related, most commonly injection site thrombosis and pyrexia, which were reported as drug-related events in <2% of patients in both drug exposure groups. In this SOC drug-related events of severe intensity were reported in 2/265 (<1%) patients in the daptomycin group and included pyrexia and weakness. The only drug-related event in the SOC Infections and Infestations reported in >1% of patients was fungal vaginosis, which was reported as drug-related in 5/265 (1.9%) of patients in both the daptomycin and comparator groups. The only severe drug-related event in this SOC was a fungal skin infection reported in one patient (<1%) in the daptomycin group. Drug-related events in the SOC Skin and Subcutaneous Tissue Disorders were reported more frequently in the comparator group (19/265; 7.2%) than in the daptomycin group (4/265; 1.5%). Drug-related pruritus and dermatitis were reported in 2 to 3% of patients in the comparator group and in 1% of patients in the daptomycin group. Only one patient in each treatment group (<1% each) experienced a drug-related event within the Respiratory System Disorders SOC. Drug-related dyspnea of moderate intensity was reported in one patient in the daptomycin group and drug-related dyspnea of moderate intensity and epistaxis of severe intensity were reported in one patient in the comparator group. Musculoskeletal, connective tissue and bone disorders assessed as drug-related were noted in 3/265 (1.1%) patients in the daptomycin group. Two of these drug-related events, arthralgia aggravated in one patient and myalgia in another were assessed by the investigator as severe in intensity. Drug-related events within the Metabolism and Nutrition Disorders SOC were reported in approximately 1% of patients in both drug exposure groups. Less than 1% of patients in the daptomycin group and 1.9% of patients in the comparator group experienced drug-related vascular disorders. One patient in the comparator group experienced hypotension of severe intensity that was assessed as possibly drug related.

Table 37: Treatment-Emergent Drug-Related AEs Occurring in ≥1% of Patients by System Organ Class and Preferred Term in Study DAP-SST-9801 (Population: Safety)

System Organ Class Preferred Term	Daptomycin N = 265	Comparator N = 265
Total Number of Patients with Drug-Related AEs	64 (24.2%)	90 (34.0%)
Gastrointestinal Disorders	21 (7.9%)	30 (11.3%)
Nausea	9 (3.4%)	15 (5.7%)
Diarrhea NOS	7 (2.6%)	10 (3.8%)
Vomiting NOS	7 (2.6%)	6 (2.3%)
Constipation	5 (1.9%)	7 (2.6%)
Diarrhea Aggravated	3 (1.1%)	2 (<1%)
Loose Stools	1 (<1%)	3 (1.1%)
Investigations	21 (7.9%)	18 (6.8%)
Blood Creatine Phosphokinase Increased	6 (2.3%)	5 (1.9%)
Blood Creatinine Increased	4 (1.5%)	5 (1.9%)
Liver Function Tests NOS Abnormal	4 (1.5%)	3 (1.1%)
Blood Alkaline Phosphatase Increased	4 (1.5%)	2 (<1%)
Aspartate Aminotransferase Increased	3 (1.1%)	2 (<1%)
Alanine Aminotransferase Increased	3 (1.1%)	2 (<1%)
General Disorders/Administration Site Conditions	13 (4.9%)	18 (6.8%)
Injection Site Thrombosis	3 (1.1%)	4 (1.5%)
Pyrexia	2 (<1%)	5 (1.9%)
Injection Site Phlebitis	3 (1.1%)	2 (<1%)
Injection Site Burning	1 (<1%)	3 (1.1%)
Weakness	3 (1.1%)	1 (<1%)
Skin & Subcutaneous Tissue Disorders	4 (1.5%)	19 (7.2%)
Pruritus NOS	3 (1.1%)	7 (2.6%)
Dermatitis NOS	3 (1.1%)	6 (2.3%)
Infections and Infestations	5 (1.9%)	12 (4.5%)
Vaginosis Fungal NOS	5 (1.9%)	5 (1.9%)
Nervous System Disorders	9 (3.4%)	7 (2.6%)
Dizziness (Excl Vertigo)	3 (1.1%)	4 (1.5%)
Headache NOS	3 (1.1%)	3 (1.1%)
Vascular Disorders	2 (<1%)	5 (1.9%)
Flushing	1 (<1%)	3 (1.1%)
Metabolism and Nutrition Disorders	3 (1.1%)	3 (1.1%)
Blood and Lymphatic System Disorders	3 (1.1%)	2 (<1%)
Musculoskeletal, Connective Tissue and Bone Disorders	3 (1.1%)	0

Adverse events leading to discontinuation of treatment - Study DAP-SST-9801

A total of 21 patients were discontinued from study treatment due to AEs, including 9/265 (3.4%) patients in the daptomycin group and 12/265 (4.5%) patients in the comparator group. The events leading to discontinuation were reported as possibly or probably related to study treatment for 4/265 (1.5%) patients in the daptomycin group and 9/265 (3.4%) patients in the comparator group. In the daptomycin group, the SAEs that resulted in discontinuation of study treatment and were assessed as drug-related included hypersensitivity reaction, anemia and thrombocytopenia, worsening of abdominal and joint pain in

a patient with sickle cell disease, and elevated serum CPK. In the comparator group, SAEs that resulted in discontinuation of study treatment and were assessed as drug-related included nausea, vomiting and rigors; elevated vancomycin levels and pruritic rash; drug fever; hypersensitivity reaction with elevations in ALT and AST; rash; nausea and vomiting; drug rash; peripheral swelling; and urticaria.

Medical Officer Comment

The Medical Officer reviewed the CRFs and patient narratives of all patients in study DAP-SST-9801 who discontinued study drug treatment due to AEs. As described below under "Serious adverse events", the Medical Officer believes that one of the patients (0070100041) with two AEs assessed by the investigator as possibly related are actually not related to study drug treatment (abdominal pain and arthralgias in a patient with sickle cell crisis). The AEs resulting in discontinuation of study drug treatment are consistent with the known AE profile of the drugs. The Medical Officer agrees with the other assessments of causality in both the comparator and daptomycin groups with the following two exceptions:

- Patient 0118100050 was a 78 year old male treated with vancomycin for 3 days for a wound infection of the left great toe. Study medication was discontinued due to severe nausea and vomiting. Deep swab of the wound grew multiple Gram-positive and Gram-negative organisms, including methicillin-sensitive *S. aureus* (MSSA). The investigator assessed the nausea and vomiting as not related to study drug; the Medical Officer considers it to be possibly related.
- Patient 0163100041 was a 43 year old female who received one dose of vancomycin for a wound infection of the right ankle which grew (methicillin-resistant *S. aureus* (MRSA). She developed urticaria after the first dose of vancomycin, and the study was discontinued. The investigator considered the urticaria to be possibly related to study drug. However, the patient received a course of vancomycin therapy after the study was discontinued without further urticaria; therefore, the Medical Officer considers this AE to be not related to study drug.

The following patient who was discontinued from the study due to AEs in the daptomycin arm of study DAP-SST-9801 is presented to demonstrate a severe allergic reaction to daptomycin.

- Patient 0053100064 was a 40 year old female with a post-operative MSSA infection of the left hip who received 5 doses of daptomycin. After the fourth dose she developed an allergic reaction consisting of fever, chills, and shortness of breath. She received the fifth dose of daptomycin the following day; at the end of the infusion, she developed tachycardia, fever to 106°F, and hypoxia, and the study drug was discontinued. The investigator considered this AE to be probably related to study drug treatment, and the Medical Officer agrees.

Serious adverse events - Study DAP-SST-9801

Table 38 below presents treatment-emergent SAEs by MedDRA SOC. A total of 64 patients, 32/265 (12.1%) in each drug exposure group, experienced 1 or more SAEs. There was no difference between the drug exposure groups for the overall incidence of any SAE. The only SAEs with reported incidence of ≥1% of patients were cellulitis and urosepsis, occurring in 4/265 (1.5%) patients and 3/265 (1.1%) patients, respectively, in the daptomycin group. All other serious events were reported in <1% of patients in both drug exposure groups. Four patients, including 2/265 (<1%) patients in each arm, experienced serious drug-related events. These included a hypersensitivity reaction and diarrhea (aggravated) in the daptomycin group; and hypersensitivity reaction and pruritic rash in the comparator group. For about one-third of the patients who experienced SAEs, at least one SAE started while on treatment. For approximately one-half of the patients in each drug exposure group who experienced SAEs, all SAE(s) started more than five days after the end of treatment.

Table 38: Treatment-Emergent SAEs by System Organ Class in Study DAP-SST-9801: Safety Population

System Organ Class Preferred Term	Daptomycin N = 265	Comparator N = 265
Total Number of Patients with SAEs	32 (12.1%)	32 (12.1%)
Infections and Infestations	18 (6.8%)	13 (4.9%)
Cellulitis	4 (1.5%)	0
Urosepsis	3 (1.1%)	0
Vascular Disorders	5 (1.9%)	3 (1.1%)
Cardiac Disorders	2 (<1%)	4 (1.5%)
Gastrointestinal Disorders	2 (<1%)	2 (<1%)
Skin & Subcutaneous Tissue Disorders	2 (<1%)	2 (< 1%)
Immune System Disorders	1 (<1%)	2 (<1%)
Metabolism and Nutrition Disorders	1 (<1%)	2 (<1%)
Nervous System Disorders	1 (<1%)	2 (<1%)
Neoplasms Benign and Malignant (including Cysts and Polyps)	2 (<1%)	1 (<1%)
Surgical and Medical Procedures	2 (<1%)	1 (<1%)
General Disorders/Administration Site Conditions	1 (<1%)	1 (<1%)
Renal and Urinary Disorders	1 (<1%)	1 (<1%)
Respiratory, Thoracic and Mediastinal Disorders	1 (<1%)	1 (<1%)
Blood and Lymphatic System Disorders	0	1 (<1%)
Congenital and Familial/Genetic Disorders	1 (<1%)	0

Medical Officer Comment

The Medical Officer reviewed the CRFs and patient narratives of all patients with SAEs. Most of the serious events in the daptomycin arm appeared to be related to the patient's underlying illness or the presenting illness. The investigator considered that three SAEs were possibly related and two AEs were probably related to study drug in the daptomycin arm. Forty-two SAEs were reported by the investigator in 32 patients. The Medical Officer agrees with these assessments with the exception of two SAE's in one patient (0070100041) with a sickle cell crisis; the investigator deemed abdominal pain and arthralgias to be possibly

related to daptomycin, and the Medical Officer considers them to be unrelated. One additional patient had an SAE that the Medical Officer considers to be possibly related to daptomycin, while the investigator assessed the SAE as unrelated; a brief summary of this case follows.

- Patient 0002100045 was a 66 year old male treated with daptomycin for four days for an abdominal wall wound infection caused by *Streptococcus constellatus* and *Streptococcus intermedius*. Serum creatinine rose from a baseline of 2.4 mg/dL to 7.1 mg/dL on d1P. Since no other etiology is evident for the patient's worsening renal insufficiency, the Medical Officer considers this SAE to be possibly related to study drug treatment.

Deaths - Study DAP-SST-9801

A total of 8/265 (3.0%) patients died during study DAP-SST-9801, including 2/265 (<1%) patients in the daptomycin group and 6/265 (2.3%) patients in the comparator group. None of the deaths were judged to be related to study treatment. Table 39 presents a list of the 8 patients who died. Six of eight (75%) patients were male and 6/8 (75%) patients were >70 years old at study entry. The primary site of infection was a wound infection in 6/8 (75%) patients; infected ulcer (not diabetic) and diabetic ulcer infection occurred in one patient each. All 8 of these patients who died had complicating medical conditions, including 4/8 (50%) with DM. One daptomycin-treated patient died of deep venous thrombosis (DVT) and pulmonary embolism, and one died of progressive lung cancer. One comparator-treated patient died of progression of underlying cancer; two died of underlying cardio- or cerebrovascular conditions; and one died of worsening of pre-existing anemia. Two comparator-treated patients died of sepsis more than 3 weeks post-treatment. The duration of study treatment in these 8 patients ranged from 4 to 10 days. Five patients died 3 to 62 days after successfully completing therapy. One patient was on d4 of study treatment at the time of death; one patient had discontinued treatment on d4 due to an AE not associated with the death and died 15 days later; and one patient had discontinued treatment due to clinical failure, was switched to non-study medication, and died 22 days later.

Medical Officer Comment

The Medical Officer reviewed the CRFs and patient narratives of all patient deaths in this study. The sponsor concluded that the causes of death in these eight patients who died during study DAP-SST-9801appeared to be directly related to pre-existing underlying conditions, and the Medical Officer agrees. No death in either group appeared to be directly related to daptomycin or comparator. Of note, however, is the fact that in some instances, documentation of the ultimate cause of death was not included with the submission. Two of these deaths fall in to this category: Patient 0204100080 in the comparator group died of severe anemia (admission hemoglobin = 4 g/dL) predating study drug administration, but no cause for the anemia is given. Patient 0104100041 died of progressive lung cancer on d30P, but no information is given regarding the terminal event.

