87 (46.0%)	90 (40.7%)	
	Clinical Failure	23 (12.2%)	32 (14.5%)	
	Failure	9 (4.8%)	13 (5.9%)	
	Unable to Evaluate	14 (7.4%)	19 (8.6%)	

Source: Table 14.2.1.27

FDA results

Table 67: Clinical Success rates by randomization stratification (Population: CE)

Diabetic Ulcer	Daptomycin (N=238)	Comparator (N=250)	95% C.I.	P-Value
Yes	16/24 (66.7%)	23/32 (71.9%)	(-33.3%, 22.9%)	0.8224
No	198/214 (92.5%)	203/218 (93.1%)	(-5.9%, 4.7%)	

Subgroup analyses

A. Enrollment sites

The SDCO at the TOC evaluation stratified by pooled study center was analyzed for both the MITT and CE populations. No differences in outcome were seen between the two treatment arms after adjustment for study center (MITT 95% CI: -5.7, 7.1; CE 95% CI: -3.6, 6.8).

Of the 20 South African sites that participated in Study 9901, five subsequently participated in study 9801. These sites enrolled patients in study 9801 only after study 9901 had been completed. No patient participated in both studies. The clinical success rates for the two treatment groups were recalculated by the sponsor excluding the data from

patients enrolled at these five sites (179 patients in the CE population and 160 in the MITT population). After this adjustment, the success rates in the MITT population were 83.1% (113/136) in the daptomycin arm and 79.1% (136/172) in the comparator arm (95% CI [comparator - daptomycin]: -12.8, 4.7). In the CE population, the success rates were 86.7% (137/158) and 86.5% (147/170) in the daptomycin and comparator treatment groups, respectively (95% CI [comparator - daptomycin]: -7.6, 7.1).

Table 68: FDA Analysis comparing South Africa with other sites Population: (ITT)

Country	Daptomycin (N=270)	Comparator (N=292)	95% C.I.	P-Value
South Africa	123/149 (82.6%)	131/154 (85.1%)	(-11.5%, 6.4%)	0.4629
Others	94/121 (77.7%)	104/138 (75.4%)	(-8.8%, 13.4%)	

MO Comments:

Success rates were higher in patients enrolled in South Africa. This finding is similar to that seen in study 9801 were success rates were higher in patients enrolled in the five sites in South Africa again reflecting differences in the nature of patients enrolled. Success rates calculated after excluding the five sites that enrolled patients in both studies showed no significant effect on overall assessments. It is thus unlikely that any bias was introduced by inclusion of these five sites.

B. Demographic and baseline characteristics

Clinical success rates by treatment group for the MITT population subdivided by gender, age and race are presented in table 69. There were no significant differences between the two treatment arms for any of these subgroups. The absolute difference in success rates exceeded 5% only for the subgroup age ≥ 65 years. Results of the FDA analyses by demographic characteristics are presented in table 71.

Table 69 (Sponsor Table 11-15): SDCO by demographic characteristics (Population: MITT)

Demographic Characteristic	Daptomycin N = 213	Comparator N = 255	95% CI
Sex			
Male	95/111 (85.6%)	113/139 (81.3%)	-13.5, 4.9
Female	85/102 (83.3%)	101/116 (87.1%)	-5.7, 13.2
Age			
< 65 years	147/169 (87.0%)	174/206 (84.5%)	-9.6, 4.6
≥ 65 years	33/44 (75.0%)	40/49 (81.6%)	-10.1, 23.4
Race			
Caucasian	87/103 (84.5%)	103/128 (80.5%)	-13.8, 5.8
Black	65/77 (84.4%)	67/78 (85.9%)	-9.7, 12.7
Other	28/33 (84.8%)	44/49 (89.8%)	-9.9, 19.8

Success rates were also analyzed by clinical characteristics at baseline, including severity of the infection as well as presence or absence of SIRS, bacteremia, and surgical intervention. These results are summarized in Table 70. There were no clinically significant differences in response rates between treatment groups for any of the subgroups. Absolute differences between treatment groups exceeded 5% only among patients who had adjunct surgical treatment of their infection.

Table 70 (Sponsor Table 11-16): SDCO by baseline disease (Population: MITT)

Baseline disease characteristic	Daptomycin N = 213	Comparator N = 255	95% CI
Severity of infection			
Severe	119/141 (84.4%)	128/153 (83.7%)	-9.1, 7.6
Not severe	61/72 (84.7%)	86/102 (84.3%)	-11.3, 10.5
SIRS			
Yes	57/71 (80.3%)	66/82 (80.5%)	-12.4, 12.8
No	123/142 (86.6%)	148/173 (85.5%)	-8.7, 6.6
Bacteremic status			
Yes	3/6 (50.0%)	3/6 (50.0%)	-7.3, 5.8
No	177/207 (85.5%)	211/249 (84.7%)	
Surgical intervention			
Yes	35/46 (76.1%)	35/51 (68.6%)	(-25.2, 10.3)
No	145/167 (86.8%)	179/204 (87.7%)	(-5.9, 7.7)

Table 71: 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%)

MO Comments:

Patients ≥ 65 years had lower cure rates compared to those < 65 years and this difference was more pronounced in the daptomycin arm. A similar pattern of lower cure rates in patients ≥ 65 years of age was seen in the daptomycin arm in study 9801.

C. Primary diagnosis

Table 72: FDA efficacy analysis by primary diagnosis (Population: ITT)

Primary Diagnosis	Daptomycin (N=270)	Comparator (N=292)	95% C.I.	P-Value
Wound Infection	81/102 (79.4%)	88/108 (81.5%)	(-13.8%, 9.6%)	0.7191
Major Abscess	52/59 (88.1%)	53/65 (81.5%)	(-7.6%, 20.7%)	
Infected diabetic ulcer	13/23 (56.5%)	21/31 (67.7%)	(-41.1%, 18.7%)	
Infected Ulcer (non-diabetic)	23/30 (76.7%)	30/37 (81.1%)	(-27.1%, 18.3%)	
Other Infection	48/56 (85.7%)	43/51 (84.3%)	(-14.0%, 16.8%)	

D. Renal insufficiency

Lower cure rates were seen in patients in the daptomycin arm. This was more evident in the ITT population rather than in the CE population. Sponsor's results stratifying patients based on creatinine clearance (30-70ml/min. versus > 70 ml/min) are presented in the following table.

