Table 10: Summary of Subject Disposition, Cubist-sponsored Phase I Studies (Population: All Subjects Treated)

	Single Dose				Multiple Dose				Total			
	Dapto		Comp		Dapto		Comp		Dapto			
Disposition	N	%	N	%	N	%	N	%	N	%	N	%
Treated	121		17		119		92		240		109	
Completed Therapy	118	97.5	16	94.1	110	92.4	90	97.8	228	95.0	106	97.2
Prematurely Discontinued	3	2.5	1	5.9	9	7.6	2	2.2	12	5.0	3	2.8
Therapy												
Adverse Event	1	0.8	0	0.0	4	3.4	2	2.2	5	2.1	2	1.8
Subject's Decision	2	1.7	1	5.9	0	0.0	0	0.0	2	0.8	1	0.9
Other	0	0.0	0	0.0	5	4.2	0	0.0	5	2.1	0	0.0

Adverse events - Cubist-sponsored Phase I studies

Similar proportions of subjects in the daptomycin and comparator treatment groups experienced at least one AE during the Cubist-sponsored Phase I studies (62/240 [25.8%] daptomycin; 32/109 [29.4%] comparator). No single AE occurred in more than 5% of the daptomycin subjects, while injection site pain occurred in 5.5% (6/109) and headache occurred in 5.5% (6/109) of subjects in the comparator groups. The majority of AEs were mild (53/240 or 22.1% in the daptomycin-treated subjects, 30/109 or 27.5% in the comparator-treated subjects) or moderate (13/240 or 5.4% in the daptomycin-treated subjects, 4/109 or 3.7% in the comparator-treated subjects) in intensity. Marked AEs occurred in 2/240 (<1%) of daptomycin-treated patients and no comparator-treated patients. Four AEs that were judged to be marked in intensity by the investigator were reported in three daptomycin subjects. These included facial palsy and syncope in two daptomycin subjects and diarrhea and vomiting in a third daptomycin subject. In single dose daptomycin studies 14.9% (18/121) of subjects experienced 1 or more AEs; no AE occurred in more than 5% of subjects. In multiple dose studies, 37% (44/119) of daptomycin-treated subjects experienced one or more AEs, and the most commonly occurring AEs (>5%) were injection site pain (7/119, 5.9%), injection site edema (6/119, 5%), increased blood creatine phosphokinase (6/119, 5%), and headache (6/119, 5%). Table 11 below gives the frequencies of all AEs in Cubist-sponsored Phase I studies.

Table 11: Adverse Events in Cubist-sponsored Phase I Studies (Population: All Subjects Treated)

System Organ Class/ Preferred Term	Single-Dose		Multiple-Dose		Total Clinical Pharmacology Studies	
	Daptomycin (N=121) N (%)	Comparator (N=17) N (%)	Daptomycin (N=119) N (%)	Comparator (N=92) N (%)	Daptomycin (N=240) N (%)	Comparator (N=109) N (%)
Total Number of Subjects with at Least One AE	18 (14.9)	2 (11.8)	44 (37.0)	30 (32.6)	62 (25.8)	32 (29.4)
Cardiac disorders	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Tachycardia NOS	1 (0.8)	0 (0.0)	0 (0)	0 (0.0)	1 (0.4)	0 (0.0)
Gastrointestinal disorders	6 (5.0)	0 (0.0)	11 (9.2)	7 (7.6)	17 (7.1)	7 (6.4)
Abdominal pain NOS	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Abdominal pain lower	0 (0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)
Constipation	0 (0)	0 (0.0)	5 (4.2)	4 (4.3)	5 (2.1)	4 (3.7)
Diarrhea NOS	2 (1.7)	0 (0.0)	1 (0.8)	0 (0.0)	3 (1.3)	0 (0.0)
Dyspepsia	1 (0.8)	0 (0.0)	2 (1.7)	0 (0.0)	3 (1.3)	0 (0.0)
Nausea	2 (1.7)	0 (0.0)	1 (0.8)	0 (0.0)	3 (1.3)	0 (0.0)
Rectal hemorrhage	0 (0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.9)
Vomiting NOS	5 (4.1)	0 (0.0)	1 (0.8)	2 (2.2)	6 (2.5)	2 (1.8)
General disorders and administration site conditions	0 (0)	2 (11.8)	19 (16.0)	10 (10.9)	19 (7.9)	12 (11.0)
Chest pain NEC	0 (0.0)	0 (0.0)	2 (1.7)	0 (0.0)	2 (0.8)	0 (0.0)
Fatigue	0 (0.0)	0 (0.0)	1 (0.8)	1 (1.1)	1 (0.4)	1 (0.9)
Groin pain	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Injection site bruising	0 (0.0)	0 (0.0)	2 (1.7)	0 (0.0)	2 (0.8)	0 (0.0)
Injection site burning	0 (0.0)	0 (0.0)	4 (3.4)	0 (0.0)	4 (1.7)	0 (0.0)
Injection site erythema	0 (0.0)	0 (0.0)	5 (4.2)	3 (3.3)	5 (2.1)	3 (2.8)
Injection site extravasation	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)
Injection site edema	0 (0.0)	0 (0.0)	6 (5.0)	3 (3.3)	6 (2.5)	3 (2.8)
Injection site pain	0 (0.0)	0 (0.0)	7 (5.9)	6 (6.5)	7 (2.9)	6 (5.5)
Injection site phlebitis	0 (0.0)	0 (0.0)	3 (2.5)	0 (0.0)	3 (1.3)	0 (0.0)
Injection site pruritus	0 (0.0)	0 (0.0)	1 (0.8)	1 (1.1)	1 (0.4)	1 (0.9)
Malaise	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.9)
Pyrexia	0 (0.0)	0 (0.0)	1 (0.8)	1 (1.1)	1 (0.4)	1 (0.9)
Rigors	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Weakness	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)
Infections and infestations	0 (0.0)	0 (0.0)	3 (2.5)	3 (3.3)	3 (1.3)	3 (2.8)
Cellulitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.9)
External ear infection NOS	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.9)
Pharyngitis viral NOS	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.9)
Tonsillitis NOS	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)
Upper respiratory tract infection NOS	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)
Urinary tract infection NOS	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)
Injury and poisoning	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Blister	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Investigations	1 (0.8)	0 (0.0)	7 (5.9)	2 (2.2)	8 (3.3)	2 (1.8)
Blood creatine phosphokinase increased	1 (0.8)	0 (0.0)	6 (5.0)	2 (2.2)	7 (2.9)	2 (1.8)
Urine analysis abnormal NOS	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)

Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	1 (0.8)	1 (1.1)	1 (0.4)	1 (0.9)
Hyperglycemia NOS	0 (0.0)	0 (0.0)	1 (0.8)	1 (1.1)	1 (0.4)	1 (0.9)
Musculoskeletal, connective tissue and bone disorders	3 (2.5)	0 (0.0)	4 (3.4)	2 (2.2)	7 (2.9)	2 (1.8)
Arthralgia	1 (0.8)	0 (0.0)	0 (0)	1 (1.1)	1 (0.4)	1 (0.9)
Arthritis NOS	0 (0.0)	0 (0.0)	0 (0)	1 (1.1)	0 (0.0)	1 (0.9)
Back pain	0 (0.0)	0 (0.0)	3 (2.5)	1 (1.1)	3 (1.3)	1 (0.9)
Muscle cramps	2 (1.7)	0 (0.0)	1 (0.8)	0 (0.0)	3 (1.3)	0 (0.0)
Pain in limb	1 (0.8)	0 (0.0)	2 (1.7)	0 (0.0)	3 (1.3)	0 (0.0)
Nervous system disorders	7 (5.8)	1 (5.9)	11 (9.2)	8 (8.7)	18 (7.5)	9 (8.3)
Dizziness (excluding vertigo)	1 (0.8)	0 (0.0)	2 (1.7)	4 (4.3)	3 (1.3)	4 (3.7)
Facial palsy	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)
Headache NOS	5 (4.1)	1 (5.9)	6 (5.0)	5 (5.4)	11 (4.6)	6 (5.5)
Hypoesthesia oral.NOS	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)
Insomnia NEC	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)
Syncope	1 (0.8)	0 (0.0)	1 (0.8)	0 (0.0)	2 (0.8)	0 (0.0)
Psychiatric disorders	1 (0.8)	0 (0.0)	0 (0)	0 (0.0)	1 (0.4)	0 (0.0)
Somnolence	1 (0.8)	0 (0)	0 (0)	0 (0.0)	1 (0.4)	0 (0.0)
Renal and urinary disorders	0 (0.0)	0 (0.0)	1 (0.8)	1 (1.1)	1 (0.4)	1 (0.9)
Difficulty in micturition	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)
Dysuria	0 (0.0)	0 (0.0)	0 (0)	1 (1.1)	0 (0.0)	1 (0.9)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)
Dysmenorrhea	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	1 (0.8)	0 (0.0)	2 (1.7)	1 (1.1)	3 (1.3)	1 (0.9)
Nasal congestion	0 (0.0)	0 (0.0)	2 (1.7)	0 (0.0)	2 (0.8)	0 (0.0)
Postnasal drip	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)
Rhonchi	1 (0.8)	0 (0.0)	0 (0)	0 (0.0)	1 (0.4)	0 (0.0)
Sinus pain	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)
Sneezing	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)
Sore throat NOS	0 (0.0)	0 (0.0)	0 (0)	1 (1.1)	0 (0.0)	1 (0.9)
Wheezing	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Skin & subcutaneous tissue disorders	1 (0.8)	0 (0.0)	1 (0.8)	5 (5.4)	2 (0.8)	5 (4.6)
Cellulitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.9)
Dermatitis NOS	0 (0.0)	0 (0.0)	1 (0.8)	1 (1.1)	1 (0.4)	1 (0.9)
Dermatitis contact	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Eczema seborrheic	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.9)
Erythema NEC	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.9)
Folliculitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.9)
Pruritus NOS	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.9)
Skin & tissue disorders	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Dermatitis NOS	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Surgical and medical procedures	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)
Injection site bruising	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)
Vascular disorders	0 (0.0)	0 (0.0)	3 (2.5)	0 (0.0)	3 (1.3)	0 (0.0)
Hypertension NOS	0 (0.0)	0 (0.0)	3 (2.5)	0 (0.0)	3 (1.3)	0 (0.0)

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

Drug related adverse events - Cubist-sponsored Phase I studies

In the Cubist sponsored Phase 1 studies, 29/240 (12.1%) of subjects who received daptomycin experienced at least one AE that was considered possibly or probably related to study treatment. Of subjects in the comparator groups, 6/109 (5.5%) experienced at least one adverse event that was considered possibly or probably related to study treatment. In both groups the Nervous System Disorders System Organ Class (SOC) were the most commonly reported AEs. In the daptomycin group, 11/240 subjects (4.6%) experienced AEs within this SOC compared with 3/109 subject (2.8%) in the comparator group. As demonstrated in Table 12 below, the most frequently reported drug-related AEs by preferred term were headache, increased CPK, and vomiting.

Table 12: Drug-Related Adverse Events Occurring in ≥1% of Subjects by System Organ Class and Preferred Term, Cubist-sponsored Phase I Studies (Population: All Subjects Treated)

System/Organ	Single Dose		Multiple Dose	
	Daptomycin N= 121 N (%)	Comparator N= 92 N (%)	Daptomycin N= 240 N (%)	Comparator N=109 N (%)
Total Number of Subjects with at Least one Related AE	10 (8.3)	19 (16.0)	6 (6.5)	29 (12.1)
Gastrointestinal disorders	4 (3.3)	3 (2.5)	1 (1.1)	7 (2.9)
Vomiting NOS	3 (2.5)	0 (0)	0 (0)	3 (1.3)
Investigations	1 (0.8)	5 (4.2)	1 (1.1)	6 (2.5)
Blood CPK increased	1 (0.8)	5 (4.2)	1 (1.1)	6 (2.5)
Nervous system disorders	5 (4.1)	6 (5.0)	3 (3.3)	11 (4.6)
Headache NOS	3(2.5)	4 (3.4)	2 (2.2)	7 (2.9)

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

Adverse events leading to discontinuation - Cubist-sponsored Phase I studies

In the Cubist-sponsored clinical pharmacology studies, seven subjects discontinued study medication due to AE's: 5/240 (2.1%) in the daptomycin group and 2/109 (1.8%) in the comparator group. Six of the seven AEs causing discontinuation were considered probably or possibly related to study medication. One subject (study DAP-00-02) in the control group (placebo) was discontinued from the study because of a mild rash with mild pruritus starting on Day 1; these events were considered to be possibly related to study medication. A second subject (study DAP-MDRI-01-03; dose = loading dose of 4 mg/kg, then 3 mg/kg on days 3, 5, 7, 11, and 13) discontinued prematurely due to elevated CPK concentrations after five doses of daptomycin (total daptomycin dose = 1767 mg). Maximum serum CPK was 4498 U/L on d10 and decreased to 649 U/L by d5P. A third subject (study DAP-QTNC-01-06; dose of 6 mg/kg q24h for a planned 14 days) discontinued the study on Day 9 of daptomycin treatment due to facial palsy considered unrelated to the study medication. In the same study, two daptomycin-treated subjects and one placebo-treated subject discontinued the study due to

elevated CPK concentrations considered probably related to study drug. One of the daptomycin-treated subjects had a maximum serum CPK (asymptomatic) of 1940 U/L on d14, which returned to normal by d25. The second daptomycin-treated subject had a maximum serum CPK (asymptomatic) of 1593 U/L on d7, which returned to normal by d10. The placebo-treated subject had a maximum serum CPK (asymptomatic) of 11,430 U/L on d14 which returned to normal by d28. All CPK isoenzymes in these patients were MM. One subject (study DAP-00-04) discontinued study medication due to severe diarrhea after receiving a single dose of 346 mg (4 mg/kg) daptomycin; the diarrhea was considered to be probably related to study drug.