Table 39: Patients who Died in Study DAP-SST-9801

Patient	Gender	Age	Complicating Medical History	Infection Diagnosis	Pathogen	SIRS (Y/N)	Days of I.v. Rx	Day of Death	Cause of Death	Relationship to study medication
Daptomycin										
0072100044	M	83	Hypertension, CAD, PVD, GI bleed, s/p decompression laminectomy	Wound Infection	*S. aureus*	Yes	4	0P	Bilateral LE DVT, Pulmonary embolism; Aspiration; acute respiratory failure	Not related
0104100041	M	83	Lung cancer, COPD, abdominal aortic aneurysm	Infected Ulcer (not diabetic)	*S. aureus*	No	6	30P	Progressive lung cancer	Not related
Comparator										
0053100051	M	76	PVD, CVA, paralysis, COPD	Wound Infection	*S. aureus; E. faecalis*	No	10	22P	Septic shock	Not related
0072100046	F	77	CHF, hypertension, lymphoma	Wound Infection	None isolated	No	7	10P	Progression of lymphoma	Not related
0118100050	M	78	Diabetes, hypertension, CVA, CAD, CHF, COPD,	Wound Infection	*S. aureus; E. faecalis*	No	4	15P	Cerebrovascular accident	Not related
0124100002	F	48	Diabetes, hypertension, PVD, obesity	Wound Infection	*S. aureus; S. agalactiae*	Yes	5	31P	Sepsis	Not related
0124100041	M	72	Diabetes, PVD, CHF, angina	Infected Diabetic Ulcer	*S. agalactiae*	Yes	8	62P	Exacerbation of CHF	Not related
0204100080	M	61	Anemia (Hct: 11%; Hgb: 4 g/dL)	Wound Infection	*S. aureus*	NR	7	3P	Worsening of anemia	Not related

Study DAP-SST-9901

Demographics

Table 40 presents a summary of the demographic characteristics for the patients in the daptomycin and comparator arms for study DAP-SST-9901. The two treatment groups were well balanced with regard to all demographic characteristics. The majority of the patients in both treatment groups were male (>54%) and Caucasian (≥50%). The mean age of the patients was 47.9 years in the daptomycin arm and 48.6 years in the comparator arm; approximately 20% of patients in both arms were ≥65 years old at study entry.

Table 40: Demographic Characteristics in Study DAP-SST-9901 (Population: ITT)

Characteristic	Daptomycin	Comparator	P-value[1]
	N = 270	N = 292	
Age (years)			
Mean ± SEM	47.9 ± 1.05	48.6 ± 0.98	0.628
Minimum, Maximum	18, 87	17, 85	
Weight (kg)			
Mean ± SEM	73.5 ± 1.20	72.7 ± 1.02	0.623
Minimum, Maximum	40, 165	40, 130	
Gender (N, %)			
Female	120 (44.4%)	132 (45.2%)	0.856
Male	150 (55.6%)	160 (54.8%)	
Race (N, %)			
Caucasian	136 (50.4%)	146 (50.0%)	0.489
Black	95 (35.2%)	91 (31.2%)	
Asian	2 (0.7%)	2 (0.7%)	
Other	37 (13.7%)	53 (18.2%)	

[1]Based on ANOVA fixed effects model with factor for treatment group for continuous variables and Chi-square test for categorical variables.

The distribution of patients by country/region is as follows: of 562 treated patients, 303 were enrolled in South Africa, 237 in Europe/Asia, and 22 in Australia.

Disposition - Study DAP-SST-9901

Table 41 below presents a summary of patient disposition during study DAP-SST-9901. A total of 571 patients were randomized to study treatment; 277 were randomized to receive daptomycin and 294 were randomized to receive comparator: vancomycin, flucloxacillin, oxacillin, or cloxacillin as designated by the investigator prior to randomization. Nine of the 571 randomized patients were discontinued from the study prior to receiving any study treatment. Among 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 patient was randomized to receive daptomycin but was administered only comparator as study medication. In all safety analyses, data for this misrandomized patient are included in the comparator drug group.

Therefore, there were 562 patients in the Safety population: 269 who received at least one dose of daptomycin, and 293 who received only comparator agents as study medication. Among the 293 patients in the comparator group, 149 received cloxacillin as study drug, 64 received vancomycin, 59 received oxacillin, 19 received flucloxacillin, and 2 received both vancomycin and flucloxacillin. Over 90% of patients in both treatment groups completed intravenous treatment as planned. There were no differences between the arms in the proportion of patients who discontinued intravenous drug therapy prematurely or in the reasons for discontinuation. Of the 269 daptomycin-treated patients, 18 (6.7%) discontinued prematurely as did 13 (4.4%) of the 293 comparator-treated patients. The most common reason for premature discontinuation in both arms was adverse event in 7/277 (2.6%) patients in the daptomycin arm and 5/294 (1.7%) patients in the comparator arm. There were no patients in study DAP-SST-9901 who discontinued study medication due to an elevation in serum CPK.

Table 41: Patient Disposition in Study DAP-SST-9901

Population	Daptomycin[1]	Comparator[1]
Randomized	277	294
Randomized But Not Treated	7	2
Intent-to-Treat Population (as randomized)	270	292
Misrandomized[1]	1	0
Safety Population (as treated)	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 (Symptomatic) Failure	4 (1.5%)	3 (1.0%)
Patient 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%)

[1] One patient (0410100063) was randomized to receive daptomycin but was administered comparator drug in error. In this table, data for this patient are included in the daptomycin column for the randomized and ITT populations but in the comparator column for all other populations.
[2] One patient (0401100057) is incorrectly included in Table 14.3.5.1 as discontinued due to an adverse event(other: skin allergy): this patient is also included in this table.

Overall adverse events - Study DAP-SST-9901

Table 42 presents treatment-emergent AEs by MedDRA SOC; the table also includes those preferred terms that were reported in ≥1% of patients in either treatment arm. There was no difference between the arms for the overall incidence of any AE. A total of 103/269 (38.3%) patients in the daptomycin group and 100/293 (34.1%) patients in the comparator group reported at least one AE during the study. The majority of events were assessed as unrelated to treatment by the investigators. There were no differences between the two arms in the incidence of all AEs reported within any MedDRA SOC. AEs were most commonly reported in the Gastrointestinal Disorders SOC, with 30/269 (11.2%) and 25/293 (8.5%) of patients in the daptomycin and comparator arms, respectively, reporting at least one AE within this system. Fewer than 10% of patients in either arm experienced events in all other SOCs. The most frequently reported AE by preferred term was headache occurring in 19 patients overall

including 11/269 (4.1%) patients in the daptomycin arm and 8/293 (2.7%) patients in the comparator arm. Other events reported in 2 to 4% of patients in either arm included constipation, nausea, injection site thrombosis, injection site phlebitis, increased CPK, insomnia, diarrhea, and dermatitis.

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Table 42: Treatment-Emergent AEs by System Organ Class Including the Most Commonly Reported Events (≥1% of Patients) in Study DAP-SST-9901 (Population: Safety)

System Organ Class Preferred Term	Daptomycin N = 269	Comparator N = 293	95% CI[1]
Total Number of Patients with AEs	103 (38.3%)	100 (34.1%)	(-12.1, 3.8)
Gastrointestinal Disorders	30 (11.2%)	25 (8.5%)	(-7.6, 2.3
Constipation	7 (2.6%)	8 (2.7%)	
Nausea	6 (2.2%)	9 (3.1%)	
Diarrhea NOS	7 (2.6%)	1 (<1%)	
Vomiting NOS	4 (1.5%)	4 (1.4%)	
Dyspepsia	1 (<1%)	4 (1.4%)	
General Disorders/Administration Site Conditions	24 (8.9%)	27 (9.2%)	(-4.5, 5.0)
Injection Site Thrombosis	6 (2.2%)	8 (2.7%)	
Injection Site Phlebitis	5 (1.9%)	6 (2.0%)	
Pyrexia	2 (<1%)	3 (1.0%)	
Injection Site Pain	3 (1.1%)	1 (<1%)	
Infections and Infestations	24 (8.9%)	21 (7.2%)	(-6.3, 2.8)
Infection NOS	1 (<1%)	4 (1.4%)	
Influenza	3 (1.1%)	2 (<1%)	
Urinary Tract Infection NOS	4 (1.5%)	0	
Cellulitis	3 (1.1%)	0	
Sepsis NOS	3 (1.1%)	0	
Investigations	18 (6.7%)	10 (3.4%)	(-6.9, 0.4)
Blood CPK Increased	7 (2.6%)	3 (1.0%)	
Aspartate Aminotransferase Increased	2 (<1%)	3 (1.0%)	
ALT Increased	1 (<1%)	3 (1.0%)	
Nervous System Disorders	19 (7.1%)	17 (5.8%)	(-5.3, 2.8)
Headache NOS	11 (4.1%)	8 (2.7%)	
Insomnia NEC	3 (1.1%)	6 (2.0%)	
Dizziness (excl Vertigo)	3 (1.1%)	1 (<1%)	
Skin & Subcutaneous Tissue Disorders	17 (6.3%)	13 (4.4%)	(-5.6, 1.9)
Dermatitis NOS	7 (2.6%)	1 (<1%)	
Vascular Disorders	10 (3.7%)	12 (4.1%)	(-2.8, 3.6)
Hypotension	5 (1.9%)	3 (1.0%)	
Metabolism and Nutrition Disorders	7 (2.6%)	7 (2.4%)	(-2.8, 2.4)
Hypokalaemia	3 (1.1%)	1 (<1%)	
Hypoglycemia NOS	1 (<1%)	3 (1.0%)	
Musculoskeletal, Connective Tissue and Bone Disorders	7 (2.6%)	5 (1.7%)	(-3.3, 1.5)
Cardiac Disorders	5 (1.9%)	6 (2.0%)	(-2.1, 2.5)
Respiratory, Thoracic and Mediastinal Disorders	5 (1.9%)	5 (1.7%)	--
Blood and Lymphatic System Disorders	3 (1.1%)	4 (1.4%)	--
Renal and Urinary Disorders	3 (1.1%)	2 (<1%)	--

[1] Two sided 95% CI around difference in proportions of AEs (comparator daptomycin) using normal approximation to the binomial, calculated at the body system level only if reported in ≥2% of patients.

Medical Officer Comment

AEs reported by SOC which occurred more commonly in the daptomycin arm included Investigations (6.7% and 3.4% in the daptomycin arm and comparator arm, respectively) and the preferred term blood CPK increased. Also higher in the daptomycin arm were the SOC Skin & Subcutaneous Tissue Disorders (6.3% and 4.4% in the daptomycin and comparator arms, respectively); the preferred term dermatitis was more common in the daptomycin arm (2.6%) versus comparator arm (<1%). There was a slightly higher incidence in the SOC Musculoskeletal, Connective Tissue and Bone Disorders (7/269 [2.6%] in the daptomycin arm versus 5/293 [1.7%] in the comparator arm). These AEs are consistent with the known adverse event profile of daptomycin.

Adverse events by intensity - Study DAP-SST-9901

A total of 208 unique treatment-emergent AEs were reported in the daptomycin arm. The majority of these events were mild (113/208; 54.3%) or moderate (65/208; 21.3%) in intensity. A total of 30/208 events (14.4%) reported in 26/269 (9.7%) were judged to be severe in intensity by the investigator. In the comparator group, a total of 190 unique treatment-emergent AEs were reported including 119 (62.6%) that were assessed as mild and 52 (27.4%) that were moderate in intensity. Nineteen events (10.0% of 190) reported in 13 patients (4.4% of 293 patients) were judged to be severe in intensity. AEs of severe intensity with incidence of ≥1% within each SOC and by preferred term are displayed in Table 43. The majority of SAEs were reported in < 1% of patients in both the daptomycin and comparator groups. The only severe event with incidence ≥1% was sepsis NOS, which was reported in 3/269 (1.1%) patients in the daptomycin group and none of the patients in the comparator group. None of these reports of sepsis were judged to be drug-related by the investigators. Only 4 patients, including 3 (1.1%) in the daptomycin group and one (<1%) in the comparator group, experienced events that were assessed as both severe in intensity and as possibly or probably related to study treatment. Three such events occurred in the daptomycin group: elevation in lactate dehydrogenase (LDH), elevation in eosinophil count, and hypotension. Elevation of serum CPK was the drug-related event of severe intensity in the comparator group. Laboratory abnormalities will be discussed further in the "Laboratory Assays" section.

Table 43: Treatment-Emergent AEs of Severe Intensity Occurring in ≥1% of Patients by System Organ Class and Preferred Term in Study DAP-SST-9901 (Population: Safety)

System Organ Class Preferred Term	Daptomycin N = 269	Comparator N = 293
Total Number of Patients with Severe AEs	26 (9.7%)	13 (4.4%)
Vascular Disorders	6 (2.2%)	5 (1.7%)
Infections and Infestations	7 (2.6%)	2 (0.7%)
Sepsis NOS	3 (1.1%)	0
Investigations (Laboratory)	4 (1.5%)	1 (0.3%)
Cardiac Disorders	3 (1.1%)	2 (0.7%)
Skin & Subcutaneous Tissue Disorders	3 (1.1%)	1 (0.3%)

Adverse events by subgroups - Study DAP-SST-9901

Table 44 below presents the overall incidence of any treatment-emergent AEs for subgroups defined by demographic characteristic. There were no differences between the treatment arms for the overall incidence of any AE or for the incidence of AEs within any SOC for any subgroup.

Table 44: Incidence of Adverse Events by Demographic Characteristics in Study DAP-SST-9901 (Population: Safety)

Demographic Characteristic	Patients with AEs in Subgroup N (%)		95% CI[1]
	Daptomycin N = 269	Comparator N = 293	
Sex			
Male	53/150 (35.3%)	53/160 (33.1%)	(-12.8, 8.4)
Female	50/119 (42.0%)	47/133 (35.3%)	(-18.7, 5.3)
Age			
< 65 years	79/216 (36.6%)	78/236 (33.1%)	(-12.3, 5.3)
≥ 65 years	24/53 (45.3%)	22/57 (38.6%)	(-25.1, 11.7)
Race			
Caucasian	58/135 (43.0%)	56/147 (38.1%)	(-16.3, 6.6)
Black	30/95 (31.6%)	22/91 (24.2%)	(-20.2, 5.4)
Other	15/39 (38.5%)	22/55 (40.0%)	(-18.5, 21.6)

[1] Two sided 95% CI around difference in proportions of AEs (comparator daptomycin) using normal approximation to the binomial, calculated at the body system level only if reported in≥2% of patients.

Medical Officer Comment

The incidence of AEs appears to be somewhat higher in females (42.0%) versus males (35.3%) in the daptomycin group. Females also had more AEs in the daptomycin arm (42.0%) than in the comparator arm (35.3%). This pattern is opposite that seen in study DAP-SST-9801, in which males had a higher AE rate than females and females had a higher AE rate in the comparator arm. Lastly, in the daptomycin arm, more AEs were reported in patients ≥ 65 years of age than in those < 65 years of age, consistent with the results in study DAP-SST-9801.