Table 73: SDCO in patients based on creatinine clearance (Population: ITT)

Clinical Response	Daptomycin	Comparator	95% CI
Clearance 30-70ml/min	**N=34**	**N=29**	-16.3, 30.7
Clinical Success	21 (61.8%)	20 (69.0%)	
Clinical Failure	13 (38.2%)	9 (31.0%)	
Clearance >70ml/min	**N=227**	**N=251**	-18.8, 18.0
Clinical Success	190 (83.7%)	209 (83.3%)	
Clinical Failure	37 (16.3%)	42 (16.7%)	

Source: TableA3 and A4, sponsor's submission 8/8/03

E. History of diabetes

Table 74: FDA efficacy analysis by history of diabetes (Population: ITT)

History of Diabetes	Daptomycin (N=270)	Comparator (N=292)	95% C.I.	P-Value
Yes	33/50 (66.0%)	49/68 (72.1%)	(-24.7%, 12.6%)	0.4918
No	184/220 (83.6%)	186/224 (83.0%)	(-6.8%, 8.0%)	

MO Comments:

Similar to study 9801, slightly higher cure rates were seen in the daptomycin arm in patients with abscesses, while lower cure rates were seen in those with infected diabetic and non-diabetic ulcers. In both arms patients with a history of diabetes had lower cure rates compared to those without a history of diabetes.

F. Oral switch

Clinical success rates by treatment group were also compared for those patients who did and did not receive oral as well as intravenous treatment. Among patients who received only intravenous therapy, the clinical success rates were 85.5% (171/200) and 86.0% (191/222) in the daptomycin and the comparator arms, respectively. Among the 46 patients in the MITT population who switched to oral therapy, the clinical success rates were 69.2% (9/13) in the daptomycin arm and 69.7% (23/33) in the comparator arm.

Table 75: SDCO by oral switch status (Population: MITT)

Oral switch	Clinical Response	Daptomycin	Comparator	95% CI
No	No of patients	200	222	
	Clinical Success	171 (85.5%)	191 (86.0%)	-6.1, 7.2
	Cure	75 (37.5%)	96 (43.2%)	
	Clinical Improvement	96 (48.0%)	95 (42.8%)	
	Clinical Failure	29 (14.5%)	31 (14.0%)	
	Failure	17 (8.5%)	16 (7.2%)	
	Unable to Evaluate	12 (6.0%)	15 (6.8%)	
Yes	No of patients	13	33	
	Clinical Success	9 (69.2%)	23 (69.7%)	
	Cure	7 (53.8%)	14 (42.4%)	
	Clinical Improvement	2 (15.4%)	9 (27.3%)	
	Clinical Failure	4 (30.8%)	10 (30.3%)	
	Failure	0	3 (9.1%)	
	Unable to Evaluate	4 (30.8%)	7 (21.2%)	

Source: Table 14.2.1.23

G. Concomitant procedures

Patients with surgical procedures (debridement, curettage, incision and drainage etc) were flagged. Results of an analysis based on presence or absence of these surgical procedures are provided in table 76.

Table 76: SDCO by concomitant surgical procedures (Population: ITT)

Concomitant Procedures	Daptomycin (N=270)	Comparator (N=292)	95% C.I.
Yes	94/113 (83.2%)	91/120 (75.8%)	-3.8%, 18.5%
No	123/157 (78.3%)	144/172 (83.7%)	-14.5%, 3.7%

D. Efficacy Conclusions

Both studies 9801 and 9901, comparing the use of daptomycin with comparator drugs (vancomycin/semi-synthetic penicillins) in the treatment of complicated skin and skin structure infections showed that daptomycin was not inferior to the comparator drugs in the treatment of these infections using a non-inferiority margin of 10%. The 95% confidence intervals around the difference in cure rates in the primary efficacy populations (ITT and CE) demonstrated that the two treatment regimens were equivalent. Analyses done by the sponsor and FDA were comparable.

Though the two studies were similar in design, they differed in the nature of patients enrolled, and in efficacy estimates for both daptomycin and

comparator. Major differences in patient characteristics and efficacy results between the two studies are summarized in the table 77:

Table 77: Salient differences between study 9801 and 9901

Characteristic	Study 9801		Study 9901	
Comparator drug used				
Vancomycin	57.7%		21.8%	
Penicillins	36.6%		77.5%	
Both	5.7%		0.7%	
	Daptomycin	Comparator	Daptomycin	Comparator
Mean age (yrs)	55.0	55	47.9	48.6
Age ≥ 65 years	34%	31%	20.0%	19.2%
H/O diabetes	40.6%	46.4%	18.5%	23.3%
H/O PVD	26.2%	30.3%	11.9%	15.8%
Conc. Antibiotics*	31.6%	31.8%	17.0%	22.3%
Conc. Procedures	39.8%	39.5%	19.6%	19.9%
Rx > 14 days	14.5%	16.9%	0.4%	2.4%
No. of MRSA isolates	34	35	5	11
Clinical success				
ITT	165/264 (62.5%)	162/266 (60.9%)	217/270 (80.4%)	235/292 (80.5%)
CE	158/208 (76.0%)	158/206 (76.7%)	214/238 (89.9%)	226/250 (90.4%)

PVD= Peripheral vascular disease

* Aztreonam and/ metronidazole

As shown in the table, patients in study 9801 were older, and more likely to have a history of diabetes and peripheral vascular disease and to receive adjunct surgical procedures and non-study antibiotics. This suggests that patients in this study were sicker and likely to have more complicated infections.

For infections due to methicillin-susceptible *S.aureus*, semi-synthetic penicillins have better bactericidal activity than vancomycin. *S.aureus* was the most common pathogen identified at baseline and a large majority of these isolates were methicillin-susceptible. In study 9801, vancomycin was used as the comparator more often than semi-synthetic penicillins. Lower cure rates seen in the comparator arm could partly be due to this fact, thereby mitigating any treatment differences.