Medical Officer Comment
The elevations in serum CPK noted in the Cubist-sponsored clinical pharmacology trials are fairly typical of this AE due to daptomycin. Serum CPK elevations were noted after approximately one week of treatment and no symptoms were present. Resolution over several days is often seen. Of note, however, is that the doses at which CPK elevations were noted are consistent with those used in the pivotal phase III trials.

Serious adverse events - Cubist-sponsored Phase I studies
There were three SAEs in the Cubist-sponsored clinical pharmacology studies. One subject (Study DAP-QNTC-01-06) developed right-sided facial numbness and weakness after receiving daptomycin 6 mg/kg q24h for 9 days; the day of symptom onset was between day 9 and 14. The diagnosis was Bell's palsy, the patient was treated with steroids, and the symptoms improved by follow-up at 6 months. The investigator considered the Bell's palsy to be unrelated to the study drug. The second subject (Study DAP-00-04) developed diarrhea, nausea, and vomiting approximately two hours after a single dose of daptomycin 4 mg/kg. His gastrointestinal symptoms resolved over the following 24 hours with symptomatic therapy, and were judged probably related to study treatment by the investigator. A third subject (Study DAP-00-04) developed nausea and vomiting approximately two hours after the infusion of daptomycin 4 mg/kg. His symptoms resolved over the following 12 hours with no treatment; the investigator considered the SAE to be probably related to study treatment.

Deaths - Cubist-sponsored Phase I studies
No deaths occurred during the Cubist-sponsored clinical pharmacology studies.

Lilly-sponsored Phase I studies
Demographics
The Lilly Phase I studies enrolled 362 subjects who received daptomycin. These human pharmacology studies included single- and multiple-dose safety and pharmacokinetic studies in healthy subjects. Multiple-dose studies examined various doses and regimens up to 4 mg/kg q12h for 14 days. Also included are *in vivo* protein binding studies; a metabolism and excretion study using radiolabeled

daptomycin, a study in subjects with various degrees of renal impairment, and drug interaction studies with tobramycin and amikacin.

Demographic data was unavailable for studies B8B-MC-AVAD (39 patients) and B8B-MC-AVAL (6 patients). Limited demographic data was available for study B8B-EW-0001 (12 patients) and the studies conducted in Japan (5 studies, 6 patients each). In the single-dose studies conducted in the US, where the data was available, the mean age was 31.6 years (range 19 to 46 years), in 35 males and 12 females. All of the subjects were Caucasian (race data was unavailable for studies B8B-EW-0001 and B8B-MC-AVAL). In the studies conducted in Japan (B8B-XO-1001, B8B-XO-1002, B8B-XO-1003, B8B-XO-1004 and B8B-XO-1005), the mean ages of the subjects were 28.5, 28.5, 34.3, 34.3, and 30.8 years, respectively. Subjects in the three repeat dose studies (B8B-LC-AVAB, B8B-LC-AVAI, B8B-MC-AVAP and B8B-LC-AVAK) had a mean age of 33.9 years (24 to 49 years) reported in 34 males. All but three of the subjects (two blacks and one with the race distinction of "other") were Caucasian. Subject demographics of Lilly-sponsored single-dose clinical pharmacology studies are shown in Table 13.

Table 13: Summary of Subject Demographics for the Lilly-sponsored Single-dose Daptomycin Phase I Studies

Study Number	B8B-LC-AVAA	B8B-LC-AVAC	B8B-LC-AVAF	B8B-LC-AVAJ	B8B-LC-AVAK	B8B-MC-AVAL	B8B-EW 0001
Variable	N=6	N=5	N=6	N=6	N=6	N=6	N=12
Age							
Mean	39.5	31.2	32.7	31.7	29.0	25.5	N/A
Range	32-46	25-36	28-37	25-41	23-35	20-33	19-46
Race							
Caucasian	6	5	6	6	6	N/A	N/A
Sex							
Male	6	5	6	6	6	3	3
Female	0	0	0	0	0	3	9
Height (in.)							
Mean	69.2	68.0	70.2	70.0	69.0	N/A	N/A
Range	67-72	64-72	69-72	61-76	65-73		
Weight (kg)							
Mean	72.0	65.8	71.8	74.3	73.0	N/A	N/A
Range	56-87	64-68	61-88	54-86	67-79		

N/A=Not available

With the exception of 12 women enrolled in Studies B8B-MC-AVAL and B8B-EW-0001, all of the subjects were male and all were Caucasian; race data is unavailable for these 2 studies B8B-MC-AVAL and B8B-EW-0001. Subjects in these studies ranged in age from 19 to 46 years. Subject demographics of Lilly-sponsored repeated-dose Clinical pharmacology studies are shown in Table 14.

Table 14: Summary of Subject Demographics for the Lilly-sponsored Repeated-dose Daptomycin Phase 1 Studies

Study Number	B8B-LC-AVAB	B8B-LC-AVAI	B8B-MC-AVAK	B8B-MC-AVAP
Variable	N=10	N=10	N=5[a]	N=14
Age (years)				
Mean	32.2	1.8	9.6	38.2
Range	24-48	25-43	23-35	26-49
Race				
Caucasian	10	9	5	11
Black	0	1	0	2
Other	0	0	0	1
Sex				
Male	10	10	5	14
Female	0	0	0	0
Height (in.)				
Mean	69.9	69.9	68.2	70.9
Range	67-75	64-77	65-73	68-74.5
Weight (kg)				
Mean	76.1	69.8	72.6	178.8
Range	62-90	58-95	67-79	122-235[b]

a. Of the 6 subjects enrolled in B8B-MC-AVAK, only 5 were dosed during the repeated dose regimen
b. weight in pounds

All subjects in the repeated-dose studies were male and the majority were Caucasian. The mean subject age was approximately 32 years in studies B8B-LC-AVAB and B8B-LC-AVAI and was slightly younger, 30 years, in study B8B-LC-AVAK, and slightly older, 38 years, in study B8B-MC-AVAP. Subject demographics of Lilly-sponsored clinical pharmacology studies conducted in Japan are shown in Table 15.

Table 15: Summary of Subject Demographics for the Lilly-sponsored Daptomycin Phase I Studies Conducted in Japan

Study Number	B8B-XO 1001	B8B-XO 1002	B8B-XO 1003	B8B-XO 1004	B8B-XO 1005	B8B-JE 0001	B8B-JE 0002
Variable	N=6	N=6	N=6	N=6	N=6	N=26	N=10
Mean age (years)	28.5	28.5	34.3	34.3	30.8	N/A	N/A
Mean weight (kg)	61.7	61.7	59.5	59.5	66.7	N/A	N/A

N/A = Not available

Adverse events - Lilly-sponsored Phase I

AEs seen in the Lilly-sponsored Phase I studies included headache, abdominal pain and pain and bruising at the venipuncture site. Daptomycin, administered intravenously at doses up to 6 mg/kg, was well-tolerated in the single-dose studies in healthy men and a small number of women. All AEs that occurred during these studies are summarized in Table 16.

Table 16: Adverse Events in Lilly-sponsored Daptomycin Single-dose Phase I Studies

Study Number	B8B-LC-AVAA Daptomycin 5,10,25 50,75 mg IV	B8B-LC-AVAC Daptomycin 1 mg/kg IV	B8B-MC-AVAD Daptomycin 1 mg/kg, 3 mg/kg IV	B8B-LC-AVAF Daptomycin 0.5,1,1.5, 2 mg/kg IV	B8B-LC-AVAJ Daptomycin 2 mg/kg IV	B8B-LC-AVAK[a] Daptomycin 2, 3, 4, 6 mg/kg IV	B8B-MC-AVAL[a] Daptomycin 3 mg/kg IV	B8B-EW-0001 Daptomycin 1 or 2 mg/kg IV
	N=6	N=5	N=45	N=6	N=6	N=6	N=6	N=12
Adverse Event	Number of Subjects (%)							
No. of subjects with at least one AE	4 (66.7)	2 (40)	1 (2.2)	3 (50)	3 (50)	6 (100)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anemia	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eye disorders	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Swelling of right eyelid	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	3 (50.0)	0 (0.0)	1 (2.2)	0 (0.0)	1 (16.7)	3 (50.0)	0 (0.0)	0 (0.0)
Abdominal cramping	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	2 (33.3)	0 (0.0)	0 (0.0)
Bloody stools	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Loose stool	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	1 (16.7)	3 (60.0)	1 (2.2)	2 (33.3)	0 (0.0)	3 (50.0)	0 (0.0)	0 (0.0)
Aching	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asthenia	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Chest pain	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Edema	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Inflammation	0 (0.0)	1 (20.0)	0 (0.0)	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site edema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	0 (0.0)	0 (0.0)
Infections and infestations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Injury and poisoning	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)
Injury (accident)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)
Investigations	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fever	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal, connective tissue and bone disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)
Back pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Myalgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Nervous system disorders	1 (16.7)	1 (20.0)	1 (2.2)	1 (16.7)	4 (66.7)	4 (66.7)	0 (0.0)	0 (0.0)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Foul taste	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	1 (16.7)	1 (20.0)	0 (0.0)	0 (0.0)	2 (33.3)	3 (50.0)	0 (0.0)	0 (0.0)
Paresthesia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)

Psychiatric Disorder	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Euphoria	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	1 (20.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinitis	0 (0.0)	1 (20.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	1 (16.7)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bruising	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin irritation	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

a. AEs listed here may have occurred during multiple dosing with 3 mg/kg daptomycin

Headache was the most frequently noted AE among subjects in the single-dose studies. In several cases, IV infiltration occurred resulting in inflammation or edema. Mild gastrointestinal disturbances were also noted. These events were not dose-related and did not persist.

AEs that occurred in the Lilly-sponsored repeat-dose Phase I studies are summarized in Table 17 below. Note that in the Lilly study report for study B8B-LC-AVAK, no distinction was made between AEs which occurred during single versus multiple dosing. Therefore, the AEs for this study are presented with the single-dose studies only (see Table 16 above). One of the five subjects who received daptomycin 3 mg/kg q12h in study B8B-MCAVAP had elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactate dehydrogenase. None of the other subjects in this dose group had any AEs reported. Among the subjects in the 4 mg/kg q12h group, 2/5 subjects experienced marked elevations in CPK levels with accompanying symptoms of muscle weakness and pain. These events led to early termination of this study. The other 3 subjects in the 4 mg/kg group had normal CPK levels and had no symptoms of muscle pain or weakness.

Table 17: Adverse Events in Lilly-sponsored Daptomycin Repeated-dose Phase I Studies

Study Number	B8B-LC-AVAB Daptomycin 1 mg/kg q24h IV N=10	B8B-LC-AVAI Daptomycin 2 mg/kg IV N=5	B8B-MC-AVAP Daptomycin 3 mg/kg or 4 mg/kg q12h N=10
	Number of Subjects (%)		
No. of Subjects with at least one AE	7 (70.0)	4 (80.0)	3 (30.0)
Ear and labyrinth disorders	1 (10.0)	0 (0.0)	0 (0.0)
Ear pain	1 (10.0)	0 (0.0)	0 (0.0)
Eye disorders	1 (10.0)	0 (0.0)	0 (0.0)
Redness left eye	1 (10.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	1 (10.0)	4 (80.0)	0 (0.0)
Abdominal pain	0 (0.0)	2 (40.0)	0 (0.0)
Diarrhea	0 (0.0)	1 (20.0)	0 (0.0)
Dyspepsia	0 (0.0)	1 (20.0)	0 (0.0)
Toothache	1 (10.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	4 (40.0)	4 (80.0)	2 (20.0)
Asthenia	1 (10.0)	0 (0.0)	0 (0.0)
Muscle weakness	0 (0.0)	0 (0.0)	2 (20.0)
Pain extraction site	1 (10.0)	0 (0.0)	0 (0.0)
Pain venipuncture site	2 (20.0)	4 (80.0)	0 (0.0)
Injury and poisoning	1 (10.0)	0 (0.0)	0 (0.0)
Injury	1 (10.0)	0 (0.0)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	3 (30.0)
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	1 (10.0)
Aspartate aminotransferase increased	0 (0.0)	0 (0.0)	1 (10.0)
Elevated creatine phosphokinase	0 (0.0)	0 (0.0)	2 (20.0)
Lactate dehydrogenase increased	0 (0.0)	0 (0.0)	1 (10.0)
Musculoskeletal, connective tissue and bone disorders	1 (10.0)	0 (0.0)	2 (20.0)
Pain in both forearms	0 (0.0)	0 (0.0)	2 (20.0)
Pain lower right hip	1 (10.0)	0 (0.0)	0 (0.0)
Nervous system disorders	1 (10.0)	3 (60.0)	0 (0.0)
Headache	1 (10.0)	2 (40.0)	0 (0.0)
Insomnia	0 (0.0)	1 (20.0)	0 (0.0)
Reproductive system and breast disorders	1 (10.0)	0 (0.0)	0 (0.0)
Testis disorder	1 (10.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	1 (10.0)	0 (0.0)	0 (0.0)
Rhinitis	1 (10.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	0 (0.0)	1 (20.0)	0 (0.0)
Rash	0 (0.0)	1 (20.0)	0 (0.0)
Vascular disorders			
Vasodilation	1 (10.0)	0 (0.0)	0 (0.0)

Table 18 below summarizes the AEs that occurred in subjects enrolled in the Phase I studies conducted in Japan.

Table 18: Incidence of Adverse Events in Lilly-sponsored Daptomycin Phase I Studies Conducted in Japan

Study Number	B8B-XO 1001 N=6	B8B-XO 1002 N=6	B8B-XO 1003 N=6	B8B-XO 1004 N=6	B8B-XO 1005 N=6	B8B- JE 0001 N=26	B8B- JE 0002 N=10
Adverse event		Number of Subjects (%)					
No. of Subjects with a least one AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (26.9)	0 (0.0)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)
Stomatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (50.0)
Activated partial thromboplastin time prolonged	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (40.0)
ALT increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)
AST increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)
Nervous system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (23.1)	0 (0.0)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (23.1)	0 (0.0)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)
Rash	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)

Medical Officer Comment

No AEs were reported in five of the seven Phase I studies conducted in Japan, consistent with the overall lower AE rate often reported from non-US sites. Headache was the most common AE reported, noted in 6/26 (23.1%) subjects in study B8B-JE0001. Of more concern are the 4/10 (40%) patients from study B8B-JE0002 who had prolongation of activated partial thromboplastin time (aPTT). Prolongation in aPTT was observed in one subject on the ninth day of 60 mg daptomycin and in 3/5 subjects at 120 mg daptomycin, according to the original study report, although the dose given is 60 mg for 7 days, 120 mg for 7 das (presumably sequentially).