Drug related adverse events - Study DAP-SST-9901

Drug-related AEs with an incidence of >1% within each SOC and preferred term are included in Table 45 below. There were no differences between the two arms in the incidence of drug-related AEs reported within any SOC. The majority of

gastrointestinal disorders were not considered related to study treatment. The only drug-related gastrointestinal disorder with a reported incidence of >1% was nausea, which was reported in 3/269 (1.1%) of patients in the daptomycin group and 4/293 (1.4%) of patients in the comparator group. Approximately 3% of patients in both arms experienced AEs in the General Disorders/Administration Site Conditions SOC that were assessed as drug-related, primarily injection site thrombosis and phlebitis. These AEs were reported as drug-related in < 2% of patients in both drug arms. Only one event within the Infection and Infestation SOC was considered related to study treatment; a candidal infection was reported in one patient in the comparator group. One patient in each arm had a severe elevation in serum CPK reported as an AE in the Investigations SOC; assessed as unrelated to treatment in the daptomycin arm and probably related to treatment in the comparator group. Less than 1% of patients in either arm experienced AEs within the Nervous System Disorders SOC that were judged to be drug-related. The majority of skin and subcutaneous tissue disorders were not considered to be drug-related. Drug-related dermatitis was reported in 4/269 (1.5%) patients and 1/293 (<1%) patient in the daptomycin and comparator groups, respectively. Less than 1% of patients in both arms experienced drug-related vascular disorders. One patient in the daptomycin group experienced hypotension of severe intensity that was assessed as possibly drug related. Less than 1% of patients in both arms experienced drug-related events within the Metabolism and Nutrition Disorders SOC. Individual preferred term events considered to be drug related within the Musculoskeletal, connective tissue and bone disorders or Cardiac disorders SOCs were reported in < 1% of patients in both arms.

Table 45: Treatment-Emergent Drug-Related AEs Occurring in ≥1% of Patients by System Organ Class and Preferred Term in Study DAP-SST-9901 (Population: Safety)

System Organ Class Preferred Term	Daptomycin N = 269	Comparator N = 293
Total Number of Patients with Drug-Related AEs	30 (11.2%)	29 (9.9%)
General Disorders/Administration Site Conditions	7 (2.6%)	10 (3.4%)
Injection Site Thrombosis	2 (<1%)	5 (1.7%)
Injection Site Phlebitis	2 (<1%)	4 (1.4%)
Investigations	10 (3.7%)	5 (1.7%)
Blood Creatine Phosphokinase Increased	5 (1.9%)	3 (1.0%)
Aspartate Aminotransferase Increased	2 (<1%)	3 (1.0%)
Alanine Aminotransferase Increased	1 (<1%)	3 (1.0%)
Skin & Subcutaneous Tissue Disorders	6 (2.2%)	2 (<1%)
Dermatitis NOS	4 (1.5%)	1 (<1%)
Gastrointestinal Disorders	5 (1.9%)	1 (<1%)
Nausea	3 (1.1%)	4 (1.4%)

Adverse events leading to discontinuation of treatment - Study DAP-SST-9901
A total of 11 patients were discontinued from study treatment due to AEs, including 6/269 (2.2%) patients in the daptomycin group and 5/293 (1.7%) patients in the comparator group. The events leading to discontinuation were reported as possibly or probably related to study treatment for 3/269 (1.1%)

patients in the daptomycin group and 2/293 (<1%) in the comparator group. In the daptomycin group, 2/269 patients were discontinued from treatment due to drug-related rash. One other patient in the daptomycin group experienced two febrile reactions thought to be drug-related, and the patient was discontinued from the study. Three patients in the daptomycin group were discontinued from study treatment due to unrelated events including diagnosis of osteomyelitis, sepsis, and pulmonary embolism. In the comparator group, 2/293 patients were discontinued from treatment due to drug-related rash. Three patients in the comparator group were discontinued from study treatment due to unrelated events including stroke, necrotizing fascitis, pulmonary edema, and bronchopneumonia.

Medical Officer Comment
The narratives and CRFs of all patients discontinuing study drug were reviewed by the Medical Officer. The Medical Officer agrees with the investigator's assessment of causality. It is of interest that two of the patients in the daptomycin arm had elevations of CPK during their hospital course. Patient 0304100063 had elevation of serum CPK to a maximum of 527 U/L on d1P which resolved by d26P; he did receive intramuscular injections during his hospital stay. Patient 0409100054 was discontinued from the study medication due to sepsis; she had an elevation of serum CPK to a maximum of 1038 U/L on d2P after 3 doses of daptomycin, but no follow-up serum CPK was obtained. The Medical Officer considers these elevations in serum CPK to be possibly related to study drug, but the elevations may also be attributable to intramuscular injections and sepsis, respectively.

Serious adverse events - Study DAP-SST-9901
Table 46 below presents treatment-emergent SAEs by MedDRA SOC and includes all events that were reported in ≥1% of patients in either drug exposure group. A total of 43 patients experienced one or more SAEs. There was no difference between the arms in the overall incidence of any SAE. A total of 26/269 (9.7%) of patients in the daptomycin arm and 17/293 (5.8%) in the comparator group experienced SAEs during the study. The only SAE with a reported incidence of ≥1% of patients was cellulitis occurring in 3/269 (1.1%) patients in the daptomycin arm and none of the patients in the comparator arm. All other serious events were reported in < 1% of patients in both arms. Only one SAE, eosinophilia, in the daptomycin arm, was assessed as possibly related to study treatment. The majority of reported SAEs were assessed as severe in intensity including 17/36 (47.2%) SAEs reported in the 26 patients with SAEs in the daptomycin group and 10/19 (52.6%) SAEs reported in the 17 patients in the comparator group who experienced serious events. For about half the patients in each drug exposure group who experienced SAEs, at least one SAE started while on treatment. For one-third of the patients in each drug exposure group, their SAE(s) started 5 to 21 days after the end of treatment. By the sponsor's analysis, there was no difference in SAEs between arms in the demographic subgroups of sex, age, and race.

Table 46: Treatment-Emergent SAEs by System Organ Class Including the Most Commonly Reported Events (≥1% of Patients) in Study DAP-SST-9901 (Population: Safety)

System Organ Class Preferred Term	Daptomycin N = 269	Comparator N = 293	95% CI[1]
Total Number of Patients with SAEs	26 (9.7%)	17 (5.8%)	(-8.3, 0.6)
Infections and Infestations	9 (3.3%)	7 (2.4%)	(-3.7, 1.8)
Cellulitis	3 (1.1%)	0	
Vascular Disorders	3 (1.1%)	6 (2.0%)	(-1.1, 3.0)
Cardiac Disorders	3 (1.1%)	2 (< 1%)	
Skin & Subcutaneous Tissue Disorders	3 (1.1%)	2 (< 1%)	
General Disorders/Administration Site Conditions	4 (1.5%)	0	

[1] Two sided 95% CI around difference in proportions of AEs (comparator daptomycin) using normal approximation to the binomial, calculated at the body system level only if reported in ≥2% of patients.

Medical Officer Comment

Although the numbers are small, it appears that there were higher number of unique treatment emergent SAEs in women in the daptomycin arm (24/119; 20.2%) than in the comparator arm (5/133; 3.8%). This difference between treatment arms in females appeared to be present in all SOCs.

The Medical Officer reviewed the narratives and CRFs for all patients in the daptomycin and comparator arms who had SAEs reported. The Medical Officer agrees with the assessment of relationship to study drug as given by the investigator; most SAEs appeared to be related to the patient's underlying illness.

Deaths - Study DAP-SST-9901

A total of 8 patients died during study DAP-SST-9901, including 6/269 (2.2%) patients in the daptomycin group and 2/293 (<1%) in the comparator group. None of the deaths were judged by the investigator to be related to study treatment. Table 47 below presents a listing of the eight patients who died. Six patients were male. The primary site of infection was a diabetic ulcer in 4/8 (50%) patients; with wound infection, abscess, infected ulcer (not diabetic), and other infection occurring in one of each of the other 4 patients. Four of the patients were reported as discontinuing treatment due to the death (or AE associated with death); all had received ≤ 6 days of treatment. Three patients had successfully completed therapy; two on the day prior to death and one 10 days before. One patient was judged a treatment failure and switched to non-study medication 6 days before death. The causes of death in these 8 patients appeared to be directly related to pre-existing underlying conditions. Four of the 8 patients were > 65 years of age; 7 had complicating medical conditions. All 4 of the patients with known cardiac disease died of complications of heart failure or infarction. Three other patients had DM; one died with sepsis and worsening hyperglycemia, one died of hypoglycemic coma, and one died with a probable cerebrovascular infarct. The remaining patient had recently had surgery and died of a pulmonary embolism.

Table 47: List of Patients who Died in Study DAP-SST-9901

Patient	Gender	Age	Complicating Medical History	Infection Diagnosis	Pathogen	SIRS (Y/N)	Days of i.v. Rx	Day of Death	Cause of Death	Relationship
Daptomycin										
0249100002	M	80	Diabetes, Bedridden, Senile dementia	Infected Diabetic Ulcer	None isolated	Yes	7	1P	Probable CVA	Not related
0303100003	F	45	Diabetes, WBC >15,000	Infected Diabetic Ulcer	*S. aureus, S. agalactiae*	No	9	6P	Sepsis, worsening of diabetes	Not related
0313100001	M	47	Diabetes, Anemia, Cardiac failure, Gross edema	Infected Diabetic Ulcer	*S. aureus, E. faecalis*	Yes	6	0P	Anemia, GI bleed, hypokalemia, pulmonary edema	Not related
0410100067	F	78	+ Blood culture, WBC > 15,000, S/P surgery	Wound Infection	*E. faecalis*	Yes	4	1P	Pulmonary embolism	Not related
0410100075	M	72	WBC > 15,000, IHD, Prior MI, Leukemia	Infected Ulcer (not Diabetic)	*S. aureus*	Yes	7	10P	Myocardial infarction	Not related
0501100042	M	71	Hypertension Cardiac failure	Abscess	None isolated	Yes	6	1P	Cardiopulmonary insufficiency	Not related
Comparator										
0302100080	M	63	+ Blood culture, Hypertension, CHF	Other: lower leg infection	*S. aureus, S. pyogenes*	Yes	2	1P	Heart failure, stroke (not confirmed)	Not related
0313100002	M	57	Diabetes	Infected Diabetic Ulcer	*S. constellatus, E. faecalis*	No	11	1P	Hypoglycemic coma	Not related

Medical Officer Comment
The narratives and CRFs of all patients who died during study DAP-SST-9901 were reviewed by the Medical Officer. The Medical Officer agrees that in no case did the cause of death appear to be study drug. However, in several of these cases, it is difficult to confirm the diagnosis given by the investigator by the data presented in the CRF and narrative. Patients 0249100002 and 0302100080 had a cerebrovascular accident (CVA) as their presumed cause of death, but no imaging studies or autopsies were performed to confirm this etiology. Patients 0410100067 and 0501100042 have pulmonary embolism as a cause of death, but no imaging study or autopsy were done to confirm this. A higher death rate in the daptomycin arm is worthy of concern, but it appears unlikely to be of clinical significance regarding daptomycin toxicity, since no death was attributable to study drug and the numbers of deaths is quite small and this higher death rate in the daptomycin arm is not replicated in study DAP-SST-9801.

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

Cubist conducted two controlled clinical trials, DAP-CAP-00-05 and DAP-CAP-00-08, of essentially identical design to evaluate daptomycin in the treatment of moderate to severe CAP due to *Streptococcus pneumoniae*, including penicillin-resistant strains. Each study was a randomized, multicenter, multinational, double-blinded, parallel group active treatment controlled trial using a dosage of 4 mg/kg q24h. The comparator in each trial was ceftriaxone 2 g q24h. At the discretion of the investigator, adjunctive treatment with aztreonam could be given for suspected Gram-negative organisms. The duration of therapy was 5 to 14 days, followed by Test-of-Cure and Post-Study visits conducted 7 to 14 and 21 to 28 days, respectively, after the last dose of study drug. Men and women who were 18 years of age or older and had pneumonia which required hospitalization and intravenous therapy for at least 5 days were eligible for the study. The infection must have been known or suspected to be due, at least in part, to Gram-positive bacteria. Patients previously treated with potentially effective anti-infective agents for more than 24 hours (or one dosing day) within 72 hours of enrollment were excluded. Protocol DAP-CAP-00-05 (with investigators in US, Europe, Canada, Australia, South America, and New Zealand) completed enrollment of a total of 714 patients in October, 2000. After completion of the study, the sponsor's analysis indicated that daptomycin did not meet the predetermined criteria for non-inferiority (which specified that the upper bound of the 95% CI for the difference in clinical success between the comparator and daptomycin be <10%) in any of the populations analyzed. Further, in multiple analyses of the Clinically Evaluable (CE) population using several different outcome measures, the success rate of the daptomycin treatment group was statistically significantly lower than that for the ceftriaxone group. The absolute observed difference between the treatment groups was greater for subgroups with more severe infection. Taken together, these results suggested that the lower success rate observed for daptomycin compared with ceftriaxone in the treatment of CAP is clinically meaningful. The lower success rate with daptomycin was also

reflected in an increased rate of AEs. These AEs were potentially caused by daptomycin's demonstrated lack of efficacy. Specifically, AEs related to the respiratory or cardiovascular systems or to host responses known to be associated with acute bacterial pneumonia may be associated with lack of efficacy rather than direct toxic effects of daptomycin. At the time the results of study DAP-CAP-00-05 became known, Study DAP-CAP-00-08 (with investigators in South America, Europe, Mexico, and South Africa) was ongoing, with 202 of the planned 700 patients enrolled. Based on the results of DAP-CAP-00-05, Cubist suspended enrollment in Study DAP-CAP-00-08. Based on knowledge of the results of the CAP studies, the Agency requested that safety data from the two CAP studies be included as part of the integrated analysis of safety submitted with this NDA. In addition, an amendment to IND 57,693 was submitted which contained additional post-hoc analyses of clinical, microbiological, and nonclinical data pertaining to treatment of pulmonary infection with daptomycin, including further subgroup analyses of the DAP-CAP-00-05 and DAP-CAP-00-08 trials.