Results of these two studies should thus be considered separately rather than in an integrated manner and in the context of the patient population intended. Results from study 9801 better reflects the likely cure rates in patients hospitalized with complicated skin and skin structure infections in the United States.

No differences between treatment groups were seen among subgroups of gender, race, or baseline pathogen. In both studies lower cure rates were seen in daptomycin-treated patients ≥65 years of age.

VII. Integrated Review of Safety

Please see Appendix B, integrated safety summary, by Dr. Susan Thompson MD.

VIII. Dosing, Regimen, and Administration Issues

The recommended dosing regimen is 4 mg/kg intravenously once every 24 hours for patients with creatinine clearance ≥ 30 mL/min and 4 mg/kg intravenously once every 48 hours for patients with creatinine clearance <30 mL/min, including those on hemodialysis and continuous ambulatory peritoneal dialysis.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

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. In study 9801, clinical cure rates were slightly higher in females in both treatment arms. In study 9901, slightly higher cure rates were seen in females in the comparator arm, and in males in the daptomycin arm.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The protocol-specified age group to be enrolled in the two studies included 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 older than those in study 9901. Majority of patients in both studies was between 40-64 years of age. Patients ≥ 65 years were more common in study 9801, while those between 18-39 years were more common in study 9901. In both studies the distribution of patients by age group was comparable in the two treatment arms. In the daptomycin arm, success rates were lower in patients ≥ 65 years of age in both studies. In the comparator arm, success rates were comparable in the two age group categories in study 9801, while they were slightly lower in patients ≥ 65 years of age in study

9901. In study 9901, the difference in success rates in patients ≥ 65 years was more pronounced in the daptomycin arm.

In study 9801, over 60 % of patients were Caucasian, ~ 20% were blacks and the remainder were Asian/others. Slightly higher cure rates were seen in black patients compared to Caucasian and others. In study 9901 ~50% of patients were Caucasian, about a third were blacks and the remainder were Asian/others. Slightly higher cure rates were seen in patients of black/other race compared to Caucasian.

C. Evaluation of Pediatric Program

Daptomycin has not been studied in patients < 18 years of age.

D. Comments on Data Available or Needed in Other Populations

Reproductive and teratology studies performed in rats and rabbits at doses of up to 75 mg/kg, 3 and 6 times the human dose respectively on a body surface area basis, have revealed no evidence of harm to the fetus due to daptomycin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. It is not known if daptomycin is excreted in human milk. No dosage modification is needed in patients with mild or moderate hepatic insufficiency. Dosage modification is needed in patients with renal impairment as described in the section on dosage and administration.

X. Conclusions and Recommendations

A. Conclusions

Based on evidence from two comparator 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 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 both studies combined, a total of 534 patients were treated with daptomycin.

The two clinical studies that were submitted by the sponsor to support this indication were similar in study design, but differed in certain patient characteristics like history of diabetes, and peripheral vascular disease that have a significant bearing on wound healing. Cure rates were thus

significantly different in the two studies. In both studies, daptomycin was demonstrated to be non-inferior to the comparator (vancomycin/semi-synthetic penicillins) using a non-inferiority margin of 10%.

Sufficient numbers of patients with complicated skin and skin structure infections such as 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 were low. Viridans group streptococci should not be included in the list of pathogens as their role as pathogens in skin infections is unclear, except for members of the *S. intermedius* (*milleri*) group. As patient characteristics and clinical success rates differed significantly between the two studies, the results of the two studies should be considered separately and not included in the product label in an integrated manner as proposed by the sponsor.

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 is available for an additional 52 patients from ongoing studies, most of which used a higher dose of 6 mg/kg. Overall, the MedDRA 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, SAEs other than death, and AEs leading to discontinuation were similar in both treatment groups. Preclinical studies had predicted that the primary target of daptomycin adverse effects was skeletal muscle; this prediction was confirmed in phase 1 studies by elevation of CPK with muscle-related symptoms in 2/5 subjects given 4 mg/kg q12h and 2/4 subjects administered daptomycin at 4 mg/kg q24h. In Phase 3 cSSSI trials, elevations in serum CPK as clinical adverse events were reported 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. Recommendations

Major changes to the proposed package insert
Following are the important changes made to the sponsor's proposed package insert:

1. Indications and Usage
The sponsor had proposed [redacted] the indications and usage section. Data were inadequate to include patients with [redacted]

[redacted] as the number of patients enrolled with [redacted] was small, errors in classification of [redacted] occurred, and the clinical success rates were low.

The sponsor had proposed to include [redacted] as a [redacted] causing complicated skin and skin structure infections. Except for members of the *S. intermedius* (*milleri*) group, the role of [redacted] as pathogens in complicated skin and skin structure infections is unclear. Hence, [redacted] were deleted from this section.

"Daptomycin is not indicated for the treatment of pneumonia" was added. 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.

2. 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.

3. 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 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.

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.

[redacted]

Addition of 3rd paragraph regarding neuropathy: " In a small number of patients in Phase 1 and Phase 2 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 small number of comparator subjects in these studies. In Phase 3 cSSSI and CAP studies 7/989 (0.7%) daptomycin-treated patients and 7/1018 (0.7%) comparator-treated patients experienced paresthesias. In animals, effects of daptomycin on peripheral nerve were observed (see ANIMAL PHARMACOLOGY). Since peripheral neuropathy characterized by axonal degeneration were observed in adult dogs and monkeys, this paragraph was added to provide the practitioner with all available clinical experience with neuropathy in human studies.

4. Geriatric Use

The following sentences were added to the geriatric use section. In the two Phase 3 clinical studies in patients with cSSSI, lower clinical success rates were seen in patients ≥65 years of age compared to those < 65 years of age. In addition, treatment-emergent adverse events were more common in patients ≥65 years old than in patients <65 years of age in both cSSSI studies.

5. Adverse Events

The second paragraph was modified to read "Clinical studies sponsored by Cubist enrolled 1,409 patients treated with daptomycin and 1,185 treated with comparator. Most adverse events reported in these clinical studies were described as mild or moderate in intensity. In Phase 3 cSSSI trials, daptomycin was discontinued in 15/534 (2.8%) patients due to an adverse event while comparator was discontinued in 17/558 (3.0%) patients." These changes were made to modify language to include AEs of severe intensity as well as to more accurately reflect the discontinuation rate due to AEs.