However, the clinical significance of the prolongation in aPTT is unclear, since this is not an AE of daptomycin predicted from the preclinical trials, nor has prolongation in aPTT been a significant finding in subsequent clinical trials. In addition, these doses are lower than the 4 mg/kg q24h proposed for use in the submitted indication of cSSSI.

Drug related adverse events - Lilly-sponsored Phase I studies
Information on study drug causality does not appear to have been systematically collected in the Lilly-sponsored Phase I studies, and this information is not contained in the study reports or ISS (either Cubist or Lilly).

AE leading to discontinuation- Lilly-sponsored Phase I studies
In study B8B-MC-AVAP, two subjects of five who received daptomycin were discontinued from the study after elevations of serum CPK. The first subject developed symptoms of bilateral forearm pain and stiffness after 6 of the planned 14 days of daptomycin 4 mg/kg q12h. His maximum serum CPK was 20,812 U/L with isoenzyme pattern MM; his symptoms resolved by 2 months post-therapy. The second subject developed symptoms of bilateral forearm pain and weakness after 11 of the planned 14 days of daptomycin 4 mg/kg q12h. Serum CPK was elevated to a maximum of >10,000 U/L. Symptoms resolved and serum CPK returned to normal when checked at 2 weeks post-therapy.

Serious adverse events - Lilly-sponsored Phase I studies
In study B8B-MC-AVAD, one male subject (age unknown) with chronic renal failure on hemodialysis received a single dose of daptomycin 2 mg/kg. Four days later, he developed bloody stools and a drop in hemoglobin. The patient was described as fluid overloaded during dialysis. No lesion was found by sigmoidoscopy and his anemia was corrected. The investigator felt that the bleeding was not related to study drug.

Deaths - Lilly-sponsored Phase I studies
No deaths occurred during the Lilly-sponsored clinical pharmacology studies.

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

currently available therapy was contraindicated. Study DAP-RRC-9804 was terminated due to slow enrollment. Study DAP-00-03 was an open-label, microbiologist-blinded, Phase III study comparing daptomycin at a dosage of 4 mg/kg q24h with ciprofloxacin 400 mg in patients with UTIs caused primarily by Gram-positive pathogens. The subject demographics of Cubist-sponsored clinical pharmacology studies are shown in Table 19.

Table 19: Demographic Characteristics, Cubist-sponsored Phase II/III Studies (Population: All Patients Treated)

Characteristic	Statistic	DAP-BAC-9803		DAP-RRC 9804	DAP-00-03		Total Other Studies	
		Dapto	Comp	Dapto	Dapto	Comp	Dapto	Comp
		(N=74)	(N=24)	(N=72)	(N=34)	(N=34)	(N=180)	(N=58)
Age (yrs)	N	74	24	72	34	34	180	58
	Mean	57.1	61.8	56.7	57.5	60.3	57.0	60.9
	SD	14.1	15.8	16.9	18.6	16.0	16.1	15.8
	Median	57.5	62.0	58.5	62.5	66.0	58.0	64.0
	Min. Max	24, 85	33, 85	18, 91	19, 87	24, 83	18, 91	24, 85
Age (yrs)	N (%)							
18 - 39		6 (8.1)	2 (8.3)	14 (19.4)	8 (23.5)	5 (14.7)	28 (15.6)	7 (12.1)
40 - 64		46 (62.2)	11 (45.8)	31 (43.1)	10 (29.4)	11 (32.4)	87 (48.3)	22 (37.9)
>=65		22 (29.7)	11 (45.8)	27 (37.5)	16 (47.1)	18 (52.9)	65 (36.1)	29 (50.0)
>=75		10 (13.5)	7 (29.2)	10 (13.9)	6 (17.6)	6 (17.6)	26 (14.4)	13 (22.4)
Gender	N (%)							
Male		47 (63.5)	12 (50.0)	38 (52.8)	18 (52.9)	16 (47.1)	103 (57.2)	28 (48.3)
Female		27 (36.5)	12 (50.0)	34 (47.2)	16 (47.1)	18 (52.9)	77 (42.8)	30 (51.7)
Race	N (%)							
Caucasian		50 (67.6)	17 (70.8)	63 (87.5)	34 100.0)	33 (97.1)	147 (81.7)	50 (86.2)
Black		18 (24.3)	4 (16.7)	5 (6.9)	0 (0.0)	0 (0.0)	23 (12.8)	4 (6.9)
Asian		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.7)
Other		6 (8.1)	3 (12.5)	4 (5.6)	0 (0.0)	0 (0.0)	10 (5.6)	3 (5.2)

Patients in these studies ranged in age from 18 to 91 years of age with a mean of 57.0 years in the daptomycin-treated patients and 60.9 years in patients treated with comparator. Comparator patients included equal numbers of patients <65 and >65 years of age, while 63.9% of the daptomycin patients were <65 years of age. A total of 65 patients who received daptomycin and 29 patients who received comparator were age 65 or older; 26 daptomycin patients and 13 comparator patients were age 75 or older. There was a greater percentage of males treated with daptomycin (57.2%) than with comparator (48.3%). Caucasians accounted for 81.7% and 86.2% of the patients who received daptomycin and comparator, respectively.

Disposition - Cubist-sponsored Phase II/III studies

Most patients in the Cubist-sponsored Phase II/III studies completed treatment as planned. In DAP-BAC-9803 and DAP-RRC-9804, 74.3% and 55.6% of patients completed therapy, respectively. In DAP-BAC-9803, the most common reason for premature discontinuation was "Adverse Event" in the daptomycin group (8/74; 10.8%). In DAP-RRC-9804, the most common reason for premature

discontinuation was "Adverse Event" in the daptomycin group (18.1%); the discontinuation rate due to clinical failure was 12.5%. Patient disposition for the Cubist Phase II/III studies is given in Table 20 below.

Table 20: Summary of Patient Disposition, Cubist-sponsored Phase II/III Studies (Population: All Patients Treated)

Study #	DAP-BAC-9803				DAP-RRC-9804		DAP-00-03			
	Daptomycin		Comparator		Daptomycin		Daptomycin		Comparator	
Disposition	N	%	N	%	N	%	N	%	N	%
Treated	74		24		72		34		34	
Completed Therapy	55	74.3	17	70.8	40	55.6	33	97.1	33	97.1
Prematurely Discontinued Therapy	19	25.7	7	29.2	32	44.4	1	2.9	1	2.9
Adverse Event	8	10.8	2	8.3	13	18.1	0	0.0	0	0.0
Clinical (Symptomatic) Failure	3	4.1	0	0.0	9	12.5	0	0.0	0	0.0
Patient's Decision	1	1.4	1	4.2	0	0.0	0	0.0	0	0.0
Other	7	9.5	3	12.5	6	8.3	1	2.9	1	2.9
Death	0	0.0	1	4.2	4	5.6	0	0.0	0	0.0

Overall adverse events - Cubist-sponsored Phase II/III studies

For Study DAP-BAC-9803, a total of 66/74 (89.2%) patients in the daptomycin group and 19/24 (79.2%) in the comparator group reported at least one AE during the study. This high rate of AEs is consistent with the critically ill status of the patients; the majority of events were assessed by the investigators as unrelated to study treatment. The most frequently reported AEs in DAP-BAC-9803 were nausea reported in 14/74 (18.9%) patients in the daptomycin group and constipation reported in 7/24 (29.2%) patients in the comparator group. Other AEs reported in more than 10% of patients in either study arm were diarrhea and nausea in the daptomycin group and nausea, agitation, cardiac failure congestive, insomnia, and dizziness in the comparator group. The majority of AEs were rated by the investigator as mild to moderate in severity.

In Study DAP-RCC-9804, AEs were most commonly reported in the SOC of gastrointestinal disorders. The most frequently reported AEs were nausea (16.7%), diarrhea (15.3%), and vomiting (15.3%). AEs by SOC were more common in the dialysis group.

Medical Officer Comment

The most frequently reported AEs in these two studies are consistent with the AE profile derived from the preclinical and Phase I studies of daptomycin. The relatively high AE rate seen in both of these studies is not surprising considering the serious underlying illness of the patients in these two Phase II studies.

For Study DAP-00-03, there was a significantly lower incidence of AEs in the daptomycin group than in the comparator group. A total of 4/34 (11.8%) patients in the daptomycin group and 13/34 (38.2%) in the ciprofloxacin group reported at least one AE during the study. There were significantly fewer patients 6/34 (2.9%) in the daptomycin group than in the ciprofloxacin group 6/34 (17.6%) who reported at least one AE in the SOC of gastrointestinal disorders. The most frequently reported AE was diarrhea occurring in 5/34 (14.7%) patients in the ciprofloxacin group. Table 21 below shows AEs by SOC including events reported in >2% of patients in any study group in Cubist-sponsored Phase II/III studies.

Table 21: Adverse Events by System Organ Class Including the Most Commonly Reported Events (≥2% of Patients in any study group), Cubist-sponsored Phase II/III Studies (Population: All Patients Treated)

System Organ Class/ Preferred Term	DAP-BAC-9803				DAP-RRC-9804		DAP-00-03			
	Daptomycin (N=74)		Comparator (N=24)		Daptomycin (N=72)		Comparator (N=34)		Daptomycin (N=34)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total Number of Patients with at Least One AE	66	(89.2)	19	(79.2)	69	(95.8)	13	(38.2)	4	(11.8)
Blood and lymphatic system disorders	10	(13.5)	2	(8.3)	5	(6.9)	0	0	0	0
Anemia NOS	6	(8.1)	1	(4.2)	2	(2.8)	0	0	0	0
Cardiac disorders	16	(21.6)	8	(33.3)	16	(22.2)	0	0	1	(2.9)
Bradycardia NOS	1	(1.4)	1	(4.2)	3	(4.2)	0	0	0	0
Cardiac arrest	0	0	0	0	4	(5.6)	0	0	0	0
Cardiac failure congestive	1	(1.4)	3	(12.5)	1	(1.4)	0	0	0	0
Cardio-respiratory arrest	1	(1.4)	1	(4.2)	4	(5.6)	0	0	0	0
Endocarditis NOS	3	(4.1)	2	(8.3)	1	(1.4)	0	0	0	0
Pulmonary edema NOS	0	0	2	(8.3)	0	0	0	0	0	0
Tachycardia NOS	1	(1.4)	1	(4.2)	4	(5.6)	0	0	0	0
Gastrointestinal disorders	36	(48.6)	14	(58.3)	43	(59.7)	6	(17.6)	1	(2.9)
Abdominal pain NOS	4	(5.4)	1	(4.2)	5	(6.9)	0	0	0	0
Abdominal pain upper	7	(9.5)	0	0	4	(5.6)	0	0	0	0
Constipation	4	(5.4)	7	(29.2)	6	(8.3)	1	(2.9)	0	0
Diarrhea NOS	8	(10.8)	1	(4.2)	11	(15.3)	5	(14.7)	0	0
Diarrhea aggravated	0	0	0	0	4	(5.6)	0	0	0	0
Dry mouth	2	(2.7)	0	0	2	(2.8)	0	0	0	0
Dyspepsia	3	(4.1)	0	0	6	(8.3)	0	0	0	0
Gastritis NOS	2	(2.7)	0	0	2	(2.8)	0	0	0	0
Gastrointestinal hemorrhage NOS	2	(2.7)	0	0	2	(2.8)	0	0	0	0
Loose stools	4	(5.4)	0	0	1	(1.4)	0	0	0	0
Nausea	14	(18.9)	5	(20.8)	12	(16.7)	0	0	0	0
Pancreatitis NOS	0	0	2	(8.3)	1	(1.4)	0	0	0	0
Vomiting NOS	5	(6.8)	2	(8.3)	11	(15.3)	0	0	0	0
General disorders and administration site conditions	30	(40.5)	10	(41.7)	26	(36.1)	1	(2.9)	1	(2.9)
Chest pain NEC	5	(6.8)	0	0	1	(1.4)	0	0	0	0
Fatigue	3	(4.1)	2	(8.3)	1	(1.4)	0	0	0	0
Injection site erythema	4	(5.4)	0	0	0	0	0	0	0	0