Medical Officer Comment
The two CAP trials were conducted using a dose of 4 mg/kg q24h, the same dose used in the two cSSSI trials. Since the CAP trials did not demonstrate equivalence of daptomycin to comparator, these trials have not been submitted for licensure. The Agency considers that an analysis of the CAP safety data base is important, not only to increase the safety data base available for the 4 mg/kg q24h dose, but also to examine more closely the issue of higher AEs including mortality in the daptomycin arm than in the comparator arm. The sponsor's postulate is that the higher AEs noted in the daptomycin arm were a result of the lower efficacy of daptomycin than comparator in the treatment of CAP. That is, some cardiorespiratory AEs which occurred on treatment were the result of progression of CAP. SAEs, deaths, and discontinuations due to AEs in the two CAP trials will be examined together with the aim of obtaining additional safety data on the 4 mg/kg q24h dose as well as examining specifically the excess AEs in the daptomycin arms.

Demographics - studies DAP-CAP-00-05/08
Table 48 presents a summary of the demographic characteristics for patients treated in the two CAP studies. Overall the treatment groups were well-balanced in terms of demographic characteristics. Patients in these studies ranged in age from 18 to 94 years of age with a mean of 55.2 years in the daptomycin group and 55.3 years in the comparator group. Just over 60% of patients in each group were <65 years of age. A total of 177/455 (38.9%) patients in the daptomycin group and 168/460 (36.5%) patients in the comparator group were age 65 or older; and 75/455 (16.5%) patients in the daptomycin group and 86/460 (18.7%) patients in the comparator group were age 75 or older. Over half the patients in each group were male. Caucasians accounted for 83.1% and 81.5% of the patients in the daptomycin and comparator groups, respectively.

Table 48: Demographic Characteristics, Community-Acquired Pneumonia Studies DAP-CAP-00-05/08 (Population: All Patients Treated)

Studies		DAP-CAP-00-05		DAP-CAP-00-08		Total CAP	
Characteristic	Statistic	Daptomycin (N=355)	Comparator (N=359)	Daptomycin (N=100)	Comparator (N=101)[a]	Daptomycin (N=455)	Comparator (N=460)
Age (yrs)	N	355	359	100	100	455	459
	Mean	55.1	54.9	55.6	56.6	55.2	55.3
	SD	19.1	18.8	20.2	19.5	19.4	19.0
	Median	56.0	56.0	58.0	56.0	57.0	56.0
	Min, Max	18,93	18,94	18,94	20,94	18,94	18,94
Age (yrs) N (%)							
18 - 39		86 (24.2)	81 (22.6)	29 (29.0)	21 (20.8)	115 (25.3)	102 (22.2)
40 - 64		133 (37.5)	148 (41.2)	30 (30.0)	41 (40.6)	163 (35.8)	189 (41.1)
>=65		136 (38.3)	130 (36.2)	41 (41.0)	38 (37.6)	177 (38.9)	168 (36.5)
>=75		57 (16.1)	61 (17.0)	18 (18.0)	25 (24.8)	75 (16.5)	86 (18.7)
Gender N (%)							
Male		218 (61.4)	219 (61.0)	44 (44.0)	47 (46.5)	262 (57.6)	266 (57.8)
Female		137 (38.6)	140 (39.0)	56 (56.0)	54 (53.5)	193 (42.4)	194 (42.2)
Race N (%)							
Caucasian		306 (86.2)	306 (85.2)	72 (72.0)	69 (68.3)	378 (83.1)	375 (81.5)
Black		34 (9.6)	38 (10.6)	1 (1.0)	2 (2.0)	35 (7.7)	40 (8.7)
Other		15 (4.2)	15 (4.2)	27 (27.0)	30 (29.7)	42 (9.2)	45 (9.8)

a. DAP-CAP-00-08 Patient Number 6020800001 did not have an age value

Medical Officer Comment

In study DAP-CAP-00-08 there were more 18-39 and >65 year old patients in the daptomycin arm than in the comparator arm; conversely, there were fewer 40-65 year old patients in the daptomycin arm than in the comparator arm. These differences are evened out somewhat when the two studies are combined. However, since differences in daptomycin AE rates were found by age group (≥65 years of age versus <65 years) these differences between study arms are worthy of note. When racial groups are examined, the arms in both studies are well balanced; there are more patients identified as Black or "other" in study DAP-CAP-00-08, reflective of the non-US population enrolled in this study.

Disposition - studies DAP-CAP-00-05/08

A summary of patient disposition in the CAP studies is presented in Table 49 below. A total of 915 patients were treated during the CAP studies; 455 received daptomycin and 460 received the comparator, ceftriaxone. Most patients in both treatment groups completed intravenous treatment as planned; however, more daptomycin-treated patients (106/455; 23.3%) than comparator patients (65/460; 14.1%) prematurely discontinued therapy. The most common reason for premature discontinuation in both treatment groups was "Clinical Failure" (44/455 [9.7%] of patients in the daptomycin group and 23/460 [5.0%] in the comparator group).

Table 49: Summary of Patient Disposition, Community-Acquired Pneumonia Studies DAP-CAP-00-05/08 (Population: All Patients Treated)

	DAP-CAP-00-05				DAP-CAP-00-08				Total CAP Studies			
	Daptomycin		Comparator		Daptomycin		Comparator		Daptomycin		Comparator	
Disposition	N	%	N	%	N	%	N	%	N	%	N	%
Treated	355		359		100		101		455		460	
Completed Therapy	271	76.3	305	85.0	78	78.0	90	89.1	349	76.7	395	85.9
Prematurely Discontinued	84	23.7	54	15.0	22	22.0	11	10.9	106	23.3	65	14.1
Therapy												
Adverse Event	8	2.3	10	2.8	7	7.0	2	2.0	15	3.3	12	2.6
Clinical (Symptomatic) Failure	35	9.9	21	5.8	9	9.0	2	2.0	44	9.7	23	5.0
Patient's Decision	6	1.7	8	2.2	4	4.0	1	1.0	10	2.2	9	2.0
Protocol Violation	7	2.0	2	0.6	1	1.0	3	3.0	8	1.8	5	1.1
Lost to Follow-up	2	0.6	0	0.0	0	0.0	1	1.0	2	0.4	1	0.2
Other	18	5.1	11	3.1	2	2.0	2	2.0	20	4.4	13	2.8
Death	15	4.2	10	2.8	6	6.0	2	2.0	21	4.6	12	2.6

Medical Officer Comment

More patients in both of the CAP clinical trials prematurely discontinued therapy in the daptomycin arm than in the comparator arm. Since the most common reason for premature discontinuation was clinical failure, the higher daptomycin discontinuation rate is not surprising, given the overall results of these clinical trial demonstrating that daptomycin is less effective than ceftriaxone in the treatment of moderate to severe CAP. The overall percentage of patients who discontinued therapy due to AEs was somewhat higher in the daptomycin arm, reflecting a small difference between arms in study DAP-CAP-00-08: 7/100 (7%) in the daptomycin arm versus 2/101 (2%) in the comparator arm discontinued due to AEs.

Overall adverse events - studies DAP-CAP-00-05/08

Table 50 below presents individual preferred terms by MedDRA SOC for AEs that were reported in ≥2% of patients within a study and in either study arm. Significantly more patients in the daptomycin arm (261/455; 57.4%) than in the comparator arm (229/460; 49.8%) experienced at least one AE in the CAP studies. SOCs in which significantly more daptomycin patients reported AEs were General Disorders and Administration Site Conditions and Infections and Infestations. In the Nervous System Disorders SOC, significantly more comparator patients than daptomycin patients reported AEs. The MedDRA SOC with the greatest numbers of reported AEs was Gastrointestinal Disorders; 86/455 (18.9%) daptomycin-treated patients and 86/460 (18.7%) comparator-treated patients reported AEs in this SOC.

Table 50: Adverse Events by System Organ Class Including the Most Commonly Reported Events (≥2% of Patients in any study group), Community- Acquired Pneumonia Studies DAP-CAP-00-05/08 (Population: All Patients Treated)

System Organ Class/ Preferred Term	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)	
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	95% CI
Total Number of Patients with at least one AE	199 (56.1)	181 (50.4)	62 (62.0)	48 (47.5)	261 (57.4)	229 (49.8)	(-14.1,-1.2)
Gastrointestinal disorders	62 (17.5)	63 (17.5)	24 (24.0)	23 (22.8)	86 (18.9)	86 (18.7)	(-5.2,4.9)
Abdominal pain NOS	3 (0.8)	7 (1.9)	0 (0.0)	3 (3.0)	3 (0.7)	10 (2.2)	
Abdominal pain upper	5 (1.4)	8 (2.2)	5 (5.0)	2 (2.0)	10 (2.2)	10 (2.2)	
Constipation	12 (3.4)	9 (2.5)	3 (3.0)	6 (5.9)	15 (3.3)	15 (3.3)	
Diarrhea NOS	10 (2.8)	18 (5.0)	7 (7.0)	6 (5.9)	17 (3.7)	24 (5.2)	
Nausea	13 (3.7)	22 (6.1)	6 (6.0)	5 (5.0)	19 (4.2)	27 (5.9)	
Vomiting NOS	7 (2.0)	12 (3.3)	2 (2.0)	3 (3.0)	9 (2.0)	15 (3.3)	
General disorders and administration site conditions	48 (13.5)	38 (10.6)	11 (11.0)	4 (4.0)	59 (13.0)	42 (9.1)	(-8.2,-0.2)
Chest pain NEC	6 (1.7)	2 (0.6)	4 (4.0)	0 (0.0)	10 (2.2)	2 (0.4)	
Injection site phlebitis	13 (3.7)	6 (1.7)	0 (0.0)	0 (0.0)	13 (2.9)	6 (1.3)	
Edema lower limb	9 (2.5)	7 (1.9)	2 (2.0)	2 (2.0)	11 (2.4)	9 (2.0)	
Infections and infestations	42 (11.8)	35 (9.7)	17 (17.0)	5 (5.0)	59 (13.0)	40 (8.7)	(-8.3,-0.3)
Herpes simplex	9 (2.5)	2 (0.6)	1 (1.0)	0 (0.0)	10 (2.2)	2 (0.4)	
Investigations	33 (9.3)	30 (8.4)	11 (11.0)	8 (7.9)	44 (9.7)	38 (8.3)	(-5.1,2.3)
ALT increased	10 (2.8)	10 (2.8)	5 (5.0)	1 (1.0)	15 (3.3)	11 (2. 4)	
AST increased	7 (2.0)	10 (2.8)	5 (5.0)	2 (2.0)	12 (2.6)	12 (2.6)	
Musculoskeletal, connective tissue and bone disorders	19 (5.4)	24 (6.7)	2 (2.0)	8 (7.9)	21 (4.6)	32 (7.0)	(-0.5,5.5)
Arthralgia	2 (0.6)	6 (1.7)	1 (1.0)	3 (3.0)	3 (0.7)	9 (2.0)	
Nervous system disorders	31 (8.7)	44 (12.3)	10 (10.0)	19 (18.8)	41 (9.0)	63 (13.7)	(0.4,8.5)
Dizziness (excl vertigo)	4 (1.1)	7 (1.9)	1 (1.0)	3 (3.0)	5 (1.1)	10 (2.2)	
Headache NOS	12 (3.4)	20 (5.6)	3 (3.0)	15 (14.9)	15 (3.3)	35 (7.6)	
Insomnia NEC	5 (1.4)	15 (4.2)	2 (2.0)	0 (0.0)	7 (1.5)	15 (3.3)	
Vascular disorders	16 (4.5)	16 (4.5)	9 (9.0)	11 (10.9)	25 (5.5)	27 (5.9)	(-2.7,3.0)
Hypertension NOS	3 (0.8)	7 (1.9)	1 (1.0)	2 (2.0)	4 (0.9)	9 (2.0)	

Note: Patients reporting more than one adverse event within a system organ class (SOC) are counted only once in the total line for that SOC. Patients reporting more than one adverse event coded to the same preferred term are counted only once in the line for that preferred term.

Adverse events by intensity - studies DAP-CAP-00-05/08

The majority of AEs were mild (193/455 or 42.4% of daptomycin-treated patients; 166/460 or 36.1% of comparator-treated patients) or moderate (119/455 or 26.2% of daptomycin-treated patients; 109/460 or 23.7% of comparator-treated patients) in intensity. AEs that were judged to be marked in intensity by the investigator were reported in 49/455 (10.8%) of daptomycin-treated patients and 37/460 (8.0%) of comparator-treated patients. In general, the frequency and

distribution of severe events within each SOC were similar between the two arms; the biggest differences were seen in the Cardiac Disorders SOC (13/455 or 2.9% in daptomycin-treated patients; 4/460 or 0.9% in comparator-treated patients) and the Respiratory, Thoracic and Mediastinal Disorders SOC (12/455 or 2.6% of daptomycin-treated patients; 4/460 or 0.9% of comparator-treated patients). The Cardiac Disorders (see figures above) and Infections and Infestations (9/455 or 2% of daptomycin-treated patients; 9/460 or 2% of comparator-treated patients) SOCs included the largest number of severe AEs.

Adverse events by subgroups - studies DAP-CAP-00-05/08

The incidence of AEs was higher in all age groups in the daptomycin arm than in the comparator arm; this difference was largest in the <65 year old age group (151/273; 54.3% versus 132/291; 45.4%, in daptomycin-treated versus comparator-treated, respectively). There was no difference in AEs reported by gender in the daptomycin arm; in the comparator arm, AEs were more frequent in females (278/522; 53.3%) than in males (309/663; 46.6%). In both arms patients in the racial group described as "Other" had higher rates of AEs than other racial groups; the difference between arms, however, was small. In the daptomycin arm, there was a higher number of AEs 111/177 (62.7%) in patients ≥65 years of age compared with the number of AEs 151/278 (54.3%) in patients <65 years of age.