The following paragraph was added in order to provide practitioners information regarding the adverse event profile of daptomycin in the treatment of CAP, as well as the cause: " In Phase 3 studies of community-acquired pneumonia (CAP), the death rate and rates of serious cardiorespiratory adverse events were higher in daptomycin-treated patients than in comparator-treated patients. These differences were due to lack of therapeutic effectiveness of daptomycin in the treatment of CAP in patients experiencing these adverse events (see INDICATIONS AND USAGE)

The sentence

[redacted]." was deleted from this section. A more complete summary of the Lilly and Cubist experience with neuropathy is now included in PRECAUTIONS. Under Laboratory Changes: The FDA proposed changes in the ADVERSE EVENTS section include the addition of a table (Table 6) showing rates of various degrees of CPK elevation in daptomycin and comparator-treated patients in cSSSI studies. This table provides information to prescribers on the relative rates of CPK elevation in the population of patients for whom daptomycin is indicated, and illustrates that extreme elevations of CPK consistent with myopathy occur in daptomycin-treated patients, although at a low rate.

6. Dosage and Administration

The following was added to the first paragraph under "Complicated Skin and Skin Structure Infections": "Doses of daptomycin higher than 4 mg/kg/day have not been studied in Phase 3 controlled clinical trials. In Phase 1 and 2 clinical studies, CPK elevations appeared to be more frequent when daptomycin was dosed more frequently than once daily. Therefore, daptomycin should not be dosed more frequently than once a day." The sentence regarding dosing was added to provide practitioners who may be considering off-label use at a higher dose than 4 mg/kg q 24h that safety data to support such use has not yet been collected. The sentence regarding frequency of dosing was added to reflect that in a Phase 1 dose-escalation study (Study B8B-MC-AVAP) conducted by Lilly daptomycin at 4 mg/kg q12h for 14 days was administered to five normal subjects. At about Day 8 of treatment, two of the five subjects experienced muscle pain and weakness as well as rapid elevations in CPK. Study medication was discontinued and the effects resolved within a few days without sequelae. Subsequent animal studies indicated that for a given level of drug exposure the frequency and severity of skeletal muscle toxicity were decreased with once daily dosing compared with divided doses.

7. Clinical studies

- The sponsor had proposed to present results of the two phase 3 clinical studies in cSSSI in an integrated manner. As the efficacy results in the two studies were different, they are discussed in the label separately. As the primary efficacy populations were the ITT and CE populations, results of FDA analyses in the ITT and CE populations were included in this section instead of the MITT and CE as proposed by the sponsor.
- Patients known to have bacteremia at baseline were excluded as this was an exclusion criterion.
- The following sentence was added: Patients with creatinine clearance between 30-70 mL/minute were to receive a lower dose of daptomycin

as specified in the protocol; however, the majority of patients in this subpopulation did not have the dose of daptomycin adjusted.

- The sentence " \ \ \ \ was deleted, as this was not a pre-defined end-point.

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XI. Appendix

Appendix 1
Sponsor's Criteria for Evaluability (DAP-SST-9801)

1. Subject never received any study drug.
2. Subject did not have a confirmed diagnosis of cSSSI.
3. Subject received the incorrect i. v. study drug.
4. Subject was judged a 'Clinical Failure' by the Investigator from Day 3 to TOC/ Day 20P.
5. Subject received a potentially effective non-study (PENS) antibiotic for lack of efficacy at any time from Day 3 to TOC/ Day 20P.
6. Subject's primary site of infection was removed by surgery from Day 3 to TOC/ Day 20P.
7. Subject had no evaluation by the Investigator at any time after the End- of-Therapy.
8. Subject received a PENS antibiotic on >2 calendar days from Day -3 to Day 1 and had no infecting pathogen isolated.
9. Subject received a PENS antibiotic on >2 calendar days from Day 1 to TOC, for reason other than lack of efficacy.
10. Subject was not judged Cured or Improved by the Investigator at Test- of-Cure Evaluation (Day 6P- 20P).
11. Subject did not receive i.v. study medication of 4 days duration.

Sponsor's Criteria for Evaluability (DAP-SST-9901)

1. Subject never received any study drug.
2. Subject did not have a confirmed diagnosis of cSSSI.
3. Subject was judged a 'Clinical Failure' by the Investigator from Day 3 to TOC/ Day 20P.
4. Subject received a Potentially Effective Non- study (PENS) antibiotic for lack of efficacy at any time from Day 3 to TOC/ Day 20P.
5. Subject's primary site of infection was removed by surgery from Day 3 to TOC/ Day 20P.
6. Subject had no Evaluation by the Investigator at any time after the End- of-Therapy.
7. Subject received the wrong study drug.
8. Subject had a response of 'Yes' for at least one of Exclusion Questions 4, 6, and 7.
9. Subject received a PENS antibiotic on >2 calendar days from Day -3 to Day 1.
10. Subject received a Potentially Effective Non- study antibiotic on >2 calendar days from Day 1 to TOC, for reason other than lack of efficacy.
11. Subject was not judged Cured or Improved by the Investigator at Test- of-Cure Evaluation (Day 6P- 20P).

12. Subject did not achieve at least 80% compliance or 4 days dosing with the dose regimen.

MO Comments:
Some of the criteria listed above exclude a patient from the evaluable population, while some others if answered in the affirmative will include a patient in the evaluable population.

Appendix 2

Population	Sponsor	FDA
ITT	Excludes rejected patients.	Includes rejected patients.
CE	Patients who received > 2 days therapy and had missing TOC visit, were classified as evaluable failures	Patients with missing TOC visits were excluded irrespective of duration of therapy.
	Only patients who received concomitant antibiotics for > 2 days for reasons other than lack of efficacy were excluded.	All patients who received concomitant antibiotics from day 2 to TOC visit excluded.
MITT	Excluded rejected patients with Gram positive pathogen at baseline	Includes rejected patients with Gram positive pathogen at baseline

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

/s/

Sumathi Nambiar
9/12/03 02:32:39 PM
MEDICAL OFFICER

David Ross
9/12/03 02:33:59 PM
MEDICAL OFFICER

Janice Soreth
9/12/03 02:38:51 PM
MEDICAL OFFICER

Appendix B to Integrated Review of Safety and Efficacy

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*

Sponsor: Cubist Pharmaceuticals, Inc.
Lexington, MA 02421

Clinical Reviewer: Susan D. Thompson, M.D.