Injection site pain	6	(8.1)	1	(4.2)	1	(1.4)	0	0	0	0
Lethargy	1	(1.4)	2	(8.3)	1	(1.4)	0	0	0	0
Mucosal inflammation NOS	0	0	0	0	4	(5.6)	0	0	0	0
Multi-organ failure	1	(1.4)	0	0	3	(4.2)	0	0	0	0
Edema NOS	2	(2.7)	1	(4.2)	4	(5.6)	0	0	0	0
Edema lower limb	7	(9.5)	2	(8.3)	2	(2.8)	0	0	0	0
Pain NOS	6	(8.1)	2	(8.3)	3	(4.2)	0	0	0	0
Peripheral swelling	1	(1.4)	0	0	4	(5.6)	0	0	0	0
Pitting edema	2	(2.7)	2	(8.3)	0	0	0	0	0	0
Pyrexia	1	(1.4)	0	0	4	(5.6)	0	0	0	(2.9)
Rigors	1	(1.4)	0	0	3	(4.2)	0	0	0	0
Weakness	2	(2.7)	1	(4.2)	2	(2.8)	0	0	0	0
Infections and infestations	26	(35.1)	12	(50.0)	33	(45.8)	0	0	0	0
Implant infection	2	(2.7)	0	0	2	(2.8)	0	0	0	0
Oral candidiasis	1	(1.4)	2	(8.3)	0	0	0	0	0	0
Pneumonia NOS	2	(2.7)	1	(4.2)	2	(2.8)	0	0	0	0
Sepsis NOS	1	(1.4)	1	(4.2)	7	(9.7)	0	0	0	0
Urinary tract infection NOS	6	(8.1)	2	(8.3)	4	(5.6)	0	0	0	0
Investigations	24	(32.4)	4	(16.7)	25	(34.7)	3	(8.8)	1	(2.9)
Alanine aminotransferase increased	1	(1.4)	0	0	1	(1.4)	2	(5.9)	1	(2.9)
Blood creatine phosphokinase increased	4	(5.4)	1	(4.2)	4	(5.6)	0	0	0	0
Blood magnesium decreased	2	(2.7)	0	0	4	(5.6)	0	0	0	0
Blood pressure decreased	0	0	0	0	6	(8.3)	0	0	0	0
Hematocrit decreased	0	0	0	0	4	(5.6)	0	0	0	0
Hemoglobin decreased	3	(4.1)	0	0	3	(4.2)	0	0	0	0
Liver function tests NOS abnormal	2	(2.7)	0	0	3	(4.2)	0	0	0	0
Oxygen saturation decreased	1	(1.4)	0	0	3	(4.2)	0	0	0	0
Metabolism and nutrition disorders	20	(27.0)	2	(8.3)	17	(23.6)	0	0	0	0
Appetite decreased NOS	3	(4.1)	0	0	2	(2.8)	0	0	0	0
Hyperglycemia NOS	4	(5.4)	1	(4.2)	4	(5.6)	0	0	0	0
Hypokalaemia	7	(9.5)	0	0	6	(8.3)	0	0	0	0
Hyponatraemia	1	(1.4)	1	(4.2)	3	(4.2)	0	0	0	0
Musculoskeletal, connective tissue and bone disorders	14	(18.9)	3	(12.5)	14	(19.4)	0	0	0	0
Arthralgia	2	(2.7)	1	(4.2)	3	(4.2)	0	0	0	0
Back pain	3	(4.1)	0	0	4	(5.6)	0	0	0	0
Pain in limb	4	(5.4)	1	(4.2)	5	(6.9)	0	0	0	0
Nervous system disorders	15	(20.3)	9	(37.5)	18	(25.0)	0	0	0	0
Dizziness (excl vertigo)	3	(4.1)	3	(12.5)	2	(2.8)	0	0	0	0
Headache NOS	3	(4.1)	1	(4.2)	3	(4.2)	0	0	0	0
Insomnia NEC	5	(6.8)	3	(12.5)	4	(5.6)	0	0	0	0
Somnolence	0	0	2	(8.3)	1	(1.4)	0	0	0	0
Psychiatric disorders	13	(17.6)	6	(25.0)	11	(15.3)	0	0	0	0
Agitation	2	(2.7)	4	(16.7)	2	(2.8)	0	0	0	0
Anxiety NEC	6	(8.1)	0	0	1	(1.4)	0	0	0	0
Confusion	2	(2.7)	0	0	3	(4.2)	0	0	0	0
Confusion aggravated	0	0	2	(8.3)	1	(1.4)	0	0	0	0
Renal and urinary disorders	9	(12.2)	4	(16.7)	15	(20.8)	0	0	0	0
Oliguria	0	0	0	0	6	(8.3)	0	0	0	0
Renal failure acute	2	(2.7)	1	(4.2)	5	(6.9)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	18	(24.3)	7	(29.2)	19	(26.4)	0	0	0	0
Breath sounds decreased	1	(1.4)	0	0	3	(4.2)	0	0	0	0

Cough	4	(5.4)	1	(4.2)	1	(1.4)	0	0	0	0
Dyspnea NOS	2	(2.7)	2	(8.3)	4	(5.6)	0	0	0	0
Pleural effusion	4	(5.4)	0	0	3	(4.2)	0	0	0	0
Respiratory failure (excluding neonatal)	2	(2.7)	0	0	3	(4.2)	0	0	0	0
Wheezing	1	(1.4)	2	(8.3)	1	(1.4)	0	0	0	0
Skin & subcutaneous tissue disorders	20	(27.0)	3	(12.5)	20	(27.8)	1	(2.9)	0	0
Dermatitis NOS	3	(4.1)	2	(8.3)	6	(8.3)	0	0	0	0
Erythema NEC	4	(5.4)	0	0	3	(4.2)	0	0	0	0
Pruritus NOS	3	(4.1)	1	(4.2)	1	(1.4)	0	0	0	0
Surgical and medical procedures	2	(2.7)	1	(4.2)	11	(15.3)	1	(2.9)	0	0
Device blockage	2	(2.7)	0	0	2	(2.8)	0	0	0	0
Vascular disorders	16	(21.6)	2	(8.3)	10	(13.9)	1	(2.9)	1	(2.9)
Hypertension NOS	3	(4.1)	1	(4.2)	0	0	0	0	1	(2.9)
Hypotension NOS	5	(6.8)	1	(4.2)	4	(5.6)	0	0	0	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.

Drug related adverse events - Cubist-sponsored Phase II/III studies

Table 22 below contains a summary of drug-related AEs by SOC class which occurred in the Cubist-sponsored Phase II/III studies. The most common AE in the daptomycin arms by SOC for both Phase II studies was gastrointestinal disorders in 9/74 (12.2%) and 14/72 (19.4%) patients for studies DAP-BAC-9803 and DAP-BAC-9804, respectively. Drug-related elevations in serum CPK were seen in 3/74 (4.1%) and 4/72 (5.6%) patients in studies DAP-BAC-9803 and DAP-BAC-9804, respectively. No drug-related AEs were reported in study DAP-00-03 in the daptomycin group.

Table 22: Drug-Related Adverse Events Occurring in More than One Patient by System Organ Class and Preferred Term, Cubist-sponsored Phase II/III Studies (Population: All Patients Treated)

System Organ Class/ Preferred Term	DAP-BAC-9803				DAP-RRC-9804		DAP-00-03			
	Daptomycin (N=74)		Comparator (N=24)		Daptomycin (N=72)		Comparator (N=34)		Daptomycin (N=34)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total Number of Patients with at Least One Related AE	28	(37.8)	9	(37.5)	26	(36.1)	5	(14.7)	0	0
Gastrointestinal disorders	9	(12.2)	3	(12.5)	14	(19.4)	4	(11.8)	0	0
Abdominal pain upper	2	(2.7)	0	0	0	0	0	0	0	0
Constipation	1	(1.4)	2	(8.3)	1	(1.4)	0	0	0	0
Diarrhea NOS	3	(4.1)	1	(4.2)	5	(6.9)	4	(11.8)	0	0
Diarrhea aggravated	0	0	0	0	3	(4.2)	0	0	0	0
Dry mouth	1	(1.4)	0	0	1	(1.4)	0	0	0	0
Loose stools	2	(2.7)	0	0	0	0	0	0	0	0
Nausea	3	(4.1)	0	0	5	(6.9)	0	0	0	0
Vomiting NOS	2	(2.7)	0	0	3	(4.2)	0	0	0	0
General disorders and administration site conditions	5	(6.8)	2	(8.3)	3	(4.2)	1	(2.9)	0	0
Injection site pain	2	(2.7)	1	(4.2)	0	0	0	0	0	0
Infections and infestations	5	(6.8)	3	(12.5)	4	(5.6)	0	0	0	0
Oral candidiasis	1	(1.4)	1	(4.2)	0	0	0	0	0	0
Urinary tract infection NOS	0	0	0	0	2	(2.8)	0	0	0	0
Vaginitis	3	(4.1)	0	0	0	0	0	0	0	0
Investigations	7	(9.5)	1	(4.2)	9	(12.5)	0	0	0	0
Blood alkaline phosphatase NOS increased	2	(2.7)	0	0	0	0	0	0	0	0
Blood creatine phosphokinase increased	3	(4.1)	0	0	4	(5.6)	0	0	0	0
Liver function tests NOS abnormal	2	(2.7)	0	0	2	(2.8)	0	0	0	0
Musculoskeletal, connective tissue and bone disorders	2	(2.7)	0	0	3	(4.2)	0	0	0	0
Muscle weakness NOS	1	(1.4)	0	0	1	(1.4)	0	0	0	0
Nervous system disorders	4	(5.4)	3	(12.5)	1	(1.4)	0	0	0	0
Headache NOS	2	(2.7)	0	0	0	0	0	0	0	0
Insomnia NEC	0	0	1	(4.2)	1	(1.4)	0	0	0	0
Skin & subcutaneous tissue disorders	3	(4.1)	0	0	8	(11.1)	0	0	0	0
Dermatitis NOS	0	0	0	0	2	(2.8)	0	0	0	0
Pruritus NOS	2	(2.7)	0	0	1	(1.4)	0	0	0	0
Rash macular	0	0	0	0	2	(2.8)	0	0	0	0

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

Adverse events leading to treatment discontinuation - Cubist-sponsored Phase II/III studies

Table 23 contains data on patients from the Cubist Phase II/III studies who were discontinued from either study due to an AE.

Table 23: Listing of Daptomycin Treated Patients with Adverse Events Leading to Withdrawal, Cubist-sponsored Phase II/III Studies (Population: All Patients Treated)

Patient ID	Age (yrs)	Sex	Total Dose (mgs)	Duration of Rx (days)	Adverse Event Leading to Study Drug Stoppage	Day*	Relationship
DAP-BAC-9803							
0012300001	73	Male	6085	24	Fatigue	1	Possible
					Muscle weakness NOS	1	Possible
0016300001	56	Male	1120	4	Endocarditis NOS	-1	Not Related
0017300001	74	Male	8835	17	Blood pressure increased	1	Not Related
					Pulmonary embolism	1	Not Related
0028300003	64	Male	900	2	Respiratory failure	0	Not Related
0034300002	41	Female	1080	3	Respiratory failure	0	Not Related
0043300004	57	Male	870	3	Endocarditis NOS	0	Not Related
0051300001	73	Male	1175	3	Atrioventricular block complete	0	Possible
0072300001	75	Male	1150	9	Weakness	-3	Possible
DAP-RRC-9804							
0011400001	71	Female	220	1	Cardiac arrest	1	Not Related
					Septicemia Gram-negative NOS	1	Not Related
0016400002	59	Male	3360	7	Anemia NOS	1	Not Related
					Multi-organ failure	3	Not Related
					Sepsis NOS	1	Not Related
0016400004	63	Male	3450	7	Dermatitis NOS	-5	Possible
0030400003	79	Male	2868	5	Blood creatinine increased	2	Possible
0048400002	49	Male	325	1	Sepsis NOS	1	Not Related
0048400005	47	Female	350	1	Cardio-respiratory arrest	0	Not Related
0048400005	47	Female	350	1	Sepsis NOS	0	Not Related
					Small intestinal obstruction NOS	0	Not Related
0048400007	70	Male	7010	35	Acute myeloid leukemia aggravated	1	Not Related
0048400009	38	Female	825	5	Sepsis NOS	-3	Not Related
0048400011	38	Male	600	3	Acute myeloid leukemia NOS	-1	Not Related
0048400013	50	Female	1422	10	Sepsis NOS	-3	Not Related
0048400017	59	Male	840	3	Endocarditis NOS	0	Not Related
					Multi-organ failure	0	Not Related
					Renal failure acute	0	Not Related
0092400001	39	Male	594	1	Blood creatine phosphokinase	1	Possible
					increased		
0092400002	74	Female	629	3	Cardiac arrest	0	Not Related

* Day relative to the last dose of study medication
Note: Patient 0048400002 was dual enrolled under the patient number 0048400004

In the Cubist-sponsored Phase II/III studies, a total of 23 patients (21 patients in the daptomycin group and 2 patients in the comparator group) were discontinued from study treatment due to AEs. In study DAP-BAC-9803, ten patients were discontinued from study treatment due to AEs, including 8/74 (10.8%) patients in the daptomycin group. Discontinuations due to AEs occurred in 5/24 (20.8%) patients in the daptomycin 4 mg/kg q24h group, 1/26 (3.8%) patients in the daptomycin 6 mg/kg q24h group, 2/24 (8.3%) patients in the daptomycin 3 mg/kg q12h group, and in 2/24 (8.3%) patients in the comparator group. The events leading to discontinuation were reported as possibly or probably related to study

treatment for three patients in the daptomycin group. A brief summary of the daptomycin-treated patients with drug-related AEs resulting in discontinuation follows:

- Patient 0012300001 was a 73 year old male who discontinued daptomycin on d24 due to fatigue and muscle weakness which were assessed as mild in severity and possibly related to the study drug by the investigator. The patient had a history of coronary artery disease (CAD), myocardial infarction (MI), supraventricular tachycardia (SVT), hypertension (HTN), s/p pacemaker placement, and diabetes mellitus (DM) and was treated with daptomycin for an infected hematoma with *S. aureus* bacteremia. Serum CPK was noted to be elevated on d16 at 514 U/L and reached a peak on d17 at 694 U/L. On d22 the daptomycin dose was decreased from 4 mg/kg to 3 mg/kg in response to the elevated serum CPK. Daptomycin was discontinued on d24 after the patient developed fatigue and muscle weakness. Serum CPK returned to normal by day 4P.
- Patient 0072300001 was a 75 year old male patient with a history of chronic obstructive pulmonary disease (COPD), DM, and atherosclerotic cerebrovascular disease (ASCVD) treated for *S. aureus* pneumonia and bacteremia who developed "weakness" on d6 of daptomycin 4 mg/kg q24h. This event was considered to be of marked intensity and possibly related to study drug. Daptomycin was discontinued due to this event on d9 and he was discharged to a nursing home, where he died of a COPD exacerbation on day 8P. Recorded serum CPK on d9 was normal.
- Patient 0051300001 developed complete atrioventricular block (AVB) block and died. This patient is discussed in "Deaths" below. His AE of complete AVB was thought by the investigator to be possibly related to study drug treatment.

Medical Officer Comment
Discontinuations due to AEs occurred disproportionately in the 4 mg/kg q24h group in study DAP-BAC-9803. The AE of increased serum CPK with fatigue and muscle weakness is consistent with the AE profile of daptomycin described in preclinical and Phase I studies. The weakness in patient 00732300001 is difficult to attribute to study drug due to its nonspecificity.