Drug-related adverse events - studies DAP-CAP-00-05/08

Drug-related AEs with an incidence of ≥1% by SOC and preferred term are included in Table 51 below.

Table 51: Drug-Related Adverse Events Occurring in ≥1% of Patients by System Organ Class and Preferred Term, Community-Acquired Pneumonia Studies DAP-CAP-00-05/08 (Population: All Patients Treated)

System Organ Class/ Preferred Term	DAP-CAP-00-05		DAP-CAP-00-08		Total CAP Studies	
	Daptomycin	Comparator	Daptomycin	Comparator	Daptomycin	Comparator
	(N=355)	(N=359)	(N=100)	(N=101)	(N=455)	(N=460)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Total Number of Patients with at Least One Related AE	69 (19.4)	61 (17.0)	23 (23.0)	23 (22.8)	92 (20.2)	84 (18.3)
Blood and lymphatic system disorders	5 (1.4)	3 (0.8)	5 (5.0)	5 (5.0)	10 (2.2)	8 (1.7)
Anemia NOS	2 (0.6)	0 (0.0)	1 (1.0)	0 (0.0)	3 (0.7)	0 (0.0)
Eosinophilia (excl pulmonary)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.2)	0 (0.0)
Leucopenia NOS	0 (0.0)	2 (0.6)	0 (0.0)	1 (1.0)	0 (0.0)	3 (0.7)
Reticulocytosis	0 (0.0)	0 (0.0)	2 (2.0)	0 (0.0)	2 (0.4)	0 (0.0)
Secondary polycythemia	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.2)	0 (0.0)
Thrombocytosis	3 (0.8)	0 (0.0)	3 (3.0)	4 (4.0)	6 (1.3)	4 (0.9)
Cardiac disorders	4 (1.1)	1 (0.3)	2 (2.0)	0 (0.0)	6 (1.3)	1 (0.2)
Angina pectoris	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.2)	0 (0.0)
Arrhythmia NOS	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.2)	0 (0.0)
Extrasystoles NOS	3 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.7)	0 (0.0)
Tachyarrhythmia	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.2)	0 (0.0)
Ear and labyrinth disorders	1 (0.3)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.2)	1 (0.2)

Vertigo NEC	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.2)
Gastrointestinal disorders	20 (5.6)	23 (6 4)	7 (7.0)	7 (6.9)	27 (5.9)	30 (6.5)
Abdominal distension	2 (0.6)	0 (0.0)	0 (0.0)	1 (1.0)	2 (0.4)	1 (0.2)
Abdominal pain upper	1 (0.3)	0 (0.0)	1 (1.0)	0 (0.0)	2 (0.4)	0 (0.0)
Constipation	1 (0.3)	3 (0.8)	0 (0.0)	2 (2.0)	1 (0.2)	5 (1.1)
Diarrhea NOS	6 (1.7)	8 (2.2)	3 (3.0)	1 (1.0)	9 (2.0)	9 (2.0)
Dyspepsia	1 (0.3)	3 (0.8)	0 (0.0)	1 (1.0)	1 (0.2)	4 (0.9)
Gastritis NOS	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.2)	0 (0.0)
Gastritis aggravated	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.2)	0 (0.0)
Nausea	6 (1.7)	5 (1.4)	2 (2.0)	3 (3.0)	8 (1.8)	8 (1.7)
Vomiting NOS	2 (0.6)	7 (1.9)	0 (0.0)	2 (2.0)	2 (0.4)	9 (2.0)
General disorders and administration site conditions	11 (3.1)	10 (2.8)	1 (1.0)	1 (1.0)	12 (2.6)	11 (2.4)
Chest pain NEC	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.2)
Injection site pain	1 (0.3)	2 (0.6)	1 (1.0)	0 (0.0)	2 (0.4)	2 (0.4)
Investigations	20 (5.6)	14 (3.9)	7 (7.0)	5 (5.0)	27 (5.9)	19 (4.1)
ALT increased	10 (2.8)	7 (1.9)	3 (3.0)	1 (1.0)	13 (2.9)	8 (1.7)
AST increased	6 (1.7)	6 (1.7)	3 (3.0)	1 (1.0)	9 (2.0)	7 (1.5)
Blood alkaline phosphatase NOS increased	2 (0.6)	1 (0.3)	1 (1.0)	1 (1.0)	3 (0.7)	2 (0.4)
Blood CPK increased	4 (1.1)	1 (0.3)	2 (2.0)	1 (1.0)	6 (1.3)	2 (0.4)
Blood glucose increased	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.2)	0 (0.0)
Blood LDH increased	1 (0.3)	1 (0.3)	1 (1.0)	0 (0.0)	2 (0.4)	1 (0.2)
International normalized ratio increased	0 (0.0)	1 (0.3)	2 (2.0)	2 (2.0)	2 (0.4)	3 (0.7)
Metabolism and nutrition disorders	2 (0.6)	3 (0.8)	1 (1.0)	0 (0.0)	3 (0.7)	3 (0.7)
Anorexia	1 (0.3)	0 (0.0)	1 (1.0)	0 (0.0)	2 (0.4)	0 (0.0)
Musculoskeletal, connective tissue and bone disorders	6 (1.7)	2 (0.6)	1 (1.0)	2 (2.0)	7 (1.5)	4 (0.9)
Myalgia	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.2)
Nervous system disorders	10 (2.8)	6 (1.7)	4 (4.0)	9 (8.9)	14 (3.1)	15 (3.3)
Depressed level of consciousness	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.2)	0 (0.0)
Dizziness (excl vertigo)	1 (0.3)	2 (0.6)	0 (0.0)	2 (2.0)	1 (0.2)	4 (0.9)
Headache NOS	5 (1.4)	2 (0.6)	2 (2.0)	9 (8.9)	7 (1.5)	11 (2.4)
Paresthesia NEC	1 (0.3)	0 (0.0)	1 (1.0)	0 (0.0)	2 (0.4)	0 (0.0)
Psychiatric disorders	2 (0.6)	1 (0.3)	1 (1.0)	2 (2.0)	3 (0.7)	3 (0.7)
Anxiety NEC	2 (0.6)	0 (0.0)	1 (1.0)	2 (2.0)	3 (0.7)	2 (0.4)
Confusion	0 (0.0)	1 (0.3)	1 (1.0)	0 (0.0)	1 (0.2)	1 (0.2)
Reproductive system and breast disorders	1 (0.3)	0 (0.0)	1 (1.0)	0 (0.0)	2 (0.4)	0 (0.0)
Vaginal discharge	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.2)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	3 (0.8)	0 (0.0)	1 (1.0)	1 (1.0)	4 (0.9)	1 (0.2)
Bronchospasm NOS	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.2)
Respiratory failure	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.2)	0 (0.0)
Skin & subcutaneous tissue disorders	9 (2.5)	3 (0.8)	3 (3.0)	3 (3.0)	12 (2.6)	6 (1.3)
Dermatitis NOS	2 (0.6)	1 (0.3)	2 (2.0)	0 (0.0)	4 (0.9)	1 (0.2)
Ecchymosis	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)	0 (0.0)	2 (0.4)
Urticaria NOS	2 (0.6)	0 (0.0)	1 (1.0)	1 (1.0)	3 (0.7)	1 (0.2)
Vascular disorders	1 (0.3)	2 (0.6)	1 (1.0)	6 (5.9)	2 (0.4)	8 (1.7)

Hypotension NOS	0 (0.0)	0 (0.0)	1 (1.0)	3 (3.0)	1 (0.2)	3 (0.7)
Phlebitis NOS	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.0)	0 (0.0)	3 (0.7)

a Includes events assessed as probably or possibly related to study treatment.
The highest relationship (probable > possible > unrelated) is tabulated.

The majority of AEs in the two CAP studies were assessed as unrelated to study drug by the investigators. A higher percentage of patients in the comparator groups than in the daptomycin groups experienced at least one AE that was considered possibly or probably related to study treatment (92/455 or 20.2% in daptomycin-treated patients and 84/460 or 18.3% in comparator-treated patients). Gastrointestinal Disorders SOC had the most drug-related AEs (27/455 or 5.9% in daptomycin-treated patients and 30/460 or 6.5% in comparator-treated patients).

Adverse events leading to discontinuation of treatment - studies DAP-CAP-00-05/08

As shown in Table 52 below, a total of 34 patients in the two CAP studies, 19/455 (4.2%) patients in the daptomycin group and 15/460 (3.3%) patients in the comparator group, were discontinued from study drug due to AEs. The events leading to discontinuation were reported as possibly or probably related to study treatment for 3/19 (15.8%) daptomycin-treated patients and 3/15 (20%) comparator-treated patients. The MedDRA SOC with the most AEs causing discontinuation was "Infections and Infestations" with 5/455 (1.1%) patients in the daptomycin group and 3/460 (<1%) patients in the comparator group discontinuing due to AEs in this SOC. The only MedDRA preferred terms reported in more than one patient were: pneumonia aggravated (4 daptomycin and 1 comparator), septic shock (2 comparator), and respiratory failure (4 daptomycin, 1 comparator). In study CAP-00-05, 3 patients (1/455 or <1% daptomycin-treated, 2/460 or <1% comparator-treated) discontinued due to AEs reported as possibly or probably related to study treatment. One patient in the daptomycin group discontinued due to acute respiratory insufficiency leading to coma that was assessed as possibly related to study treatment. One patient in the comparator group discontinued due to drug-related neutropenia, and one patient in the comparator group discontinued due to a drug-related allergic reaction. In the daptomycin group of study CAP-00-08, one patient discontinued due to severe respiratory failure assessed as possibly related to treatment. In the comparator group of that study, one patient discontinued from treatment due to drug-related severe urticaria.

Table 52: Adverse Events Leading to Withdrawal, Community-Acquired Pneumonia Studies DAP-CAP-00-05/08 (Population: All Patients Treated)

System Organ Class/ Preferred Term	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)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total Number of Patients with at Least One AE	11	(3.1)	11	(3.1)	8	(8.0)	4	(4.0)	19	(4.2)	15	(3.3)
Blood and lymphatic system disorders	0	0	1	(0.3)	0	0	1	(1.0)	0	0	2	(0.4)
Anemia NOS	0	0	0	0	0	0	1	(1.0)	0	0	1	(0.2)
Neutropenia	0	0	1	(0.3)	0	0	0	0	0	0	1	(0.2)
Cardiac disorders	4	(1.1)	1	(0.3)	0	0	0	0	4	(0.9)	1	(0.2)
Cardiac failure NOS	1	(0.3)	0	0	0	0	0	0	1	(0.2)	0	0
Cardio-respiratory arrest	1	(0.3)	0	0	0	0	0	0	1	(0.2)	0	0
Cardiopulmonary failure	0	0	1	(0.3)	0	0	0	0	0	0	1	(0.2)
Left ventricular failure	1	(0.3)	0	0	0	0	0	0	1	(0.2)	0	0
Tachyarrhythmia	1	(0.3)	0	0	0	0	0	0	1	(0.2)	0	0
Gastrointestinal disorders	1	(0.3)	1	(0.3)	0	0	1	(1.0)	1	(0.2)	2	(0.4)
Abdominal pain NOS	1	(0.3)	0	0	0	0	0	0	1	(0.2)	0	0
Gastrointestinal hemorrhage NOS	0	0	0	0	0	0	1	(1.0)	0	0	1	(0.2)
Nausea	0	0	1	(0.3)	0	0	0	0	0	0	1	(0.2)
General disorders and administration site conditions	0	0	0	0	1	(1.0)	0	0	1	(0.2)	0	0
Rigors	0	0	0	0	1	(1.0)	0	0	1	(0.2)	0	0
Immune system disorders	0	0	1	(0.3)	0	0	0	0	0	0	1	(0.2)
Hypersensitivity NOS	0	0	1	(0.3)	0	0	0	0	0	0	1	(0.2)
Infections and infestations	2	(0.6)	2	(0.6)	3	(3.0)	1	(1.0)	5	(1.1)	3	(0.7)
Endocarditis bacterial NOS	1	(0.3)	0	0	0	0	0	0	1	(0.2)	0	0
Pneumonia aggravated	1	(0.3)	0	0	3	(3.0)	1	(1.0)	4	(0.9)	1	(0.2)
Septic shock	0	0	2	(0.6)	0	0	0	0	0	0	2	(0.4)
Investigations	1	(0.3)	1	(0.3)	0	0	0	0	1	(0.2)	1	(0.2)
Cardiac enzymes increased	1	(0.3)	0	0	0	0	0	0	1	(0.2)	0	0
HIV test positive	0	0	1	(0.3)	0	0	0	0	0	0	1	(0.2)
Neoplasms benign and malignant (including cysts and polyps)	0	0	1	(0.3)	0	0	0	0	0	0	1	(0.2)
Lung neoplasm NOS	0	0	1	(0.3)	0	0	0	0	0	0	1	(0.2)
Nervous system disorders	2	(0.6)	0	0	0	0	1	(1.0)	2	(0.4)	1	(0.2)
Anoxic encephalopathy	0	0	0	0	0	0	1	(1.0)	0	0	1	(0.2)
Cerebrovascular accident NOS	1	(0.3)	0	0	0	0	0	0	1	(0.2)	0	0
Coma NEC	1	(0.3)	0	0	0	0	0	0	1	(0.2)	0	0
Psychiatric disorders	1	(0.3)	1	(0.3)	0	0	0	0	1	(0.2)	1	(0.2)
Alcoholic withdrawal symptoms	1	(0.3)	0	0	0	0	0	0	1	(0.2)	0	0
Delirium tremens	0	0	1	(0.3)	0	0	0	0	0	0	1	(0.2)
Respiratory, thoracic and mediastinal disorders	3	(0.8)	1	(0.3)	3	(3.0)	0	0	6	(1.3)	1	(0.2)
Chronic obstructive airways disease exacerbated	1	(0.3)	0	0	0	0	0	0	1	(0.2)	0	0
Pleural effusion	1	(0.3)	0	0	0	0	0	0	1	(0.2)	0	0

Respiratory failure	1	(0.3)	1	(0.3)	3	(3.0)	0	0	4	(0.9)	1	(0.2)
Skin & subcutaneous tissue disorders	0	0	1	(0.3)	0	0	1	(1.0)	0	0	2	(0.4)
Dermatitis NOS aggravated.	0	0	1	(0.3)	0	0	0	0	0	0	1	(0.2)
Urticaria NOS	0	0	0	0	0	0	1	(1.0)	0	0	1	(0.2)
Vascular disorders	1	(0.3)	0	0	1	(1.0)	1	(1.0)	2	(0.4)	1	(0.2)
Arterial embolism limb	1	(0.3)	0	0	0	0	0	0	1	(0.2)	0	0
Hypotension NOS	0	0	0	0	1	(1.0)	0	0	1	(0.2)	0	0
Pulmonary embolism	0	0	0	0	0	0	1	(1.0)	0	0	1	(0.2)

Note: Patients reporting more than one adverse event within a system organ class (SOC) are counted only once in the total line for that SOC. Patients reporting more than one adverse event coded to the same preferred term are counted only once in the line for that preferred term.