Date of Submission: December 19, 2002

Date Assigned: December 19, 2002

Date Review Begun: December 19, 2002

Date Review to Supervisor: August 31, 2002

PDUFA Deadline: September 19, 2002

Integrated Review of Safety

A. Brief Statement of Conclusions

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 most common toxicities of daptomycin are gastrointestinal disorders including nausea, constipation, diarrhea, and vomiting. During Phase I and Phase II studies, both asymptomatic CPK elevations as well as several cases of elevated serum CPK associated with myopathy were described. In the Phase III cSSSI trials, elevations in serum CPK were reported as adverse events (AEs) in 2.8% of daptomycin-treated patients, compared to 1.8% of comparator-treated patients. Symptoms of myopathy and serum CPK elevations have resolved in the cases for which follow-up is available, and there have been no reports of further complications such as rhabdomyolysis. During Phase I and Phase II studies, daptomycin administration was associated with decreases in NCV and with AEs such as paresthesias and Bell's palsy in a small number of patients, which may be reflective of peripheral or cranial neuropathy. In Phase III cSSSI and CAP studies equal numbers of daptomycin-treated patients and comparator-treated patients experienced paresthesias. There were no cases of new or worsening peripheral neuropathy diagnosed in any of these patients.

Safety data from the two CAP studies conducted by Cubist were submitted with this NDA. 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 and respiratory SAEs. These differences were attributable to the lower efficacy of daptomycin in the treatment of CAP. This is reflected in the failure of daptomycin to demonstrate noninferiority to comparator in these two CAP trials. Examination of the preclinical data, as well as the body of evidence derived from Phase I, Phase II, and Phase III studies, does not suggest evidence of daptomycin cardiotoxicity.

In both of the cSSSI trials, treatment-emergent AEs were more common in patients $\geq$65 years old than in patients <65 years of age. The pharmacokinetics and risk profile of daptomycin appear similar in patients with renal impairment and a creatinine clearance of more than 30 mL/min to the general population.

B. Description of Patient Exposure

Cubist-sponsored Phase I studies

In the Cubist-sponsored clinical pharmacology studies, a total of 349 subjects were treated; 240 received daptomycin and 109 received a comparator. Table 1 presents a summary of duration of exposure to daptomycin for the Cubist-sponsored clinical

pharmacology studies. The greatest number of the subjects receiving daptomycin 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.

Table 1: Duration of Exposure, Duration and Total Daptomycin Dose, Cubist- sponsored Phase I Studies (Populations: All Subjects Treated)

Exposure	Single Dose		Multiple Dose		Total Clinical Pharmacology Studies	
	Daptomycin (N=121)	Comparator (N=17)	Daptomycin (N=119)	Comparator (N=92)	Daptomycin (N=240)	Comparator (N=109)
	N %	N %	N %	N %	N %	N %
Total Dose Administered[a]						
<= 1 g	120 (92.2)				120 (50.0)	
> 1 to 2 g	1 (0.8)		8 (6.7)		9 (3.8)	
> 2 to 3 g			11 (9.2)		11 (4.6)	
> 3 to 4 g			14 (11.8)		14 (5.8)	
> 4 g			86 (72.3)		86 (35.8)	
Duration of I.V. Therapy						
Single dose	121 (100.0)	17 (100.0)	0 (0.0)	0 (0.0)	121 (50.4)	17 (15.6)
<= 1 day	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.9)
7 to 14 days	0 (0.0)	0 (0.0)	119 (100.0)	91 (98.9)	119 (49.6)	91 (83.5)

[a] Daptomycin only.

Lilly-sponsored Phase I studies

In the Lilly-sponsored Clinical Pharmacology studies 362 subjects were exposed to daptomycin. In single-dose Phase 1 clinical pharmacology studies, 102 subjects were administered daptomycin at doses ranging from 5 mg to 6 mg/kg. Table 2 below summarizes the number of subjects exposed to various dose levels of daptomycin in the single-dose Lilly-sponsored Phase 1 studies.

Table 2: Number of Subjects Exposed to Single Doses of Daptomycin in Lilly-sponsored Phase I Studies

Study Number	B8B-IT PP01	B8B-LC AVAA	B8B-LC AVAC	B8B-MC AVAD	B8B-LC AVAF	B8B-LC AVAJ[a]	B8B-LC AVAK	B8B-MC AVAL	B8B-EW 0001[b]	TOTAL #/DOSE
Daptomycin Dose i.v.	N=10	N=6	N=5	N=45	N=5	N=6	N=6	N=6	N=12	
5 mg	--	6	--	--	--	--	--	--	--	6
10 mg	--	5	--	--	--	--	--	--	--	5
25 mg	--	5	--	--	--	--	--	--	--	5
50 mg	--	5	--	--	--	--	--	--	--	5
75 mg	--	2	--	--	--	--	--	--	--	2
150 mg	10	--	--	--	--	--	--	--	--	10
0.5 mg/kg	--	--	--	--	5	--	--	--	--	5
1.0 mg/kg	--	3	5	39	5	--	--	--	6	58
1.5 mg/kg	--	--	--	--	5	--	--	--	--	5
2.0 mg/kg	--	--	--	--	5	6	6	--	6	23
3.0 mg/kg	--	--	--	6	--	--	6	6	--	18
4.0 mg/kg	--	--	--	--	--	--	6	--	--	6
6.0 mg/kg	--	--	--	--	--	--	6	--	--	6
Total Unique Subjects	10	6	5	45	6	6	6	6	12	102

a. Subjects received daptomycin 2 mg/kg i.v. alone and in combination with tobramycin 1 mg/kg on separate days
b. Subjects received daptomycin 1 or 2 mg/kg i.v. alone and in combination with amikacin 500 mg or vancomycin 500 mg on separated days.