In study DAP-RRC-9804, 14/72 (17.1%) patients had study treatment discontinued due to an AE, including 2/23 (8.7%) in the 4 mg/kg q24h group, 6/34 (17.6%) in the 6 mg/kg q24h group, 3/11 (27.3%) in the 3 mg/kg q12h group, and 2/6 (33.0%) in the dialysis group. Three patients had AEs that were considered by the investigator to be possibly related to study drug, all in the 6 mg/kg q24h group. Brief summaries of these three patients follow:

- Patient 0016400004 was a 64 year old male treated with 6 mg/kg q24h for an IAI with positive blood cultures for *Enterococcus faecalis* and *Enterococcus faecium*. He developed a rash on d2; daptomycin was

discontinued due to the rash on d7. The rash was thought to be possibly related to study drug.

- Patient 003040003 was a 79 year old male with multiple medical problems acutely ill with sepsis treated with daptomycin 6 mg/kg q24h for an IAI with cultures positive for *E. faecalis* and *E. faecium*. On d1P he developed severe acute respiratory distress syndrome (ARDS) and decreased urine output; daptomycin was discontinued on day 2P due to elevated creatinine (marked severity, investigator assessed as possibly related) with progression to acute renal failure and death on d9P.
- Patient 0092400001 was a 39 year old male hospitalized for pneumonia (blood culture grew VRE) who was intubated due to respiratory failure and who had a CPK = 52 U/L on d0P at 1545 U/L, and then received daptomycin 6 mg/kg. Daptomycin was discontinued the following day when his CPK rose to 2895 U/L. CPK remained elevated until day 14P, then resolved; isoenzyme pattern was MM. This AE was considered of marked severity and possibly related to study drug. No definite symptoms of myopathy were noted, although the patient was intubated and paralyzed.

No patient in study DAP-00-03 was discontinued due to an adverse event.

Medical Officer Comment
Renal toxicity was not described in the AEs in the preclinical studies of daptomycin; in the case described above, other etiologies of the elevated creatinine appear to be more likely than daptomycin.

Serious adverse events - Cubist-sponsored Phase II/III studies
In DAP-BAC-9803, 25/74 (33.8%) daptomycin-treated patients and 7/24 (29.2%) comparator-treated patients reported SAEs. In Study DAP-BAC-9803, a total of 32 patients experienced one or more SAEs, including 25/74 (33.8%) patients in the daptomycin group and 7/24 (29.2%) patients in the comparator group. There was no difference between the drug exposure groups for the overall incidence of SAEs. The only difference between drug exposure groups for incidence of SAEs in any MedDRA SOC was observed in the Respiratory, Thoracic and Mediastinal Disorders; significantly more patients in the daptomycin group (6/71; 8.1%) than the comparator group (0/24) experienced SAEs in this system. However, none of the SAEs in this system were judged as possibly or probably related to study treatment. There was a higher incidence of SAEs reported in the 6 mg/kg q24h daptomycin group (12/26; 46.2%) than in the 4 mg/kg q24h (5/24; 20.8%) or the 3 mg/kg q12h groups (8/24; 33.3%); however, no SOC was represented disproportionately in the 6 mg/kg q24h group.

In Study DAP-RRC-9804 a total of 45/72 (62.5%) daptomycin-treated patients experienced a total of 86 SAEs including 13/23 (56.5%) in the 4 mg/kg q24h group, 19/34 (55.9%) in the 6 mg/kg q24h group, 7/11 (63.6%) in the 3 mg/kg q12h group, and 6/7 (85.7%) in the dialysis group. The high incidence of SAEs reported in the dialysis group may reflect the severity of disease at baseline.

There was no apparent difference among the four dose groups for the overall incidence of any SAE.

In Study DAP-00-03, 2/68 (2.9%) patients (1/34 daptomycin-treated, 2.9%; 1/34 comparator-treated, 2.9%) experienced a total of 3 SAEs: arrhythmia and paralytic ileus in a daptomycin-treated patient, and deep venous thrombosis in a comparator-treated patient.

In the Cubist-sponsored Phase II/III studies, six patients in the daptomycin group had a total of six SAEs assessed as possibly or probably related to study treatment; these patients are summarized in table 24 below.

Table 24: Listing of Daptomycin-Treated Patients with Serious Adverse Events, Cubist-sponsored Phase II/III Studies (Population: All Patients Treated)

Patient ID	Age (yrs)	Sex	Dose (mgs)	Duration of Rx (Days)	Serious Adverse Event	Day[a]	Relationship
DAP-BAC-9803							
0007300005	24	Female	14280	42	Cholecystitis acute NOS	3	Possible
0023300001	54	Male	3135	10	Leukopenia NOS	3	Possible
0032300002	57	Male	11200	28	Pericardial effusion	0	Possible
0051300001	73	Male	1175	3	Atrioventricular block complete	0	Possible
DAP-RRC-9804							
0030400003	79	Male	2868	5	Renal failure acute	4	Possible
					Thrombocytopenia aggravated	-6	Possible

[a] Day of AE relative to the last dose of study medication

Medical Officer Comment

The high rate of SAEs described in these two Phase II clinical trials is most likely a result of the severe underlying conditions and serious presenting illnesses (endocarditis, Gram-positive bacteremia, and Gram-positive infections of the patients in these two studies). Examination of all of the narratives for the SAEs in the daptomycin arms were examined by the Medical Officer. The Medical Officer agrees with the assessment of not related for all but six patients in the daptomycin arm. A causal association of these six cases cannot be ruled out, but appears to be unlikely.

Deaths - Cubist-sponsored Phase II/III studies

A total of 37 deaths were reported in Cubist-sponsored Phase II/III studies. AEs with an outcome of death in patients receiving daptomycin are shown in table 25 below; table 26 shows the reasons for death in patients receiving comparator. In study DAP-BAC-9803, ten daptomycin-treated patients and two comparator-treated patients died. In study DAP-RRC-9804, 25 daptomycin-treated patients died. The cause of death was considered by the investigator to be not related to study drug treatment in all but one case; most of the deaths were felt to be due to underlying illnesses. A brief summary (derived from the narrative and the CRF) of the only death thought to be possibly related to study drug treatment from study DAP-BAC-9803 follows.

- Patient 0051300001 was a 73 year old BM who received daptomycin 3 mg/kg q12h for a complicated UTI (suprapubic catheter and *S. aureus* bacteremia). His past medical history (PMH) was significant for severe rheumatoid arthritis, MI, ischemic heart disease (IHD), cardiac dysrhythmia (including atrial fibrillation and atrial flutter), congestive heart failure (CHF) and HTN. On d2 of treatment, worsening of atrial flutter and atrial fibrillation were observed, and an ECG on d3 showed bundle branch block. He developed complete heart block on d3 and could not be intubated due to deformities resulting from his rheumatoid arthritis, and cardiorespiratory resuscitation (CPR) was unsuccessful. The investigator considered that a relationship of the heart block to the study drug was unlikely but could not be excluded.

Medical Officer Comment
Preclinical studies did not define cardiovascular toxicity of daptomycin, and a Phase I study designed to look at conduction effects of daptomycin did not demonstrate any abnormalities. Although the temporal relationship of this death to study drug administration is concerning, it appears unlikely that there is a causal relationship to daptomycin administration.

Table 25: Listing of Daptomycin Treated Patients Who Died, Cubist-sponsored Phase II/III Studies (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-BAC-9803								
0010300003	41	Female	8880	20	Progression of Ovarian Cancer	13P	13P	Not Related
0012300004	58	Male	4018	9	Non-Hodgkin's Lymphoma	7	14P	Not Related
					Renal Failure	11P	14P	Not Related
0023300001	54	Male	3135	10	Gram Negative Sepsis	9P	16P	Not Related
0028300003	64	Male	900	2	Respiratory Failure	0P	0P	Not Related
0034300002	41	Female	1080	3	Worsening Respiratory Failure	0P	4P	Not Related
0037300008	75	Female	3420	6	Multisystem Organ Failure	13P	13P	Not Related
0051300001	73	Male	1175	3	Third Degree Heart Block	0P	0P	Possible
0061300001	58	Male	3776	8	Cardio Pulmonary Arrest	18P	18P	Not Related
0061300002	76	Male	2510	7	Probable Massive Pulmonary Embolism	0P	0P	Not Related
0072300001	75	Male	1150	9	Exacerbation Of COPD	8P	8P	Not Related
DAP-RRC-9804								
0006400001	58	Female	4216	9	Hepatic Failure	3P	10P	Not Related
					Multisystem Organ Failure	10P	10P	Not Related
					Renal Failure	3P	10P	Not Related
					Sepsis	4P	10P	Not Related
0008400003	25	Male	868	2	Lower Gastrointestinal Bleed	21P	24P	Not Related
0011400001	71	Female	220	1	Gram Negative Sepsis	1P	2P	Not Related
0016400002	59	Male	3360	7	Multi-Organ System Failure	3P	3P	Not Related
0016400005	53	Male	4000	8	Cardio Pulmonary Arrest	0P	0P	Not Related
0030400001	53	Female	780	3	Progression of Advanced Adenocarcinoma of Uterus	13P	13P	Not Related
0030400002	59	Female	3817	11	Cardiopulmonary Arrest Secondary To ARDS	0P	0P	Not Related
0030400003	79	Male	2868	5	Sepsis	2P	9P	Not Related
0030400004	74	Female	280	1	Advanced Cancer	15P	15P	Not Related
0046400001	33	Male	6014	50	Cardiac Arrest	0P	0P	Not Related
					Paravalvular Leak	44	0P	Not Related
0046400002	45	Male	680	1	Refractory Shock	1P	1P	Not Related
0048400002[b]	49	Male	325	1	Overwhelming Sepsis	1P	1P	Not Related
0048400005	47	Female	350	1	Cardiopulmonary Arrest	0P	1P	Not Related
					Overwhelming Sepsis	0P	1P	Not Related
					Worsening Small Bowel Obstr	0P	1P	Not Related
0048400006	35	Male	12050	28	Cardiopulmonary Arrest	13P	13P	Not Related
0048400007	70	Male	7010	35	Progression Of AML	1P	2P	Not Related
					Cardiopulmonary Arrest	2P	2P	Not Related
0048400009	38	Female	825	5	Progressive Sepsis	2	1P	Not Related
0048400011	38	Male	600	3	AML Recurrence	2	1P	Not Related
0048400013	50	Female	1422	10	Progressive Sepsis	7	3P	Not Related
0048400017	59	Male	840	3	Multisystem Organ Failure	0P	3P	Not Related
0051400004	69	Female	3640	7	Small Bowel Obstruction	10P	11P	Not Related
0051400006	68	Female	2555	7	Ventricular Fibrillation	16P	16P	Not Related
					Ventricular Tachycardia	16P	16P	Not Related
0053400002	56	Male	1566	21	Unresponsive	6P	6P	Not Related
0060400001	45	Male	4950	12	Septic Shock	25P	29P	Not Related

0080400001	78	Female	2275	7	Worsening COPD of Asthma Acute Respiratory Failure (Worsening)	2P 2P	2P 2P	Not Related Not Related
0092400002	74	Female	629	3	Cardiac Arrest	0P	0P	Not Related

[a] In relative day format .
[b] Patient 0048400004 in second enrollment

Table 26: Listing of Comparator Treated Patients Who Died, Cubist-sponsored Phase II/III Studies (Population: All Patients Treated)

Patient ID	Age (yrs)	Sex	Duration of Rx (Days)	Adverse Event (Verbatim) With An Outcome Of Death	Start Day[a]	Stop Day[a]	Relationship
DAP-BAC-9803							
0043300002	82	Male	27	Worsening Gastric Adenocarcinoma	7P	7P	Not Related
0044300001	76	Male	6	Sepsis	1P	1P	Not Related

[a] In relative day format

In study DAP-BAC-9803, death occurred in 3/24 (12.5%) patients in the daptomycin 4 mg/kg q24h group, 4/26 (15.4%) patients in the daptomycin 6 mg/kg q24h group, 3/24 (12.5%) patients in the daptomycin 3 mg/kg q12h group, and in 2/24 (8.3%) patients in the comparator group. In study DAP-RRC-9804, death occurred in 6/23 (26.1%) patients in the 4 mg/kg q24h group, 10/33 (30.3%) patients in the 6 mg/kg q24h group, 5/10 (50.0%) patients in the 3 mg/kg q12h group, and four of six (66.7%) patients in the dialysis group. Of the 37 patients who died in the Cubist-sponsored Phase II/III studies, 22 were male and 15 were female. Fourteen of the 37 patients were ≥ 65 years of age and 23 were < 65 years of age. Duration of study treatment among the 37 patients who died varied, ranging from one to 50 days in the daptomycin group and from 6 to 27 days for the two comparator patients. Nineteen of the 37 deaths (18 daptomycin-treated, 1 comparator-treated) occurred while patients were on study drug or up to three days after the drug had been stopped. The other 18 deaths (17 daptomycin-treated, 1 comparator-treated) occurred 4 to 29 days after treatment with the study drug had been stopped.

Medical Officer Comment
The relatively high mortality rate in study DAP-RRC-9804 is not unexpected given the serious underlying illnesses in this patient population; there was no comparator arm in this study. The death rate appears to be unrelated to dose, although the high dose group in study DAP-RRC-9804 had a somewhat higher mortality rate; the small numbers preclude definitive conclusions.

No deaths occurred in the prematurely discontinued Phase III study, DAP-00-03.

Lilly-sponsored Phase II studies

Demographics

Three Phase II studies were conducted by Lilly during the years 1987 - 1990. Demographic data collected in the Lilly-sponsored Phase II studies was limited to the parameters of age and sex. Study B8B-MC-AVAE/B8B-EW-AVAG was a randomized, blinded, multi-center study in patients with various Gram-positive infections; daptomycin was given at 2 mg/kg q24h for up to 25 days. The mean age of patients treated with daptomycin was 49.2 years (range 18 to 86 years) and 50.6 years (range 21 to 90 years) in patients in the comparator group. The daptomycin-treated group contained 47 males and 33 females; 50 males and 31 females were treated with comparator.