Medical Officer Comment

The Medical Officer reviewed the narratives and CRFs of all patients in studies DAP-CAP-005 and DAP-CAP-008 who were discontinued from study drug treatment due to AEs. Three patients in the daptomycin arm had AEs resulting in discontinuation either possibly or probably attributable to daptomycin by the investigator. In the opinion of the Medical Officer, these three events are unrelated to daptomycin administration; brief case summaries of these three patients are presented below.

- Patient 0056500001 (study DAP-CAP-005) was a 68 year old female who developed increased cardiac enzymes which were considered to be possibly related to daptomycin. However, she received only one dose of study drug, and it appears from the CRF that her cardiac enzymes were elevated prior to study drug administration.
- Patient 0231500001 (study DAP-CAP-005) was a 81 year old male who developed respiratory insufficiency and coma after one dose of daptomycin. This AE was described by the investigator as possibly related to daptomycin. His hospital course appears to be more consistent with progressive CAP and subsequent respiratory failure.
- Patient 6353800001 (study DAP-CAP-008) was a 72 year old female who developed respiratory failure considered by the investigator to be possibly related to study drug. This patient's death appears to be due to progressive MSSA pneumonia, and not a result of drug effect.

Neutropenia, hypersensitivity, and urticaria were described as possibly/probably related AE's resulting in study drug discontinuation in the comparator arm; these AE's are consistent with the known AE profile of ceftriaxone.

Serious adverse events - studies DAP-CAP-00-05/08

Table 53 presents SAEs by MedDRA SOC and includes all events that were reported in ≥1% of patients in CAP studies DAP-CAP-005 or DAP-CAP-008 in either treatment arm. A total of 100 patients, 62/455 (13.6%) in the daptomycin group and 38/460 (8.3%) in the comparator group, experienced one or more SAEs. The only SAEs with a reported incidence of ≥1% of patients in either of the 2 studies were pneumonia aggravated, chronic obstructive airways disease exacerbated and respiratory failure, occurring in 6/455 (1.3%) patients, 5/455 (1.1%) and 7/455 (1.5%) patients, respectively, in the daptomycin arm and 2/460

(0.4%) patients, 1/460 (0.2%) patient and 1/460 (0.2%) patient, respectively, in the comparator arm. All other SAEs were reported in <1% of patients in both arms. In 4/100 patients with SAEs, three patients in the daptomycin arm and 1 patient in the comparator arm, the SAEs were considered drug-related. These included coma, tachyarrhythmia and respiratory failure in the daptomycin arm, and neutropenia in the comparator arm.

Table 53: Serious Adverse Events by System Organ Class Including the Most Commonly Reported Events (≥ 1% of Patients), Community- Acquired Pneumonia Studies DAP-CAP-00-05/08 (Population: All Patients Treated)

	DAP-CAP-00-05		DAP-CAP-00-08		Total CAP Studies	
System Organ Class/ Preferred Term	Daptomycin	Comparator	Daptomycin	Comparator	Daptomycin	Comparator
	(N=355)	(N=359)	(N=100)	(N=101)	(N=455)	(N=460)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Total Number of Patients with at Least One Serious AE	43 (12.1)	30 (8.4)	19 (19.0)	8 (7.9)	62 (13.6)	38 (8.3)
Cardiac disorders	13 (3.7)	4 (1.1)	3 (3.0)	2 (2.0)	16 (3.5)	6 (1.3)
Gastrointestinal disorders	0 (0.0)	3 (0.8)	1 (1.0)	1 (1.0)	1 (0.2)	4 (0.9)
General disorders and administration site conditions	1 (0.3)	1 (0.3)	2 (2.0)	0 (0.0)	3 (0.7)	1 (0.2)
Infections and infestations	12 (3.4)	10 (2.8)	8 (8.0)	3 (3.0)	20 (4.4)	13 (2.8)
Pneumonia aggravated	1 (0.3)	1 (0.3)	5 (5.0)	1 (1.0)	6 (1.3)	2 (0.4)
Neoplasms benign and malignant (including cysts and polyps)	3 (0.8)	4 (1.1)	2 (2.0)	0 (0.0)	5 (1.1)	4 (0.9)
Renal and urinary disorders	1 (0.3)	1 (0.3)	1 (1.0)	0 (0.0)	2 (0.4)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	10 (2.8)	3 (0.8)	5 (5.0)	0 (0.0)	15 (3.3)	3 (0.7)
Chronic obstructive airways disease exacerbated	5 (1.4)	1 (0.3)	0 (0.0)	0 (0.0)	5 (1.1)	1 (0.2)
Respiratory failure	3 (0.8)	1 (0.3)	4 (4.0)	0 (0.0)	7 (1.5)	1 (0.2)
Surgical and medical procedures	0 (0.0)	1 (0.3)	0 (0.0)	1 (1.0)	0 (0.0)	2 (0.4)
Vascular disorders	2 (0.6)	4 (1.1)	1 (1.0)	1 (1.0)	3 (0.7)	5 (1.1)

Medical Officer Comment

The differences in the occurrence of these SAEs between the two treatment groups may well be attributed to the inferior efficacy of daptomycin relative to comparator in this population with significant co-morbidity and/or severe baseline infections. The Medical Officer reviewed the patient narratives of all patients who had SAEs reported in the two CAP trials. The Medical Officer agrees with causality as determined by the Investigator.

Deaths - studies DAP-CAP-00-05/08

A total of 33 patients (21/455 or 4.6% of daptomycin-treated patients; 12/460 or 2.6% of comparator-treated patients) died during the CAP studies. All of the deaths appeared to be directly related to pre-existing underlying conditions, including the presenting condition of CAP, and all were assessed by the investigator as unrelated to study treatment. Among the 33 patients who died, 18 were male and 15 were female; 21 were ≥ 65 years of age and 12 were < 65 years

of age. Twenty-two (16 daptomycin-treated, 6 comparator-treated) of the 33 deaths occurred while patients were on study drug or up to three days after study drug had been stopped. The other 11 (5 daptomycin-treated, 6 comparator-treated) deaths occurred 4 to 51 days after treatment with study drug had stopped. Table 54 and Table 55 below list the patients who died in the daptomycin and comparator treatment groups, respectively. According to the sponsor's assessment, in study DAP-CAP-00-05 10/15 (67%) of the deaths in the daptomycin group were potentially related to lack of efficacy; in study DAP-CAP-00-08 2/6 (33%) deaths in the daptomycin group were potentially related to lack of efficacy. In study DAP-CAP-00-05, 60% of patients who died had severe underlying cardiac or respiratory conditions; all except one of the remaining patients had other serious preexisting underlying conditions. The patients in study DAP-CAP-00-05 who died also tended to enter the study with more serious CAP, in that 10/15 (67%) of the daptomycin patients who died and 4 /10 (40%) of ceftriaxone patients entered the study with Fine Score Grades IV or V. In study DAP-CAP-00-08 all six of the patients in the daptomycin arm who died entered the study with Fine Score Grade IV. Four of these six patients had serious underlying cardiac or respiratory preexisting conditions.

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Table 54: Listing of Daptomycin-treated Patients Who Died, Community-Acquired Pneumonia Studies DAP-CAP-00-05/08 (Population: All Patients Treated)

Patient ID	Age (yrs)	Sex	Total Dose (mgs)	Duration of Rx (Days)	Adverse Event (Verbatim)With an Outcome of Death	Start Day[a]	Stop Day[a]	Relationship
DAP-CAP-00-05								
0006500002	68	Male	2320	8	COPD Exacerbation	1P	1P	Not Related
0056500001	68	Female	160	1	Respiratory Failure Secondary to COPD Exacerbation	1P	2P	Not Related
0161500006	89	Female	1250	5	Heart Failure	0P	1P	Not Related
0161500007	73	Female	1800	9	Acute Renal Insufficiency	19P	21P	Not Related
0164500004	78	Male	3476	11	Empyema	1P	1P	Not Related
0178500003	60	Male	567	3	Sepsis	2	0P	Not Related
0203500005	76	Male	252	1	Worsening Respiratory Insufficiency	1P	30P	Not Related
0238500003	51	Male	480	2	Acute Cardiac Insufficiency	1P	1P	Not Related
0326500007	78	Male	1400	5	Congestive Heart Failure (Worsening)	2	1P	Not Related
0326500009	73	Male	5370	15	COPD Exacerbation	6P	7P	Not Related
0342500013	49	Male	380	1	Sudden Arrest of Breathing and Heart Rhythm	1P	1P	Not Related
0344500007	86	Male	1248	4	Cerebral Stroke	0P	0P	Not Related
0357500008	40	Female	828	3	Cardio-Respiratory Distress	0P	0P	Not Related
0360500008	44	Female	1008	3	Diabetic Ketoacidosis	0P	0P	Not Related
0360500018	23	Female	618	3	Respiratory Failure	0P	1P	Not Related
DAP-CAP-00-08								
1803800007	69	Female	148	1	Respiratory Insufficiency Worsened	0P	3P	Not Related
6131800011	56	Male	1068	6	Dyspnea Worsening Pneumonia	0P	1P	Not Related
6135800008	71	Male	400	2	Respiratory Failure	15P	15P	Not Related
6357800004	77	Male	2400	10	Lung Cancer	1P	51P	Not Related
6365800003	83	Female	240	1	Cardiac Arrest	1P	1P	Not Related
6471800007	90	Female	520	2	Respiratory Failure	0P	0P	Not Related

Table 55: Listing of Comparator-treated Patients Who Died, Community-Acquired Pneumonia Studies DAP-CAP-00-05/08 (Population: All Patients Treated)

Patient ID	Age (yrs)	Sex	Duration of Rx	Adverse Event (Verbatim)With an Outcome Of Death	Start Day[a]	Stop Day[a]	Relationship
DAP-CAP-00-05							
0017500005	77	Female	1	Exacerbation of Pneumonia	13p	13P	Not Related
0161500014	56	Male	1	Septic Shock	0p	0P	Not Related
0163500004	77	Male	14	Cerebral Metastases	13	26P	Not Related
0169500006	43	Male	9	Multiple Metastases of Liver	1p	27P	Not Related
0215500001	73	Male	1	ARDS Septic Shock	5P 0P	10P 10P	Not Related Not Related
0216500001	69	Male	4	Sudden Death – Cardiac Arrest	5P	5P	Not Related
0239500004	42	Female	2	Breathing And Cardiac Insufficiency	1	0P	Not Related
0321500007	67	Female	1	Pulmonary Embolus	2P	2P	Not Related
0344500002	77	Male	3	Acute Pulmonary Embolism Suspected	1P	1P	Not Related
0360500001	50	Female	6	Septicemia with Septic Shock	18P	19P	Not Related
DAP-CAP-00-08							
1803800008	77	Female	1	Worsening of Pneumonia	1P	2P	Not Related
6017800001	37	Female	5	Pulmonary Embolism	0P	0P	Not Related

a In relative day format

Medical Officer Comment

The narratives and CRFs of all patients who died in studies DAP-CAP-005 and DAP-CAP-008 were reviewed by the Medical Officer. In study DAP-CAP-005, the Medical Officer agrees with the sponsor's conclusion that the 15 deaths in the daptomycin arm are not drug-related. In the opinion of the Medical Officer, none of the ceftriaxone deaths are related to study drug. In study DAP-CAP-008, the Medical Officer agrees that the six daptomycin deaths and two comparator deaths are not related to study drug.

Preclinical toxicity, including histopathology studies, were not predictive of cardiac muscle as a target of daptomycin toxicity. Of note, there is no signal from the cSSSI studies of excess deaths or cardiorespiratory AEs in the daptomycin arm. The sponsor has conducted further animal studies to clarify the unexpected low efficacy of daptomycin in the treatment of CAP, and found that daptomycin has relatively poor alveolar penetration with lower efficacy in inhalationally-acquired pneumonia as compared with hematogenous pneumonia. In conclusion, the excess deaths in the daptomycin arms of the CAP studies are most likely the result underlying illness and/or progression of CAP due to daptomycin's lower efficacy in this indication, rather than an expression of cardiac toxicity.

120-Day Safety Update

The sponsor submitted a 120-day safety update to the daptomycin NDA which covers the period June 1, 2002 through February 1, 2003. The sponsor has ongoing studies in endocarditis/bacteremia due to *S. aureus* (DAP-IE-01-02; enrolled 11 daptomycin-treated and 12 comparator-treated patients) and VRE (DAP-VRE-00-07; enrolled 48 patients). Both studies use a dose of 6 mg/kg q24h; the latter study was discontinued due to slow enrollment and was still blinded at the time of this submission. The third study DAP-SST-9801B (enrolled 16 daptomycin-treated patients) is a pharmacokinetic study in patients with cSSSI; enrollment is completed, and the study report is currently in progress. The fourth study is DAP-EAP-02-01 (enrolled 2 patients), a compassionate use protocol. Daptomycin was also available for emergency use.