Phase I repeated-dose clinical pharmacology studies sponsored by Lilly assessed doses of 1 mg/kg q24h to 4 mg/kg q24h in a total of 25 subjects. In the repeated-dose daptomycin Phase I studies conducted in the US, subjects were exposed to daptomycin doses from 1 mg/kg q24h to 4 mg/kg q12h. A total of 10 subjects received repeated doses of daptomycin 3 mg/kg q12h and 5 subjects received the highest dose, 4 mg/kg q12h for a total of 28 doses. The extent of exposure in doses per subject at each dose level is shown in Table 3.

Table 3: Extent of Exposure (Doses/Subject) in Daptomycin Repeated-dose in US-based Lilly-sponsored Phase I Studies

Study #	B8B-LC-AVAB		B8B-LC-AVAI		B8B-MC-AVAP		B8B-LC-AVAK	
Dose i.v. q24h	N	Doses /Subject	N	Doses /Subject	N	Doses /Subject	N	Doses /Subject
1 mg/kg i.v	5	10	--	--	--	--	--	--
2 mg/kg i.v.	--	--	5	14	--	--	--	--
3 mg/kg i.v.	--	--	--	--	5	28	5	5
4 mg/kg i.v.	--	--	--	--	5	28	--	--
Total Unique Subjects	5	--	5	--	10	--	5	5

In Phase I single and repeated-dose Lilly-sponsored studies conducted in Japan, 66 subjects were given daptomycin intravenously at doses from 7.5 mg to 3.0 mg/kg q12h. The extent of exposure to daptomycin in single- and repeated-dose studies conducted in Japan is shown in Table 4 below.

Table 4: Extent of Exposure to Daptomycin in Single- and Repeated-dose Lilly-sponsored Phase I Studies Conducted in Japan

Study Numbers	B8B-XO 1001	B8B-XO 1002	B8B-XO 1003	B8B-XO 1004	B8B-XO 1005	B8B-JE 0001	B8B-JE 0002
Single-dose - Number of Subject	N=6	N=6	N=6	N=6	N=6	N=26	N=10
7.5 mg i.v.	--	--	--	--	--	26	--
15 mg i.v.	--	--	--	--	--	26	--
30 mg i.v.	--	--	--	--	--	26	--
60 mg i.v.	--	--	--	--	--	26	--
90 mg i.v.	--	--	--	--	--	26	--
120 mg i.v.	--	--	--	--	--	26	--
1.5 mg/kg i.v.	6	--	--	--	--	--	--
3.0 mg/kg i.v.	--	6	--	--	--	--	--
6.0 mg/kg i.v.	--	--	6	--	--	--	--
Repeated-dose - Doses/Subject							
60 mg i.v.	--	--	--	--	--	--	5
120 mg i.v.	--	--	--	--	--	--	5
3.0 mg/kg i.v. q12h	--	--	--	6[a]	6	--	--
6.0 mg/kg i.v. q12h	--	--	--	6[a]	6[b]	--	--
Total Unique Subjects	6	6	6	6	6	26	10

a. First dose was 6.0 mg/kg followed 12 hours later by 3.0 mg/kg IV.
b. Subjects were first given 6.0 mg/kg i.v. then 3.0 mg/kg IVq 12 hr up to Day 7

Phase II studies

Cubist-sponsored Phase II/III studies

A total of 238 subjects were treated during the two Phase II and one Phase III studies conducted by Cubist; 180 patients received daptomycin and 58 patients received a comparator. Study DAP-00-03 was terminated prematurely due to slow enrollment.

In study DAP-BAC-9803, the majority of subjects in both groups received study treatment for at least fourteen days. A smaller percentage of daptomycin subjects than comparator subjects received >14 days of treatment, 12.2% and 25.0%, respectively. Thirty-two daptomycin-treated subjects received >4g of study medication. In DAP-RRC-9804, the majority of subjects received daptomycin treatment for at least fourteen days. Twenty-seven subjects received >14 days of daptomycin treatment, and 37 subjects >4g of daptomycin. In study DAP-00-03, the majority of subjects received study treatment for 2 to 14 days. No subjects were treated for more than 14 days. In these three Phase II/III Cubist-conducted studies, sixty-nine daptomycin-treated subjects received >4g of daptomycin.

Table 5 below presents a summary of duration of exposure to daptomycin for the two Phase II and one Phase III Cubist-sponsored studies.

Table 5: Duration of Exposure, and Total Daptomycin Dose, Cubist-sponsored Phase II/III Studies (Populations: All Subjects Treated)

Exposure	Daptomycin		Comparator		Daptomycin		Daptomycin		Comparator	
	N (74)*	%	N (24)	%	N (72)	%	N (34)	%	N (34)	%
	DAP-BAC-9803				DAP-RRC-9804		DAP-00-03			
Total Dose Administered[a]										
<= 1 g	8	10.8			13	18.1	1	2.9		
> 1 to 2 g	13	17.6			5	6.9	17	50.0		
> 2 to 3 g	7	9.5			8	11.1	13	38.2		
> 3 to 4 g	14	18.9			9	12.5	3	8.8		
> 4 g	32	43.2			37	51.4				
Duration of I.V. Therapy										
<= 1 day	2	2.7	0	0.0	5	6.9	1	2.9		
2 to 6 days	13	17.6	7	29.2	11	15.3	16	47.1	14	41.2
7 to 14 days	50	67.6	11	45.8	29	40.3	17	50.0	20	58.8
> 14 days	9	12.2	6	25.0	27	37.5				

[a]Daptomycin only.

Medical Officer Comment
Of note, four patients were enrolled twice each in study DAP-RRC-9804. The number of subjects who received daptomycin in Study DAP-RRC-9804 given in the table above as 72 as well as the number of daptomycin-treated patients in the remainder of this safety review reflect the actual number of patients enrolled in the study. The number of "treatment courses" is 76, since two subjects received the same dose and two other subjects received a different dose for a second treatment course.