The second Phase II study, B8B-MC-AVAM, was a randomized, open-label study in which patients with endocarditis and bacteremia were given daptomycin (loading dose of 6 mg/kg followed by 3 mg/kg q12h) for up to 42 days; pharmacodynamic data was collected in this study. The mean age in daptomycin-treated patients was 51.7 years (range 21 to 93 years) and in comparator-treated patients was 48.4 years (range 21 to 93 years). The daptomycin-treated group was made up of 64 males and 25 females; there were 25 males and 10 females treated with comparator.

The third Phase II study, B8B-EW-AVAH, was an open-label, uncontrolled study to evaluate the efficacy of daptomycin in patients with Gram-positive skin and skin structure infections. This study was terminated after only 4 of the planned 50 patients were enrolled. No demographic information was provided for the four enrolled patients.

Medical Officer Comment

The Lilly-sponsored Phase II studies were conducted more than a decade prior to submission of this NDA. Significant advances in critical care have occurred during this time period, which may have resulted in higher AE rates than might be seen in a similar study today. The lack of significant demographic information also limits interpretation of these trials.

Overall adverse events - Lilly-sponsored Phase II studies

In study B8B-MC-AVAE/B8B-EW-AVAG, a total of 166 AEs were reported by 53/80 (66.3%) patients treated with daptomycin 2 mg/kg q24h; 226 events were reported by 53/81 (65.4%) patients randomized to conventional therapy. The most commonly occurring events across both treatment groups were nausea, vomiting, pruritis, diarrhea, headache, rash and phlebitis. In study B8B-MC-AVAE/B8B-EW-AVAG, the majority of reported AEs were likely due to the severity of the patient's underlying illnesses.

In study B8B-MC-AVAM, 52/89 (58.4%) daptomycin-treated patients (6 mg/kg loading dose followed by 3 mg/kg q12h for up to 44 days) and 20/35 (57.1%) comparator-treated patients had at least one treatment emergent AE. Table 27

below summarizes the AEs in this study that were reported by over 4% of the study population. The most commonly reported AEs occurring in >10% of patients across both treatment groups included cardiovascular disorder, constipation, nausea, edema, pain, insomnia, vaginitis, rash and surgical procedure.

Table 27: Incidence of Treatment Emergent Adverse Events[a] in Lilly-sponsored Study B8B-MC AVAM[b] Treatment Group

	Daptomycin 3 mg/kg q 2hr[c] N=89	Conventional Therapy N=35
Adverse event	**Number of Patients (%)**	
No. of patients with at least one event	52 (58.4)	20 (57.1)
Cardiac disorders	9 (10.1)	3 (8.6)
	9 (10.1)	3 (8.6)
Gastrointestinal disorders	26 (29.2)	13 (37.1)
Constipation	11 (12.4)	3 (8.6)
Diarrhea	4 (4.5)	2 (5.7)
Dyspnea	6 (6.7)	3 (8.6)
Nausea	5 (5.6)	5 (14.3)
General disorders and administrative site conditions	23 (25.8)	9 (25.7)
Edema	9 (10.1)	2 (5.7)
Pain	14 (15.7)	7 (20.0)
Investigations	5 (5.6)	1 (2.9)
Hypotension	5 (5.6)	1 (2.9)
Nervous system disorders	13 (14.6)	6 (17.1)
Headache	8 (9.0)	1 (2.9)
Insomnia	5 (5.6)	5 (14.3)
Reproductive system and breast disorders	4 (16.0)	0 (0.0)
Vaginitis	4 (16.0)[d]	0 (0.0)
Skin and subcutaneous tissue disorders	7 (7.9)	5 (14.3)
Rash	7 (7.9)[e]	5 (14.3)
Surgical and medical procedures	19 (21.3)	7 (20.0)
Surgical procedure	19 (21.3)	7 (20.0)
Vascular disorders	4 (4.5)	1 (2.9)
Phlebitis	4 (4.5)	1 (2.9)

a. Limited to those that occurred in over 4% of the study population. Some patients also received concomitant aminoglycoside therapy.
b. There were no statistically significant differences between treatment groups in the incidences of these AEs
c. 6 mg/kg loading dose administered, then 3 mg/kg q 12 hr
d. Calculated based on 25 women in the daptomycin group
e. Only one daptomycin-treated patient had a rash suggestive of a hypersensitivity reaction.

Drug related adverse events - Lilly-sponsored Phase II studies

The majority of the events reported in the Lilly-sponsored Phase II studies were ascribed by the investigator to the patient's underlying illness. Table 28 below summarizes AEs in study B8B-MC-AVAE/B8B-EW AVAG which have a possible or probable causal relationship to study drug administration.

Table 28: Incidence of Possibly or Probably Treatment-related Adverse Events in Lilly-sponsored Study B8B-MC-AVAE/B8B-EW AVAG

Adverse events	No. of events	
	Daptomycin[a] 2 mg/kg i.v. q24h N=80	Comparator N=81
Blood and lymphatic system disorders	0	5
Hemolysis	0	1
Neutropenia	0	4
Ear and labyrinth disorders	1	0
Tinnitus	1	0
Eye Disorders	1	0
Blurred vision	1	0
Gastrointestinal disorders	10	17
Diarrhea	5	5
Nausea	4	9
Vomiting	1	3
Infections and infestations	0	3
Moniliasis	0	3
Nervous system disorders	6	7
Dizziness	2	2
Headache	2	4
Paresthesia	2	1
Renal and urinary disorders	2	2
Renal insufficiency	2	2
Skin and subcutaneous tissue disorders	5	10
Pruritus	1	5
Rash	4	5
Vascular disorders	6	7
Phlebitis	6	7

a. Other antimicrobials may also have been administered

Medical Officer Comment

It is unclear how this table was constructed, since the CRFs for studies B8B-MC-AVAE/B8B-EW-AVAG and B8B-MC-AVAM do not contain space for the investigator to assess the relationship of AEs to study drug administration. The drug-related AEs listed are consistent with the AEs described in the preclinical studies and Phase I clinical trials. There is no written information or summarizing table contained in the ISS, Lilly ISS, or study report regarding drug related AEs in study B8B-MC-AVAM. It is likely that most reported AE's from both of these studies are related to the severity of the patient's underlying illnesses, since these were hospitalized patients with serious Gram-positive infections.

Adverse events leading to treatment discontinuation - Lilly-sponsored Phase II studies

AEs led to study discontinuation in two of the Lilly Phase II studies. In Study B8B-MC-AVAE/G, 7/80 (8.8%) of patients in the daptomycin treatment group and 3/81 (3.7%) of patients given comparator were discontinued from the study

due to AEs. These events included abscess, blurred vision, cardiogenic shock, edema, hemolytic anemia, injection site pain, pneumonia, rash and sepsis. In Study B8B-MC-AVAM, 10/89 (11.2%) of patients in the daptomycin treatment group and 2/35 (5.7 %) of those patients given comparator were discontinued from the study due to AEs. Allergic reaction, aortic insufficiency, cardiovascular disorder, elevated CPK, elevated liver function tests (LFTs), exacerbation of lymphoproliferative disorder, neuropathy, rash and sepsis were the events which lead to discontinuation. Table 29 below presents a list of patients who discontinued study drug due to AEs in the Lilly studies.

Table 29: Listing of Patients with Adverse Events Leading to Withdrawal, Lilly-sponsored Phase II Studies (Population: All Patients Treated)

Study No.	Patient	Age	Sex	Race	Adverse Event	Indication for Treatment and Co-Morbid Condition
B8B-MC-No. Daptomycin						
AVAE/G	02-0051	47	Male	Caucasian	Post-obstructive pneumonia	Wound infection and sepsis due to *S. aureus* and *S. pneumoniae*
AVAE/G	02-0063	62	Male	Caucasian	Aortic valve ring abscess	Endocarditis
AVAE/G	05-0204	N/A	Female	N/A	Abscess	Skin and soft tissue infection
AVAE/G	06-0255	26	Male	Black	Rash	Osteomyelitis
AVAE/G	08-0302	44	Female	Caucasian	Edema	Cellulitis
AVAE/G	16-0701	57	Male	Caucasian	Blurred vision	Septic arthritis
AVAE/G	16-0707	65	Female	Hispanic	Sepsis	Endocarditis
AVAM	01-0001	73	Male	Caucasian	Neuropathy	*S.aureus* endocarditis
AVAM	02-1017	35	Male	Caucasian	Rash	Bacteremia due to Group A Streptococccus
AVAM	07-1085	78	Male	Caucasian	Exacerbation of lymphoprolifrative disorder	Enterococcus endocarditis
AVAM	09-1097	67	Male	Black	Elevated CPK	Endocarditis due to *Enterococcus faecalis*
AVAM	10-0122	35	Female	Black	Aortic insufficiency	Endocarditis due to *Staphylococcus epidermis*
AVAM	11-0133	63	Male	Caucasian	Sepsis	Bacteremia due to *S.aureus*
AVAM	11-0135	35	Male	Black	Cardiovascular disorder	*S.aureus* endocarditis
AVAM	11-0136	24	Female	Caucasian	Elevated liver function tests	*S. aureus* endocarditis
AVAM	11-1136	43	Male	Black	Elevated CPK	Endocarditis
AVAM	13-0155	33	Female	Caucasian	Allergic reaction	Not stated
AVAP	001-0010	42	Male	Black	Elevated CPK	Healthy volunteer
AVAP	001-0008	43	Male	Caucasian	Elevated CPK	Healthy volunteer
Comparator						
AVAE/G	01-0006	32	Female	Black	Hemolytic anemia	Skin and soft tissue infection
AVAE/G	02-0066	40	Male	Caucasian	Pain at injection site	Skin and soft tissue infection
AVAE/G	13-0554	35	Male	Caucasian	Cardiogenic shock	Bacteremia
AVAM	04-1041	44	Female	Caucasian	Rash	Bacteremia
AVAM	21-0266	30	Male	Caucasian	Rash	Endocarditis

It was not possible to determine investigator assessment of causality, since this information was not captured on the patient narratives or CRFs. Review of these sources by the Medical Officer for relationship of the AE to study drug revealed the following:

Study B8B-MC-AVAE/B8B-EW-AVAG: One of the seven AEs resulting in discontinuation was a rash in daptomycin-treated patient 06-0255 which was possibly due to study drug.

Medical Officer Comment
For study B8B-MC-AVAE/B8B-EW-AVAG, a table (Lilly ISS page 32) gives the incidence of possibly or probably treatment-related AEs by SOC and preferred term; this data is not broken down by patient. However, it is unclear how this data was derived, since there is no place on the case report form for causality. No similar table is presented for study B8B-MC-AVAM.

Study B8B-MC-AVAM: Six of the ten AEs resulting in discontinuation are possibly or probably related to study drug in the daptomycin arm; these AEs are presented below.

- Patients 02-1017 and 13-0155 developed a rash and allergic reaction, respectively. These AEs were probably related to study drug administration.
- Patient 01-001 developed a neuropathy which was probably related to study drug administration. A brief summary of this case follows.
    - Patient 01-001 was a 73 year old male treated with daptomycin 3 mg/kg q12h for *S. aureus* endocarditis. NCVs done on d4 as a routine study procedure were normal. On d12 he complained of tingling in one foot that lasted for one day; repeat NCVs on d18 demonstrated findings consistent with moderate to severe neuropathy, and he was withdrawn from the study. He did not return for follow-up. The neurologist at the site noted that sensory sural nerve test showed "no action potentials either proximally or distally." He commented that "these are abnormal findings and are consistent with a rather moderate to severe neuropathy with a marked drop in amplitude, suggesting that the medication under question has most probably affected his nervous system."
- Patients 11-136 and 09-1097 developed elevated serum CPK which was probably related to study drug administration. Brief summaries of these cases follow.
    - Patient 11-136 was a 67 year old male who received daptomycin 3 mg/kg q12h for 21 days for *E. faecalis* endocarditis. He was found to have an elevated serum CPK on d19, and daptomycin was discontinued on d21; he died of gastric aspiration on d24. Serum CPK on last determination day 23 = 159 U/L.
    - Patient 09-1097 was a 43 year old male with AIDS treated with daptomycin 3 mg/kg q12h for *S. aureus* endocarditis. On d16 his serum CPK was 889 U/L from a baseline of 84 U/L, on d17 1027

U/L, on d18 821 U/L, and daptomycin was discontinued. The patient was asymptomatic. One d28 serum CPK was 29 U/L.

- Patient 11-0136 developed elevated LFTs which were possibly related to daptomycin administration. A brief case summary follows.
  - Patient 11-0136 was a 24 year old HIV positive female admitted with *S. aureus* endocarditis and treated with daptomycin 3 mg/kg q12h. LFTs were normal on entrance into the study, with marked elevation during week 3 (SGPT: 698, 1374, and 932 IU/L; SGOT: 298, 357, and 208 IU/L). Daptomycin was discontinued, and two weeks later the patient's LFTs had improved (SGPT: 470 IU/L; SGOT: 270 IU/L). Four weeks later her LFTs were normal.

Serious adverse events - Lilly-sponsored Phase II studies

SAEs were reported in all three of the Lilly-sponsored Phase II studies. One of the four patients enrolled in study B8B-EW-AVAH was discontinued from that study due to a 50% decrease in NCV amplitude after a 1 mg dose of daptomycin; no further details are available from the study report. In study B8B-MC-AVAE/AVAG, 6/80 (7.5%) of daptomycin-treated patients and 6/81 (7.4%) of patients in the comparator-treated group had SAEs reported. These SAEs included angina, UTI, cerebral hemorrhage, pancreatitis, decreased NCV, renal failure, aortic valve replacement, MI, pulmonary embolism, edema, labial pain and neutropenia. In study B8B-MC-AVAM, 6/89 (6.7%) of patients in the daptomycin-treated group had SAEs These events included candida endocarditis, epidural abscess, acute renal failure, mitral valve vegetation, vasovagal episode, and mediastinal emphysema. There were no reported SAEs for patients in the comparator-treated group in study B8B-MC-AVAM. Table 30 below presents a list of patients with SAEs in the Lilly-sponsored studies.