In studies DAP-IE-01-02 and DAP-VRE-00-07, most patients reported at least one AE. In study DAP-SST-9801B, 6/16 (37.5%) of patients reported at least one AE. For each of these studies, the MedDRA SOC with the greatest percentages of reported treatment-emergent AEs was Gastrointestinal Disorders. No SAEs or deaths considered to be study drug related were reported in the daptomycin arm of these studies. One patient in study DAP-SST-9801B discontinued study drug due to elevations in multiple serum enzymes (AST, ALT, LDH, alkaline phosphatase), some of which were elevated at baseline. Three patients treated with daptomycin on an emergency-use basis discontinued treatment due to elevations in serum CPK (maximum of 700 U/L). Follow-up information is available for only one of these three patients, and symptoms/CPK elevations resolved in this patient.

LABORATORY ASSAYS

Measures of central tendency

Complicated skin/skin structure studies

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

CPK analyses

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

Community-acquired pneumonia studies

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

CPK outlier analysis

In the cSSSI studies, there were similar proportions of patients with on-therapy outlier values and similar on-therapy maximum values for all laboratory parameters between treatment arms except for CPK. Figure 1 shows the distribution of CPK values obtained on therapy in daptomycin and comparator patients in cSSSI trials. Table 56 shows the incidence of CPK elevations from baseline values for patients in the pooled cSSSI database. Although there were 534 daptomycin-treated patients and 558 comparator-treated patients in cSSSI

trials, not all patients had valid baseline or on-therapy CPK assessments. For purposes of these analyses, the upper limit of normal for CPK was 200 U/L.

Table 56 Incidence of patients with elevations of CPK from baseline in cSSSI studies DAP-SST-9801 And DAP-SST-9901

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

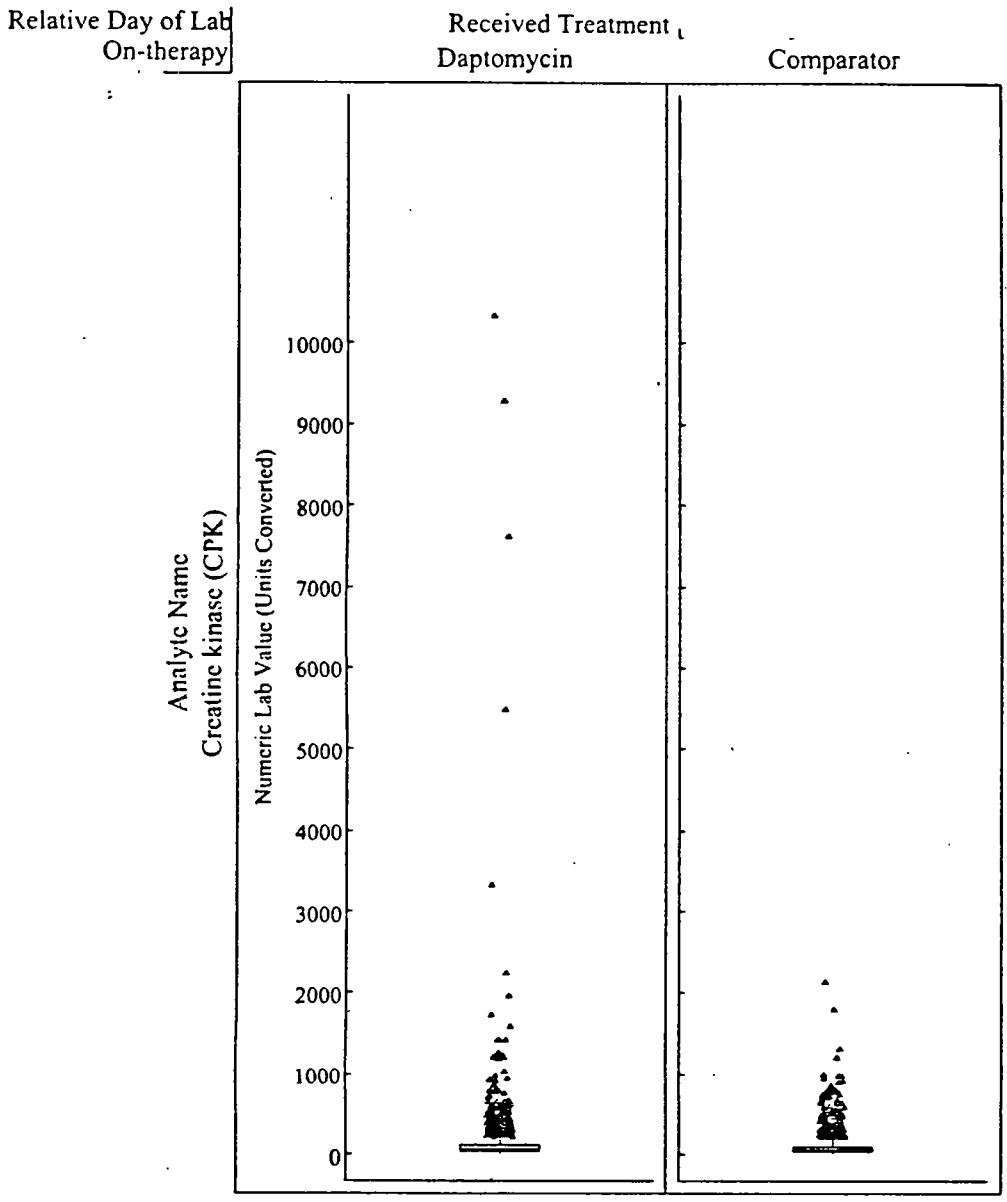

Figure 1. Distribution of CPK values in daptomycin and comparator-treated patients in cSSSI trials. Values are expressed in U/L. The narrow boxes at the bottom of each panel represent the interquartile range, with the median shown as a horizontal line within the box; red triangles represent outlier values.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

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

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

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

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

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

CPK elevations in the CAP studies did not show significant differences between daptomycin and comparator-treated patients overall (Table 57); however; there was a slight excess of higher CPK elevations in daptomycin-treated patients.

Table 57 Incidence of patients with elevations of CPK from baseline

in CAP studies DAP-CAP-00-05 and DAP-CAP-00-08				
Increase in CPK	All patients		Patients with normal CPK at baseline	
	Daptomycin (N=344)	Comparator (N=358)	Daptomycin (N=277)	Comparator (N=305)
>1x ULN	32 (9.3%)	27 (7.5%)	20 (7.2%)	26 (8.5%)
>2x ULN	15 (4.4%)	12 (3.4%)	7 (2.5%)	8 (2.6%)
>4x ULN	7 (2.0%)	5 (1.4%)	3 (1.1%)	2 (0.7%)
>5x ULN	6 (1.7%)	3 (0.8%)	3 (1.1%)	1 (0.3%)
>10x ULN	2 (0.6%)	1 (0.2%)	1 (0.3%)	0 (0.0%)

Liver function test outlier analyses

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

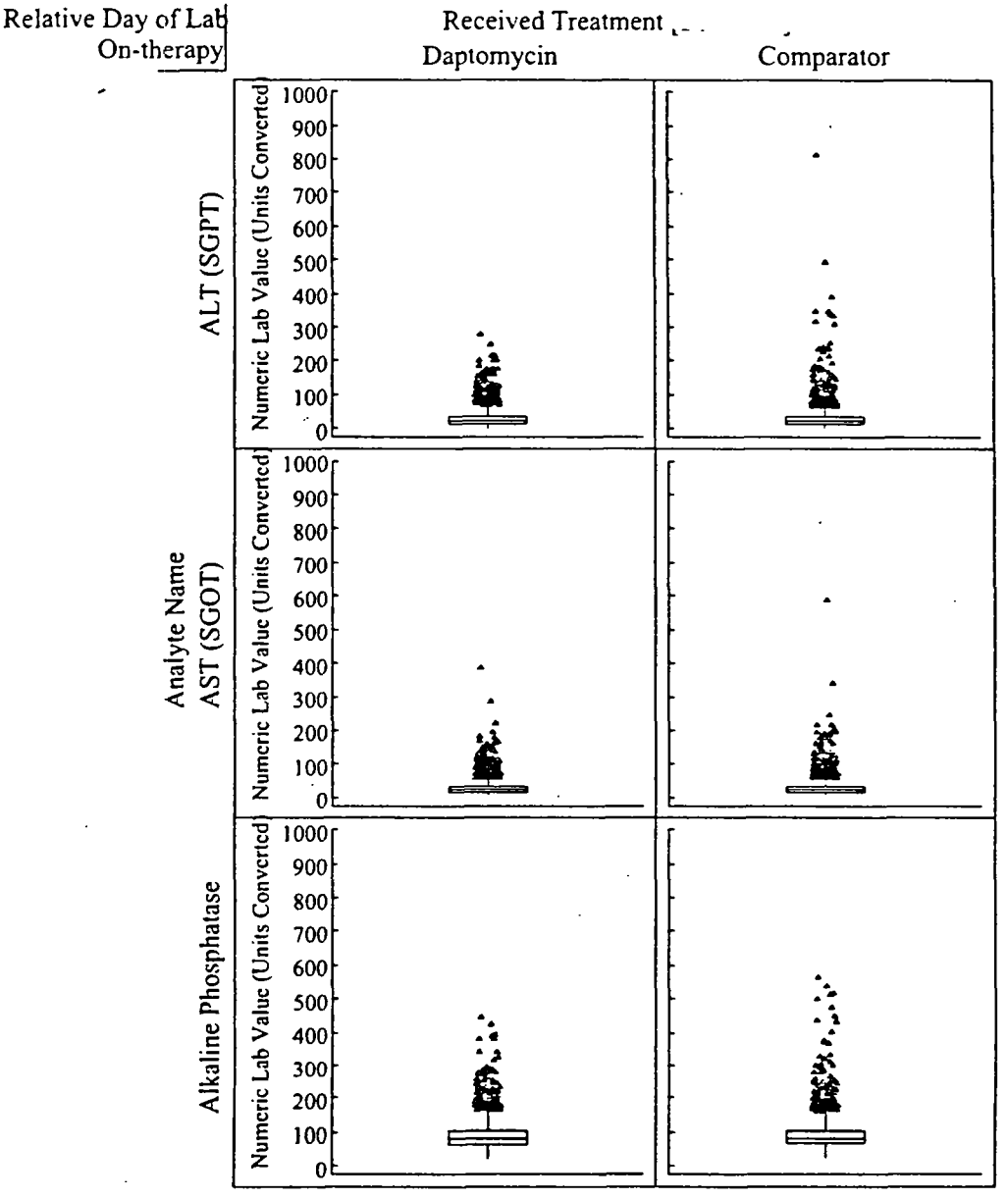

Figure 2. Distribution of ALT, AST, and alkaline phosphatase values in daptomycin and comparator-treated patients in cSSSI trials. Values are expressed in U/L. The narrow boxes at the bottom of each panel represent the interquartile range, with the median shown as a horizontal line within the box; red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

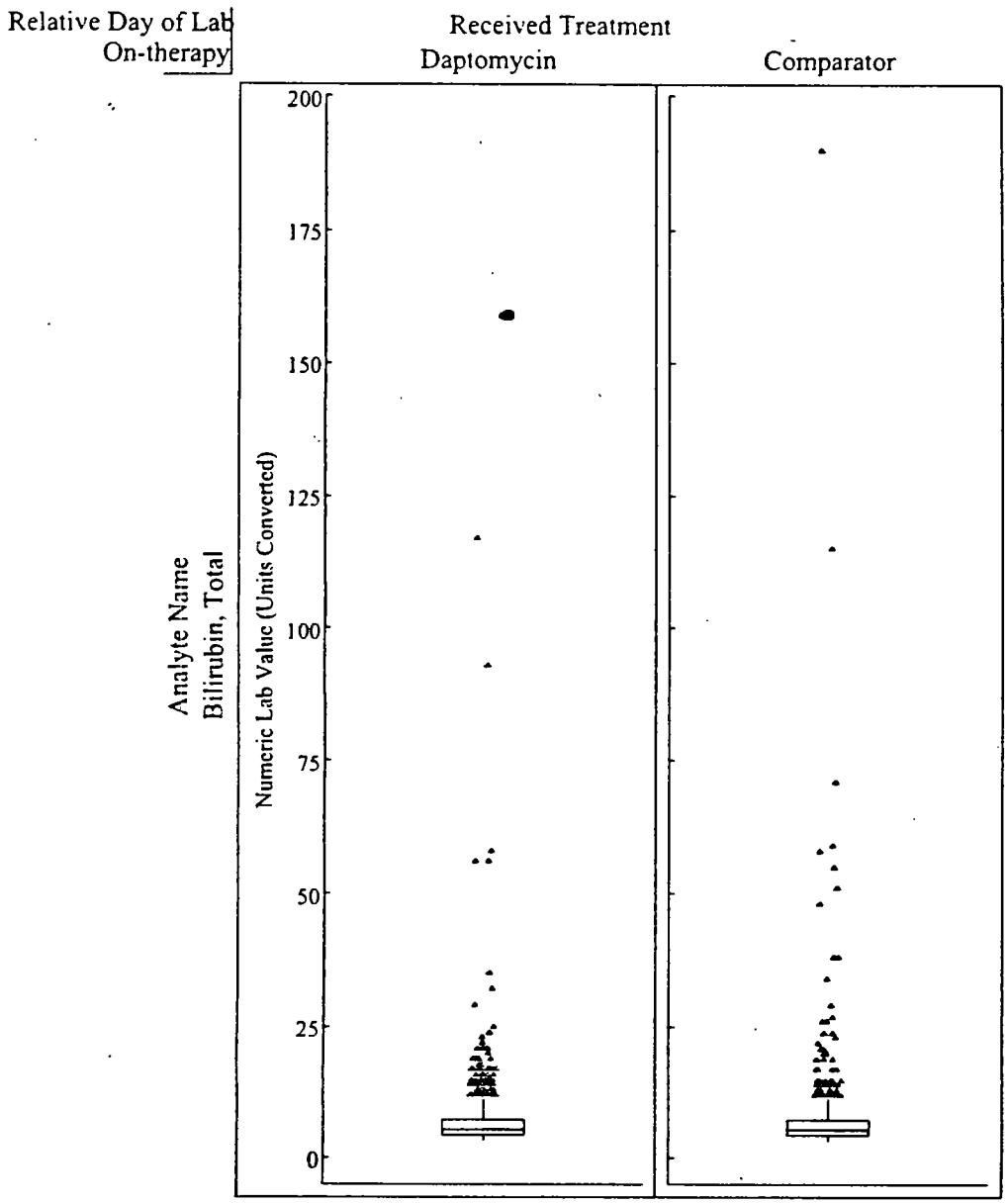

Figure 3. Distribution of total bilirubin values in daptomycin and comparator-treated patients in cSSSI trials. Values are expressed in µmol/L. The narrow boxes at the bottom of each panel represent the interquartile range, with the median shown as a horizontal line within the box; red triangles represent outlier values. Multiple lab values were obtained for each patient; therefore, the number of outliers may exceed the number of corresponding patients. Analyses were conducted using the maximum on-therapy value for each patient.

