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.

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