Medical Officer Comment

As described above in "Methods and Specific Findings of Safety Review", SAEs were not reported in all of the Clinical Study Reports provided by Lilly. Additional information regarding SAEs was obtained by Cubist from a search conducted of a safety database at Eli Lilly. This database contained information about SAEs, including deaths and discontinuations, that did not appear in the original Lilly study reports.

Table 30: Listing of Patients with Serious Adverse Events, Lilly-sponsored Phase II Studies (Population: All Patients Treated)

Study No. B8B-MC-	Patient No.	Age	Sex	Race	Adverse Event	Indication for Treatment and Co-Morbid Condition
Daptomycin						
AVAD	001-0014	N/A	Male	N/A	Anemia	None noted
EW- AVAH	02-0002	53	Female	N/A	Decreased nerve conduction	Cellulitis
AVAE/G	01-5003	27	Female	N/A	Cerebral hemorrhage	*S. aureus* septicemia and mitral valve endocarditis
AVAE/G	02-0060	74	Male	Caucasian	Pancreatitis	Pacemaker-associated wound infection
AVAE/G	06-0255	26	Male	Black	Renal failure	None noted
AVAE/G	08-0302	44	Female	Caucasian	Labial pain, edema	Cellulitis
AVAE/G	08-0309	48	Male	Caucasian	Surgery for aortic valve replacement	Enterococcal endocarditis
AVAE/G	103-5104	43	Male	Caucasian	Decreased nerve conduction	Infection of the pleural cavity
AVAM	02-0018	37	Female	Caucasian	Candida endocarditis	Endocarditis
AVAM	04-1043	59	Male	Caucasian	Epidural abscess	Bacteremia due to *S. aureus*
AVAM	10-0123	32	Female	Caucasian	Acute renal failure	Enterococcus-induced endocarditis
AVAM	11-0135	35	Male	Black	Mitral valve vegetation	*S. aureus*-induced endocarditis
AVAM	12-1073	54	Female	Caucasian	Vasovagal attack	Bacteremia
AVAM	21-0265	22	Male	Caucasian	Mediastinal emphysema	Endocarditis due to *S. aureus*
Comparator						
AVAE/G	01-0001	59	Male	Black	Angina	Cellulitis
AVAE/G	01-5002	85	Male	N/A	Urinary tract infection	Bacteremia
AVAE/G	06-0252	32	Male	Black	Decreased nerve conduction	Endocarditis
AVAE/G	10-0401	55	Female	Black	Myocardial infarction	Bacteremia
AVAE/G	13-0552	30	Male	Caucasian	Neutropenia	Bacteremia
AVAE/G	103-5102	30	Male	Caucasian	Pulmonary embolism	Endocarditis

As described above in "Adverse events leading to treatment discontinuation" for Lilly Phase II studies, it is not possible to determine causality for a given SAE in a specific patient from these Lilly-sponsored studies. The Medical Officer reviewed the SAEs, and most of the SAEs appear to be related to the serious nature of the patient's underlying illnesses. The following SAEs from study B8B-MC-AVAE/G

are presented briefly because they may be representative of daptomycin neurotoxicity.

- Patient 103-5104 was a 43 year old male with a malignant mesothelioma and an infected pleural effusion. He was treated with daptomycin 2 mg/kg q24h. NCVs decreased from baseline values on d2 by 50% on d10, d9P, and d16P. The patient was asymptomatic and did not return for follow-up.
- Patient 006-0252 was a 32 year old male who received gentamicin and vancomycin in standard doses for the treatment of native valve endocarditis. Baseline NCVs were conducted on d3; follow-up NCVs on d9, d17, d5P, and d37P showed a decrease in NCV of the sural nerve by 33-50%.

Medical Officer Comment
The decrease in NCVs seen in patient 103-5104 is consistent with the neurotoxic effects of the drug predicted from the preclinical studies. However, similar NCV findings noted in patient 06-0252 who received the comparator agents demonstrate the difficulty in this moderate to severely ill patient population of demonstrating causality of SAEs. Patient 013-0552 developed neutropenia, a known adverse event of vancomycin therapy.

Deaths - Lilly-sponsored Phase II studies

A total of 32 patients died during the Lilly-sponsored Phase II studies, including 20 patients treated with daptomycin and 12 patients treated with comparator. Patient deaths in the Phase II studies occurred at similar rates for both treatment groups. In study B8B-MC-AVAE/G, 7/80 (8.7%) patients in the daptomycin treatment group and 6/81 (7.4%) patients in the comparator group died during their participation in the study. Causes of death included cardiac arrest, cerebral hemorrhage, lung cancer, renal failure, respiratory failure, sepsis, shock, and sudden death. In study B8B-MC-AVAM, 13/89 (14.6%) daptomycin-treated patients and 6/35 (17.1%) patients in the comparator arm died during the study. Causes of death included abscess, cardiac arrest, cirrhosis of the liver, CHF, end stage pulmonary disease, gastrointestinal hemorrhage, gastric aspiration, metastatic carcinoma, multi-organ system failure, peritonitis, post-operative complications, respiratory failure, and sepsis. None of the patient deaths were attributed by the investigator to daptomycin administration. Table 31 presents a listing of the patients who died in the daptomycin and comparator treatment groups in the Lilly-sponsored Phase II studies.

Table 31: Listing of Patients Who Died, Lilly-sponsored Phase II Studies (Population: All Patients Treated)

Study No. B8B-MC-	Patient No.	Age	Sex	Race	Adverse Event	Indication for Treatment and Co-Morbid Condition
Daptomycin						
AVAE/G	02-0072	N/A	Male	N/A	Lung cancer	Mediastinitis
AVAE/G	05-0201	74	Female	Caucasian	Sepsis	Bacteremia
AVAE/G	07-0104	86	Female	Caucasian	Shock	Skin and skin structure infection due to *S. aureus*
AVAE/G	10-0402	57	Female	Caucasian	Cerebral hemorrhage	Bacteremia
AVAE/G	22-1003	66	Female	Caucasian	Shock	Bacteremia
AVAE/G	22-1005	62	Male	Caucasian	Renal failure	Bacteremia
AVAE/G	103-5101	67	Female	Caucasian	Sudden death	Cellulitis
AVAM	02-1024	39	Male	Hispanic	Gastrointestinal hemorrhage	Bacteremia due to *S. aureus*
AVAM	03-1026	67	Male	Caucasian	Peritonitis	Bacteremia due to *S. epidermidis*
AVAM	05 0050	92	Male	Caucasian	Congestive heart failure	Endocarditis
AVAM	06-1066	51	Male	Caucasian	Renal and respiratory failure	Bacteremia due to enterococcus
AVAM	09-1097	67	Male	Black	Massive gastric aspiration	Endocarditis due to *Enterococcus faecalis*
AVAM	10-0121	62	Male	Black	Post-operative complications	Endocarditis
AVAM	10-1122	47	Female	Caucasian	Metastatic carcinoma	Bacteremia due to *S. epidermidis*
AVAM	10-1123	65	Female	Black	End stage pulmonary disease	Bacteremia
AVAM	11-0133	63	Male	Caucasian	Sepsis	Bacteremia due to *Staphylococcus aureus*
AVAM	11-1138	39	Male	Caucasian	Cirrhosis of the liver	*S. aureus* bacteremia
AVAM	13-0148	42	Male	Black	Gastrointestinal bleed	Endocarditis
AVAM	14-0157	45	Male	Caucasian	Cardiac arrest	Endocarditis due to *S. aureus*
AVAM	19-0219	28	Male	Black	Abscess	Bacteremia

Comparator						
AVAE/G	08-0313	64	Male	Caucasian	Respiratory arrest	Cellulitis
AVAE/G	20-0905	59	Male	Caucasian	Respiratory failure	Cellulitis
AVAE/G	08-0306	35	Male	Hispanic	Cardiac arrest	Bacteremia
AVAE/G	08-0320	71	Male	Caucasian	Renal failure	Bacteremia
AVAE/G	16-0706	83	Female	Caucasian	Renal failure	Endocarditis
AVAE/G	103-5103	31	Female	Caucasian	Sepsis	Bacteremia
AVAM	02-0022	41	Male	N/A	Cardiac arrest	Bacteremia
AVAM	11-0138	48	Male	Black	Respiratory failure	Endocarditis
AVAM	06-1072	66	Male	Caucasian	Respiratory failure	Bacteremia
AVAM	11-0134	56	Male	Black	Post-operative complications	Endocarditis
AVAM	04-1039	77	Female	Caucasian	Multi-organ system failure	Endocarditis
AVAM	04-1044	50	Male	Caucasian	Respiratory failure	Bacteremia and pneumonia

Medical Officer Comment

In study B8B-MC-AVAM, the clinical efficacy of daptomycin 3 mg/kg q12h in the treatment of S. aureus infective endocarditis was lower that that of comparator (usually nafcillin/gentamicin). Cubist's analysis of this Lilly-sponsored trial data postulated that this lower efficacy rate in the treatment of S. aureus endocarditis was due to low daptomycin peaks and troughs with q12h dosing; analysis by the Agency did not confirm that daptomycin peaks and troughs were lower in patients with S. aureus endocarditis. Daptomycin did appear to be equivalent to comparator in the treatment of S. aureus bacteremia or bacteremia/endocarditis caused by organisms other than S. aureus. Therefore, it is possible that some of the deaths in the daptomycin group occurred as a result of lack of efficacy of daptomycin in S. aureus endocarditis. Cubist proposed a new trial DAP-IE-01-02 in infective endocarditis using daptomycin 6 mg/kg q24h. Since patients with left-sided endocarditis might experience more severe consequences in terms of morbidity or mortality should daptomycin be inferior to comparator, given the intrinsically more fulminant course of left-sided infective endocarditis, the Agency agreed to the proposed trial initially in patients with right-sided endocarditis only. A Data Management Committee will be convened following completion of the first 30 patients (15 patients per arm) to review the safety and efficacy in these 30 patients prior to enrollment of patients with left-sided endocarditis. This analysis as well as preliminary pharmacokinetic data will be submitted to the Agency.

Phase III Studies

Study DAP-SST-9801

Demographics

Study DAP-SST-9801 is a multicenter, randomized, parallel group, investigator-blinded study in cSSSI caused by Gram-positive organisms. cSSSIs included in this study were wound infections (traumatic injury, surgical incision, animal or human bites, foreign body), major abscesses (with or without recognized preceding trauma), infected ulcers (associated with diabetes, vascular insufficiency, or pressure) or infections in immunosuppressed patients such as:

- Patients known to be HIV-infected (provided CD4 counts >200 cells/mm^3)
- Patients on chronic systemic steroids (>20 mg prednisone daily or the equivalent)
- Patients with DM necessitating treatment with oral hypoglycemic agents and/or insulin.

This trial was conducted at 69 study sites, 64 in the United States and 5 in South Africa, and compared daptomycin at a dose of 4 mg/kg q24h for 7-14 days to comparator (either a semi-synthetic penicillin or vancomycin). The study was completed in March, 1999.

Table 32 below presents a summary of the demographic characteristics for the daptomycin and comparator treatment groups in study DAP-SST-9801. The two treatment groups were well balanced with regard to all demographic characteristics. The majority of the patients in both treatment groups were male (>53%) and Caucasian (>62%). Mean age of the patients was 55 years in both treatment groups; 34% of patients in the daptomycin treatment group and 31% in the comparator group were ≥ 65 years old at study entry. Of the 517 patients in the sponsor-defined ITT population, 421 were enrolled in the US and 96 were enrolled in South Africa.

Medical Officer Comment

The protocol for study DAP-SST-9801 was originally written to include only US sites. However, due to slower than anticipated enrollment, the five largest enrollers in the companion pivotal study DAP-SST-9901 were added to study DAP-SST-9801. In general, the Agency discourages the use of investigators in more than one pivotal trial, in order gain experience with the drug in the widest possible patient population. Use of overlapping investigators in the two pivotal cSSSI trials is of concern, since the AE profile is quite different between trials in the sense of point estimates, although the relative frequency of AEs between treatment arms is not remarkably different in the two trials. As described in depth by Dr. Nambiar in Appendix A, the point estimates of the efficacy outcomes between these two trials are quite different, although in both instances efficacy is similar to comparator. These findings regarding safety and efficacy differences between the two trials are probably explained by the differences in enrolled patient demographics and characteristics between the two studies. In study DAP-

SST-9901 patients were younger and less likely to have complicated underlying illnesses, presenting infections, or resistant etiologic organisms.

Table 32: Demographic Characteristics in Study DAP-SST-9801 (Population: ITT)

Characteristic	Daptomycin N = 256	Comparator N = 261	P-value[1]
Age (years)			
Mean ± SEM	55.0 ± 1.10	55.5 ± 1.09	0.754
Minimum, Maximum	18, 91	18, 93	
Weight (kg)			
Mean ± SEM	87.4 ± 2.11	86.8 ± 1.74	0.835
Minimum, Maximum	36, 274	44, 193	
Gender (N, %)			
Female	119 (46.5%)	118 (45.2%)	0.771
Male	137 (53.5%)	143 (54.8%)	
Race (N, %)			
Caucasian	170 (66.4%)	162 (62.1%)	0.690
Black	49 (19.1%)	60 (23.0%)	
Asian	2 (0.8%)	3 (1.1%)	
Other	35 (13.7%)	36 (13.8%)	

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

Medical Officer Comment

The "ITT" population as defined above by the sponsor contains 517 patients (256 in the daptomycin arm and 261 patients in the comparator arm). However, 530 patients were treated with the appropriate randomized drug and should constitute the "safety population" - that is, all patients who were randomized and actually received at least one dose of the appropriate drug. The difference between the two defined populations are 13 patients who were found to have osteomyelitis in study DAP-SST-9801. These patients should properly have been excluded from the evaluable population but not from the ITT or safety population. The analyses in this review have been derived from the sponsor's and these 13 patients are included in the safety population and the safety analyses which follow.