Drug-Drug Interactions

Because of the concern over possible additive myotoxicity, concomitant administration of HMG CoA-reductase inhibitors to patients receiving daptomycin was an exclusion in the cSSSI protocols. However, 34/534 (6.4%) daptomycin-treated patients did receive a statin or fibrate during these studies. There was no difference in the incidence of AEs, particularly CPK elevations, in daptomycin-treated patients who received a statin or fibrate versus those who did not, relative to comparator The incidence of CPK elevations was, however, increased in the CAP studies in daptomycin-treated patients who received a statin (1/34; 6.3%) compared with those daptomycin-treated patients who did not receive a statin (5/500; 1.0%); the small numbers involved make any conclusions difficult. A placebo-controlled pharmacokinetic study (DAP-STAT-01-10) in which 10 subjects received concomitant daptomycin and simvastatin did not show any increase in AEs in these subjects; however, the power of this study to detect a difference in specific AE rates was quite limited.

Drug-drug interaction studies were also performed with daptomycin and aztreonam, tobramycin, warfarin, and probenecid. No significant effect on the pharmacokinetics of either drug were noted when administered together, and no unexpected AEs were reported.

Drug-Demographic Interactions

The following studies were conducted by Cubist in demographic subgroups:

- Study DAP-GER-01-11 was a Cubist sponsored Phase I study in 12 geriatric subjects (age > 75 years); 12 subjects age 18-30 years served as controls. Daptomycin was administered in a single dose of 4 mg/kg. One geriatric subject had one adverse event (vomiting); three controls had three AEs (headache in two subjects and one rash).

Drug-Disease Interactions

The following Phase I studies were conducted by Cubist in subjects with renal insufficiency:

- DAP-00-01: 4 mg/kg single dose daptomycin was administered to subjects with varying degrees of renal insufficiency. Eight AEs were noted in four subjects of 29 enrolled: tachycardia, blister, arthralgia, muscle cramps, pain in limb, rhonchi, and wheezes. All were deemed unrelated to study drug by the investigator.
- DAP-MDRI-01-09: 4 or 6 mg/kg/day for 14 days or 6 mg/kg/day for 11 days in subjects with moderately impaired renal insufficiency (creatinine clearance<30-50). Two AEs were noted in 2 subjects of 8 enrolled: one elevation in serum CPK (peak of 8107 U/L on day 15 with return to normal by d21, subject asymptomatic, probably related per investigator) and one burning at IV site.
- DAP-MDRI-01-03: Loading dose of 4 or 6 mg/kg then 3 mg/kg on days 3, 5, 7, 9, 11, and 13 in subjects with ESRD on hemodialysis. Nine AEs were

described in five of seven subjects enrolled: Abdominal pain, vomiting, IV site burning, back pain, muscle cramps, dizziness, headache (two subjects), and elevated serum CPK (peak of 4990 U/L on d15 which returned to normal by several months after treatment, probably related according to the investigator).

The Phase I study B8B-MC-AVDD was conducted by Lilly in subjects with renal insufficiency; however, no safety data were included in the study report of this pharmacokinetic study.

Medical Officer Comment
The AE profile in subjects with renal impairment is consistent with the AE profile in subjects without renal dysfunction. Of note are the two subjects with renal dysfunction who developed significant elevations of serum CPK in the absence of symptoms. The incidence of this adverse event 2/44 (5%) appears to be somewhat higher that the incidence in the general population, although the numbers are small.

The following study was conducted by Cubist in subjects with hepatic impairment (Child-Pugh B):

- DAP-HEP-00-09: Subject were given a single dose of daptomycin 6 mg/kg. Four of the 10 hepatically impaired subjects enrolled had six AEs; none of the nine controls without hepatic impairment had AEs reported. The AEs reported were diarrhea, vomiting, dizziness, headache (two subjects), and somnolence.

Medical Officer Comment
The AEs reported in this group of subjects with Child-Pugh B hepatic insufficiency are typical of those seen in other Phase I studies with normal hepatic function.

Use in Pregnancy
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. No pregnant women have been studied in Phase III clinical trials, as pregnancy was an exclusion criterion for the cSSSI and CAP studies.

D. Adequacy of Safety Testing

The safety data base for the 4 mg/kg q 24 hour for 7 to 14 days dose is derived from the 534 patients from the two cSSSI studies, as well as from the 455 patient from the two CAP studies, for a total of 989 patients studied in Phase III. In addition, about 96 patients were studied at a dose of 4 mg/kg q24h for 7 to 14 days in Phase I and Phase II studies. This number of patients gives a reasonably robust safety data base for the 4 mg/kg q24h daptomycin dose. It is worthy of note that doses of daptomycin higher than 4 mg/kg/day have not yet been studied in completed Phase III controlled clinical trials, nor have durations of longer than 14 days. The sponsor has an ongoing trial in patients with infective endocarditis

(DAP-IE-01-02) which uses a daptomycin dose of 6 mg/kg q24h for 4 to 6 weeks, which will provide more safety information on this higher dose and longer duration. The clinical trial of daptomycin in the treatment of VRE infections (DAP-VRE-00-07) also uses a dose of 6 mg/kg q24h; this trial, however, was terminated due to slow enrollment.

Studies were performed to assess the pharmacokinetic parameters of daptomycin in renal insufficiency. Based on the results of these studies, a dose of 4 mg q48h is recommended for patients with a creatinine clearance <30mL/min, including those on dialysis. The protocols for the cSSSI studies dictated a dose adjustment in patients with creatinine clearance of 30-70 mL/min to 4 mg/kg loading dose followed by 3 mg/kg q36h. Patients with a creatinine clearance <30mL/min were to be excluded from these cSSSI studies. Despite some procedural concerns regarding the pharmacokinetic studies (please see Dr. Bonapace's Pharmacokinetics review), this data was considered sufficient to support the labeled daptomycin dose of 4 mg/kg q48h for patients with a creatinine clearance less than 30 mL/min. However, given the paucity of clinical safety data in patients with renal insufficiency, a Phase IV study will be conducted in patients with a creatinine clearance of 30-50 mL/min, and in those with a creatinine clearance of <30, including those on hemodialysis and chronic ambulatory peritoneal dialysis. This study will collect further safety and efficacy data on the use of daptomycin for the treatment of cSSSI in this patient population, as well as collecting further pharmacokinetic data in patients with renal insufficiency.

In a Phase I 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. Two of the five subjects experienced muscle pain and weakness as well as rapid elevations in CPK after about eight days of treatment. The effects resolved within a few days without sequelae after discontinuation of study medication. 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. Therefore, subsequent studies have used only once daily or less than once daily dosing.

E. Summary of Critical Safety Findings and Limitations of Data

The safety database comprised data on 602 daptomycin-treated subjects in Phase I studies, 349 daptomycin-treated patients in Phase II studies, and 989 patients in Phase III studies. There were no critical differences between the sponsor's and the Medical Officer's assessment of the safety data. Analysis of this data demonstrates that the most common toxicities of daptomycin are gastrointestinal disorders including nausea, constipation, diarrhea, and vomiting. Gastrointestinal AEs occurred in approximately equal frequencies in the daptomycin-treated patients (20.4%) and comparator-treated patients (19.9%). Preclinical animal studies predicted that skeletal muscle would be a target of daptomycin toxicity.

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 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 majority of cases for which follow-up is available, and there have been no reports of further complications such as rhabdomyolysis. Preclinical studies also predicted peripheral nerve as a target for daptomycin toxicity, although at a higher dose than that associated with skeletal muscle toxicity. 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. Nerve conduction deficits were also detected in a similar number of comparator subjects in these studies. In Phase III cSSSI and CAP studies 0.7% of daptomycin-treated patients and 0.7% of comparator-treated patients experienced paresthesias. There were no cases of new or worsening peripheral neuropathy diagnosed in any of these patients.

Although the sponsor did not submit efficacy data in support of the indication of CAP, 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 SAEs (3.5% in daptomycin-treated and 1.3% in comparator-treated) and respiratory SAEs (3.3% in daptomycin-treated and 0.7% in comparator-treated). These differences were attributable to the lower efficacy of daptomycin in the treatment of CAP, rather than toxicity; suboptimal alveolar penetration by daptomycin is the most likely explanation for this phenomenon, based on data from animal models. This is reflected in the failure of daptomycin to show noninferiority to comparator in these two CAP trials. Examination of the preclinical data, as well as the body of Phase I, Phase II, and Phase III studies does not suggest evidence of daptomycin cardiotoxicity. Data from the cSSSI trials indicated that SAEs and deaths did not appear to be causally associated with the use of daptomycin.

As described in depth in Dr. Nambiar's efficacy review "Appendix A", there were significant differences in the patient populations enrolled in the two pivotal cSSSI studies, as well as differences between the two studies of point estimates of efficacy, although equivalence to comparator was demonstrated in both studies. Patients in DAP-SST-9801 were older, more likely to have a history of DM and peripheral vascular disease, and more likely to receive adjunct surgical procedures and non-study antibiotics when compared with the patients in study DAP-SST-9901. In addition, they were more likely to receive vancomycin (instead of semisynthetic penicillins) in the comparator arm and they were more likely to have a resistant pathogen such as MRSA isolated. The clinical success rate was higher in both the daptomycin and comparator arms in study DAP-SST-9901 than in DAP-SST-9801 (in both the ITT and CE populations). The population in study

DAP-SST-9801 had the majority of patients enrolled from US centers. It is not surprising given these facts that patients in DAP-SST-9801 had a higher overall AE rate than did patients in study DAP-SST-9901. Since the patient population of study DAP-SST-9801 is more representative of patients who will be treated with daptomycin in the US, the higher AE rate as well as the lower efficacy rate will likely be encountered in practice.

The pharmacokinetics and risk profile of daptomycin appears similar in most special populations (by gender, obesity, or subjects with hepatic impairment) to the general population. In both of the cSSSI trials, treatment-emergent AEs were more common in patients ≥65 years old than in patients <65 years of age. However, pharmacokinetic studies in the elderly do not support a change in dose for those ≥65 years of age. Because of the limited size of these populations in the safety database, the safety profile in such populations may not be fully characterized, and post-marketing surveillance may provide additional information. The pharmacokinetics and risk profile of daptomycin appear similar in patients with renal impairment (creatinine clearance of ≥30 mL/min) to the general population. Further data are required to completely characterize the safety profile of daptomycin in renal insufficiency.

Major modifications of the daptomycin product label based on the safety review are described below.

INDICATIONS AND USAGE

- Add "Daptomycin is not indicated for the treatment of pneumonia".

WARNINGS

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

PRECAUTIONS

- Under the "Skeletal Muscle" section, rates of CPK elevations (as clinical AEs) among patients in cSSSI trials are added. No recommendation against instituting daptomycin in patients who have an elevated serum CPK at baseline, since the rate of CPK elevations or in such patients was not higher than in those receiving comparator. A recommendation to monitor CPK values weekly in patients receiving daptomycin, with more frequent monitoring in patients who develop CPK elevations was added; all patients receiving daptomycin should be monitored for the development of muscle pain or weakness, particularly of the distal extremities. The recommendations for daptomycin discontinuation were modified to the following: in patients with CPK elevations to >5x ULN who have symptoms, or in asymptomatic patients with elevations to >10x ULN. The threshold of 10x ULN is based on the recommendations contained in labeling for another class of myotoxic agents, HMG-CoA reductase inhibitors.

- Second paragraph: The sentence "In addition, concomitant administration of agents associated with rhabdomyolysis such as HMG-CoA reductase inhibitors should be avoided in patients receiving Cubicin" was added. Although drug interaction studies with daptomycin and simvastatin in 10 subjects 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.
- A description of the findings regarding neuropathy from preclinical, Phase I, Phase II, and Phase III studies was added, as well as the sentence: "Therefore, physicians should be alert to the possibility of signs and symptoms of neuropathy in patients receiving Cubicin."

GERIATRIC USE

- The following sentence was added: "In addition, treatment-emergent AEs were more common in patients ≥65 years old than in patients <65 years of age in both cSSSI studies."

ADVERSE EVENTS

- The second paragraph was modified to include AEs of severe intensity as well as to more accurately reflect the discontinuation rate due to AEs.
- A paragraph was added to describe the higher cardiorespiratory SAE rate as well as the higher mortality rate in daptomycin-treated patients in the CAP studies, as well as the lower efficacy of daptomycin than of ceftriaxone in the treatment of CAP.
- Under Laboratory Changes: A table was added showing rates of various degrees of CPK elevation in daptomycin and comparator-treated patients in the cSSSI studies.

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 III 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."

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