Lilly-sponsored Phase II studies

A total of 169 subjects were given daptomycin at doses of either 2.0 mg/kg q24h or 3 mg/kg q12h after a loading dose of 6.0 mg/kg in the two Phase II studies that Lilly conducted. In study B8B-MC-AVAM, 89 subjects received a 6 mg/kg loading dose of daptomycin followed by 3 mg/kg q12h for up to 42 days in subjects with endocarditis or bacteremia. In study B8B-MC-AVAE/AVAG, 80 subjects received 2 mg/kg daptomycin q24h for up to 25 days in subjects with a variety of different infections.

Phase III studies
Study DAP-SST-9801

The safety population for study DAP-SST-9801 is defined as all patients who received one or more doses of study medication; in this population, 265 patients are in the daptomycin arm and 265 patients in the comparator arm. Table 6 below

presents a summary of duration of exposure to daptomycin and the comparator. The mean duration of intravenous treatment was 10.1 days in the daptomycin group and 10.2 days in the comparator group. Over 63% of subjects in both drug exposure groups received 7 to 14 days of intravenous study medication. A total of 54 subjects also received oral antibiotics as study medication ("oral switch therapy"). These included 22 (8.3%) subjects in the daptomycin group and 32 (12.3%) in the comparator group.

Table 6: Exposure to Study Drug in Study DAP-SST-9801 (Population: Safety)

Days on i.v. therapy:	Daptomycin N = 265	Comparator N = 265
Mean ± SD	10.1 ± 5.7	10.2 ± 5.1
Median	8.0	8.0
Minimum, Maximum	1, 33	1, 28
< 7 days	59 (22.3%)	51 (19.2%)
7 to 14 days	167 (63.0%)	171 (64.5%)
>14 days	39 (14.7%)	43 (16.2%)

Study DAP-SST-9901

The Safety Population for study DAP-SST-9901 is defined as all patients who received one or more doses of study medication; in this population, 269 patients are in the daptomycin arm and 293 patients in the comparator arm. Table 7 below presents a summary of duration of exposure to daptomycin and the comparator drugs. The mean duration of intravenous treatment was 7.2 days in the daptomycin arm and 7.9 days in the comparator arm. Over 75% of subjects in both drug exposure groups received intravenous therapy for 7 to 14 days. A total of 57 subjects switched to oral therapy including 19 (7.1%) subjects in the daptomycin group and 38 (13.0%) in the comparator group.

Table 7: Exposure to Study Drug in study DAP-SST-9901 (Population: Safety)

Days on i.v. therapy:	Daptomycin N = 269	Comparator N = 293
Mean ± SD	7.2 ± 2.0	7.9 ± 2.5
Median	7.0	8.0
Minimum, Maximum	1, 15	1, 21
< 7 days	54 (20.1%)	56 (19.1%)
7 to 14 days	214 (79.6%)	230 (78.5%)
>14 days	1 (0.4%)	7 (2.4%)

Medical Officer Comment

The exposures described above for both studies DAP-SST-9801 and DAP-SST-9801 are typical of what would be expected in the use of daptomycin for the proposed indication of complicated skin and skin structure infection (cSSSI). However, if the product is used off-label for such conditions as vancomycin-resistant Enterococcal (VRE) infection, it is likely that higher doses (6

mg/kg/q24h) and longer durations would be used. Caution should be exercised in extrapolation of the safety data provided for the indication of cSSSI in this NDA to other potential indications.

Studies DAP-CAP-00-05 and DAP-CAP-00-08

Table 8 below presents a summary of duration of exposure to daptomycin for the two CAP studies. 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. A total of 14 patients received more than 14 days of treatment with daptomycin, and 38 patients received a total dose of daptomycin >4g. Seven comparator patients received more than 14 days of therapy.

Table 8: Duration of Exposure and Total Daptomycin Dose, Community-Acquired Pneumonia Studies DAP-CAP-00-05/08 (Populations: All Patients Treated)

	DAP-CAP-00-05				DAP-CAP-00-08				Total CAP Studies			
	Daptomycin (N=355)		Comparator (N=359)		Daptomycin (N=100)		Comparator (N=101)		Daptomycin (N=455)		Comparator (N=460)	
Exposure	n	%	N	%	n	%	n	%	n	%	n	%
Total Dose Administered												
<= 1 g	44	12.4			13	13.0			57	12.5		
> 1 to 2 g	126	35.5			33	33.0			159	34.9		
> 2 to 3 g	113	31.8			28	28.0			141	31.0		
> 3 to 4 g	41	11.5			19	19.0			60	13.2		
> 4 g	31	8.7			7	7.0			38	8.4		
Duration of I.V. Therapy												
<= 1 day	11	3.1	10	2.8	4	4.0	5	5.0	15	3.3	15	3.3
2 to 6 days	134	37.7	137	38.2	27	27.0	22	21.8	161	35.4	159	34.6
7 to 14 days	201	56.6	209	58.2	64	64.0	70	69.3	265	58.2	279	60.7
> 14 days	9	2.5	3	0.8	5	5.0	4	4.0	14	3.1	7	1.5

a Daptomycin only.

Medical Officer Comment

Despite a higher rate of early discontinuation in the daptomycin arm, a similar proportion of patients received 7-14 days of therapy in both arms - 58.2% in the daptomycin arm and 60.7% in the comparator arm. The safety information derived from this trial should also be relevant to usage of the drug in cSSSI, since the dose and duration of therapy in this study are similar to that studied in the cSSSI trials. It is of interest that when the data from the combined CAP studies were 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 receiving daptomycin were necessary due to slow clinical response.

C. Methods and Specific Findings of Safety Review

Data is excerpted from the sponsor's final study reports and Cubist's integrated summary of safety (ISS), as well as the Lilly ISS constructed by Cubist. The clinical pharmacology (Phase I) studies consist of a total of 31 human pharmacology studies conducted on daptomycin. Lilly conducted 19 studies and

Cubist conducted 12 studies. AEs from Phases I, II, and III will be considered separately. Three Phase II studies conducted by Lilly will be presented together, as well as two Phase II studies and one Phase III study conducted by Cubist; the latter study was discontinued early due to poor enrollment. The two pivotal Phase III cSSSI will be considered separately. The two CAP studies will be considered together, since the protocols were essentially identical and the second study was terminated prematurely. Data from the use of daptomycin Requests for Emergency Use (18 patients) and data from a blinded Phase III study (DAP-VRE-00-07; 34 patients) which was submitted with the original NDA will be presented, together with additional data derived from these two studies submitted as a 120-day Safety Report to the IND on April 18, 2003. Also contained in the 120-day Safety Report is safety data from the three studies which started enrollment after submission of the NDA: DAP-IE-01-02 (infective endocarditis [IE]/bacteremia due to *Staphylococcus aureus)*, DAP-SST-9801B a pharmacokinetic study derived from DAP-SST-9801, and DAP-EAP-02-01, a compassionate use protocol. This is followed by a discussion of laboratory abnormalities in Phases I, II, and III.

METHODS

Adverse Events

Definitions

The reviewer used the same definitions and terms for AEs, drug-related AEs, serious adverse events (SAEs), and abnormal laboratory values as the applicant.

Mortality analysis

Study reports and narratives for all study deaths were reviewed. The case report forms for all study deaths (for both daptomycin-treated and comparator-treated patients) in the Phase III studies were reviewed.

Discontinuations

All cases of discontinuations due to AEs were reviewed. Discontinuations were examined for evidence of a relationship to study drug, or for evidence of lack of drug efficacy.

Serious adverse events

SAEs were reviewed, including examination of SAE's that might represent lack of drug efficacy. SAE's were not reported in all of the Clinical Study Reports provided by Lilly to Cubist. Additional reports of SAEs were obtained from a search conducted of a safety database at Eli Lilly. This database contained information about SAEs, including deaths and discontinuations, that did not appear in the study reports generated by Lilly.

Lilly-sponsored studies

Since electronic databases were not available for data collected by Lilly, the data contained in the ISS was compiled from Clinical Study Reports prepared and originally submitted by Lilly to the IND. Additional information regarding SAEs

was obtained from a search conducted of a safety database at Lilly. This database contained information about SAEs, including deaths and discontinuations, that did not appear in the study reports. Adverse event verbatim terms have not been coded using a standardized coding dictionary but have been grouped for purposes of the current application according to MedDRA SOC. Patient narratives for deaths, discontinuations due to AEs, and other SAEs were written by Cubist based on the information contained in the case report forms (CRFs) provided by Lilly. Additionally, all IND Safety reports submitted by Lilly were reviewed by Cubist and included. A separate Lilly Integrated Summary of Safety for the Lilly studies was prepared and submitted as an appendix to Cubist's ISS.

For description of the methodology used by the sponsor for collecting laboratory data, please refer to Appendix B, the clinical efficacy review by Dr. Sumati Nambiar. Laboratory data were submitted electronically in SAS Transport V format and analyzed using

and Baseline values were considered by both the sponsor and the reviewer to include any value obtained from three days before stat of study drug (d-3) to the first day of therapy (d1). On-therapy values were considered by the Medical Officer to be any value obtained from d2 of study drug administration until the last day of study drug administration (d0P); in contrast, the sponsor categorized on-therapy values as including laboratory values from d3 to d5P.

SPECIFIC FINDINGS

ADVERSE EVENTS

Cubist-sponsored Phase I studies

Demographics

The 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. Subject demographics of Cubist-sponsored clinical pharmacology studies are shown in Table 9.

Table 9: Demographic Characteristics, Cubist-sponsored Phase I Studies (Population: All Subjects Treated)

		Single Dose		Multiple Dose		Total Clinical Pharmacology Studies	
Characteristic	Statistic	Daptomycin	Comparator	Daptomycin	Comparator	Daptomycin	Comparator
Age (yrs)		(N=121)	(N=17)	(N=119)	(N=92)	(N=240)	(N=109)
	N	114	17	119	92	233	109
	Mean	47.9	42.8	44.6	44.4	46.2	44.2
	SD	17.0	12.3	11.2	11.0	14.4	11.2
	Median	47.0	45.0	43.0	44.0	45.0	44.0
	Min, Max	18, 82	18, 58	20, 75	20, 69	18, 82	18, 69
Age (yrs)	N (%)						
18 - 39		35 (28.9)	5 (29.4)	40 (33.6)	32 (34.8)	75 (31.3)	37(33.9)
40 - 64		58 (47.9)	12 (70.6)	75 (63.0)	59 (64.1)	133 (55.4)	71 (65.1)
>=65		21 (17.4)	0 (0.0)	4 (3.4)	1 (1.1)	25 (10.4)	1 (0.9)
>=75		12 (9.9)	0 (0.0)	1 (0.8)	0 (0.0)	13 (5.4)	0 (0.0)
Gender	N (%)						
Male		66 (54.5)	12 (70.6)	68 (57.1)	0 (54.3)	134 (55.8)	62 (56.9)
Female		55 (45.5)	5 (29.4)	51 (42.9)	42 (45.7)	106 (44.2)	47 (43.1)
Race	N (%)						
Caucasian		43 (35.5)	10 (58.8)	57 (47.9)	63 (68.5)	100 (41.7)	73 (67.0)
Black		30 (24.8)	3 (17.6)	21 (17.6)	7 (7.6)	51 (21.3)	10 (9.2)
Other		48 (39.7)	4(23.5)	41 (34.5)	22(23.9)	89 (37.1)	26 (23.9)

Medical Officer Comment
Demographic information was not recorded in all studies, especially those conducted by Lilly in Japan. Therefore, the number of subjects in each column does not necessarily match the total number of subjects.

Subjects in these studies ranged in age from 18 to 82 years of age with a mean of 46.2 years in the daptomycin group and 44.0 years in the comparator group. Of the 240 subjects in the daptomycin group, 25 were at least 65 years of age and 13 were at least 75 years of age. Over half of the subjects in each group were male. Caucasians accounted for 41.7% and 67% of the subjects in the daptomycin and comparator groups, respectively.

Disposition - Cubist-sponsored Phase I studies

A summary of subject disposition in the Cubist-sponsored Phase I studies is presented in Table 10 below. A total of 349 subjects were treated during the these studies; 240 received daptomycin and 109 received comparator. Most subjects in both treatment groups completed treatment as planned (95.0% daptomycin, 97.2% comparator).