Disposition - Study DAP-SST-9801

Table 33 below presents a summary of patient disposition during study DAP-SST-9801. A total of 547 patients were randomized to study treatment; 272 were randomized to receive daptomycin and 275 were randomized to receive comparator (vancomycin, nafcillin, oxacillin or cloxacillin as designated by the investigator prior to randomization). Seventeen of the 547 randomized patients discontinued from the study prior to receiving any study treatment. Among the 530 patients who received at least 1 dose of study drug, 264 had been randomized to the daptomycin arm and 266 to the comparator arm. One patient was randomized to receive comparator, but was administered one dose of daptomycin in error on d2 of a 10-day course of vancomycin. This patient is referred to as

"misrandomized" in Table 36 below. In the safety analyses for study DAP-SST-9801 which follows data for this patient is included in the daptomycin group.

Therefore, in the safety population 265 patients were in the daptomycin group and 265 patients were in the comparator group. The comparator group was divided as follows: 153 received vancomycin, 46 received cloxacillin, 39 received nafcillin, 12 received oxacillin, and 15 received vancomycin in combination with nafcillin (12 patients) or oxacillin (3 patients). Over 80% of patients in both treatment groups completed treatment as planned. There were no apparent differences between the arms in the proportion of patients who discontinued drug therapy prematurely or in the reasons for discontinuation. Of the daptomycin-treated patients, 46/265 (17.4%) discontinued prematurely as did 45/265 (17.0%) of the comparator-treated patients. The most common reason for premature discontinuation in both treatment groups was AE (3.4% and 4.5% of patients in the daptomycin and comparator groups, respectively). One patient in the daptomycin group discontinued study treatment due to an elevation in serum CPK. One additional patient in the daptomycin group was switched from daptomycin to oral antibiotics due to an elevation in serum CPK. For 21 patients (13 daptomycin-treated, 8 comparator-treated) the investigator indicated "Other" as the reason study medication was discontinued prematurely. Review of these patients revealed that 9 were found to have osteomyelitis rather than cSSSI; 4 had culture results that the Investigator considered inappropriate for continued inclusion (e.g., only Gram-negative pathogens); 3 had intercurrent procedures (e.g., arterial revascularization) or other infections (e.g., UTI); 2 had technical problems (e.g., unable to maintain intravenous access); 2 of the patients in the "other" reason category had treatment stopped due to clinical failure; and one had treatment stopped due to resolution of infection.

Table 33: Patient Disposition in Study DAP-SST-9801

Population	Daptomycin[1]	Comparator[1]
Randomized	272	275
Randomized But Not Treated	8	9
Treated Population (as randomized)	264	266
Misrandomized[1]	0	1
Safety Population (as treated)	265 (100.0%)	265 (100.0%)
Completed Therapy	219 (82.6%)	220 (83.0%)
Prematurely Discontinued Therapy	46 (17.4%)	45 (17.0%)
Adverse Event	9 (3.4%)	12 (4.5%)
Elevated CPK	1 (0.4%)	0 (0.0%)
Clinical (Symptomatic) Failure	15 (5.7%)	16 (6.0%)
Patient s Decision	4 (1.5%)	4 (1.5%)
Protocol Violation	2 (0.8%)	0 (0.0%)
Lost to Follow-up	2 (0.8%)	5 (1.9%)
Death	1 (0.4%)	0 (0.0%)
Other	13 (4.9%)	8 (3.0%)

[1] One patient (0169100044) was randomized to receive comparator drug but was administered one dose of daptomycin in error. This patient is included in the comparator group for the safety analysis.

Overall adverse events - study DAP-SST-9801

Table 34 below presents treatment-emergent AEs in study DAP-SST-9801 by SOC including events reported in ≥1% of patients. A slightly lower proportion of patients in the daptomycin arm (171/265, 64.5%) experienced at least one AE during the study as compared to patients in the comparator arm (193/265, 72.8%).

In both arms the Gastrointestinal Disorders SOC comprised the most commonly reported AEs. A lower proportion of patients in the daptomycin arm (73/265; 27.5%) experienced AEs within this SOC compared with the comparator arm (98/265; 37.0%). The most frequently reported gastrointestinal disorders were nausea, constipation, diarrhea, vomiting, dyspepsia and sore throat. Nausea was reported more frequently among patients receiving the comparator agents (41/265; 15.5%) than among patients receiving daptomycin (23/265; 8.7%); all other gastrointestinal disturbances were reported with similar frequency between the two arms.

Nervous system disorders, primarily reports of insomnia, headache, and dizziness, were reported in approximately 21% of patients in both groups.

Approximately 20% of patients in both arms reported AEs within the General Disorders/Administration Site Conditions SOC; the most common events were pyrexia, injection site inflammation, and weakness, each of which was reported in ≤3% of patients in both arms. Other injection site reactions, including thrombosis, phlebitis, pain, burning, erythema and edema, were each reported in <2% of patients in both arms.

In the daptomycin arm 42/265 (15.8%) patients and 54/265 (20.4%) patients in the comparator arm experienced at least one AE within the Infections and Infestations SOC. The most common AEs reported in this SOC were fungal vaginosis, fungal skin infection and urinary tract infection, each reported in ≤3% of patients in both arms.

Skin and subcutaneous tissue disorders were reported as AEs in 42/265 (16.2%) and 53/265 (20.0%) of patients in the daptomycin and comparator arms, respectively. The most commonly reported events with this SOC were pruritus, dermatitis (not otherwise specified), and pressure sore.

Respiratory system disorders, primarily reports of dyspnea and cough, were reported in 31/265 (11.7%) and 26/265 (9.8%) of patients in the daptomycin and comparator arms, respectively.

Musculoskeletal, connective tissue and bone disorders were reported in 26/265 (9.8%) and 30/265 (11.3%) of patients in the daptomycin and comparator arms, respectively.

A total of 24/265 (9.1%) and 19/265 (7.2%) of patients in the daptomycin and comparator arms experienced AEs in the Metabolism and Nutrition Disorders SOC. Hypokalemia and hypoglycemia were the most commonly reported AE within this SOC.

Vascular disorders were reported in 19/265 (7.2%) in both the daptomycin and comparator arms; the most commonly reported event within this SOC was hypotension, reported in 7/265 (2.6%) and 4/265 (1.5%) of patients in the daptomycin and comparator groups, respectively.

Renal and urinary system disorders, psychiatric disorders and blood and lymphatic system disorders were reported in 5% to 6% of patients in both drug exposure groups. No individual preferred term events within any of these SOCs were reported in >2% of patients in either arm. Less than 5% of patients in both drug exposure groups experienced AEs in any of the other SOCs.

Table 34: Treatment-Emergent AEs by System Organ Class Including the Most Commonly Reported Events (≥1% of Patients) in Study DAP-SST-9801 (Population: Safety)

System Organ Class Preferred Term	Daptomycin N = 265	Comparator N = 265	95% CI[1]
Total Number of Patients with AEs	171 (64.5%)	193 (72.8%)	(0.4, 16.2)
Gastrointestinal Disorders	73 (27.5%)	98 (37.0%)	(1.5, 17.4)
Nausea	23 (8.7%)	41 (15.5%)	
Constipation	22 (8.3%)	28 (10.6%)	
Diarrhea NOS	14 (5.3%)	15 (5.7%)	
Vomiting NOS	13 (4.9%)	14 (5.3%)	
Dyspepsia	2 (<1%)	9 (3.4%)	
Sore throat	3 (1.1%)	7 (2.6%)	
Diarrhea aggravated	4 (1.5%)	3 (1.1%)	
Loose stools	3 (1.1%)	4 (1.5%)	
Constipation aggravated	4 (1.5%)	2 (<1%)	
Abdominal Pain Upper	2 (<1%)	3 (1.1%)	
Nausea aggravated	2 (<1%)	3 (1.1%)	
Abdominal distension	4 (1.5%)	0	
Nervous System Disorders	55 (20.8%)	58 (21.9%)	(-5.8, 8.1)
Insomnia NEC	21 (7.9%)	24 (9.1%)	
Headache NOS	17 (6.4%)	20 (7.5%)	
Dizziness (excl Vertigo)	9 (3.4%)	10 (3.8%)	
General Disorders/Administration Site Conditions	50 (18.9%)	57 (21.5%)	(-4.2, 9.5)
Pyrexia	7 (2.6%)	5 (1.9%)	
Injection Site Inflammation	3 (1.1%)	8 (3.0%)	
Weakness	4 (1.5%)	7 (2.6%)	
Chest Pain NEC	5 (1.9%)	5 (1.9%)	
Edema Lower Limb	7 (2.6%)	3 (1.1%)	
Injection Site Thrombosis	3 (1.1%)	5 (1.9%)	
Fatigue	2 (<1%)	5 (1.9%)	

Injection Site Phlebitis	4 (1.5%)	2 (<1%)	
Injection Site Pain	3 (1.1%)	3 (1.1%)	
Pain NOS	2 (<1%)	4 (1.5%)	
Rigors	3 (1.1%)	2 (<1%)	
Injection Site Burning	1 (<1%)	3 (1.1%)	
Injection Site Erythema	1 (<1%)	3 (1.1%)	
Injection Site Edema	0	4 (1.5%)	
Lethargy	4 (1.5%)	0	
Fall	0	3 (1.1%)	
Feeling Jittery	3 (1.1%)	0	
Infections and Infestations	42 (15.8%)	54 (20.4%)	(-2.0, 11.1)
Vaginosis Fungal NOS	6 (2.3%)	8 (3.0%)	
Skin Fungal Infection NOS	4 (1.5%)	7 (2.6%)	
Urinary Tract Infection NOS	7 (2.6%)	2 (<1%)	
Infection NOS	2 (<1%)	3 (1.1%)	
Fungal Infection NOS	3 (1.1%)	2 (<1%)	
Cellulitis	4 (1.5%)	0	
Oral Candidiasis	0	3(1.1%)	
Upper Respiratory Tract Infection NOS	0	3 (1.1%)	
Upper Respiratory Tract Infection Viral NOS	0	3 (1.1%)	
Urosepsis	3 (1.1%)	0	
Investigations	47 (17.7%)	40 (15.1%)	(-8.9, 3.7)
Blood Creatine Phosphokinase Increased	8 (3.0%)	7 (2.6%)	
Blood Alkaline Phosphatase NOS Increased	7 (2.6%)	2 (<1%)	
Blood Creatinine Increased	4 (1.5%)	5 (1.9%)	
Liver Function Tests NOS Abnormal	5 (1.9%)	3 (1.1%)	
Aspartate Aminotransferase Increased	4 (1.5%)	3 (1.1%)	
Blood Glucose Increased	3 (1.1%)	3 (1.1%)	
Blood Urea Increased	3 (1.1%)	3 (1.1%)	
Alanine Aminotransferase Increased	3 (1.1%)	2 (<1%)	
Body Temperature Increased	1 (<1%)	4 (1.5%)	
Skin & Subcutaneous Tissue Disorders	43 (16.2%)	53 (20.0%)	(-2.8, 10.3)
Pruritus NOS	11 (4.2%)	20 (7.5%)	
Dermatitis NOS	11 (4.2%)	16 (6.0%)	
Pressure Sore	7 (2.6%)	1 (<1%)	
Erythema NEC	4 (1.5%)	2 (<1%)	
Contusion	1 (<1%)	3 (1.1%)	
Dermatitis Contact	3 (1.1%)	1 (<1%)	
Sweating Increased	1 (<1%)	3 (1.1%)	
Respiratory, Thoracic and Mediastinal Disorders	31 (11.7%)	26 (9.8%)	(-7.2, 3.4)
Dyspnea NOS	7 (2.6%)	6 (2.3%)	
Cough	4 (1.5%)	6 (2.3%)	
Rales	4 (1.5%)	1 (<1%)	

Epistaxis	1 (<1%)	3 (1.1%)	
Pleural Effusion	4 (1.5%)	0	
Rhonchi	0	3 (1.1%)	
Musculoskeletal, Connective Tissue and Bone Disorders	26 (9.8%)	30 (11.3%)	(-3.7, 6.7)
Pain in Limb	7 (2.6%)	9 (3.4%)	
Arthralgia	3 (1.1%)	10 (3.8%)	
Back Pain	5 (1.9%)	4 (1.5%)	
Myalgia	4 (1.5%)	2 (<1%)	
Muscle Cramps	3 (1.1%)	1 (<1%)	
Metabolism and Nutrition Disorders	24 (9.1%)	19 (7.2%)	(-6.5, 2.8)
Hypoglycemia NOS	7 (2.6%)	4 (1.5%)	
Hypokalaemia	2 (<1%)	8 (3.0%)	
Anorexia	2 (<1%)	4 (1.5%)	
Appetite Decreased NOS	3 (1.1%)	2 (<1%)	
Vascular Disorders	19 (7.2%)	19 (7.2%)	(-4.4, 4.4)
Hypotension	7 (2.6%)	4 (1.5%)	
Flushing	1 (<1%)	4 (1.5%)	
Gangrene NOS	3 (1.1%)	1 (<1%)	
Renal and Urinary Disorders	14 (5.3%)	16 (6.0%)	(-3.2, 4.7)
Dysuria	1 (<1%)	3 (1.1%)	
Renal Impairment NOS	3 (1.1%)	1 (<1%)	
Urinary Frequency	0	3 (1.1%)	

Psychiatric Disorders	12 (4.5%)	15 (5.7%)	(-2.6, 4.9)
Anxiety NEC	3 (1.1%)	5 (1.9%)	
Confusion	2 (<1%)	4 (1.5%)	
Agitation	3 (1.1%)	0	
Blood and Lymphatic System Disorders	12 (4.5%)	14 (5.3%)	(-2.9, 4.4)
Anemia NOS	3 (1.1%)	2 (<1%)	
Anemia NOS Aggravated	4 (1.5%)	4 (1.5%)	
Cardiac Disorders	13 (4.9%)	12 (4.5%)	(-4.0, 3.2)
Tachycardia NOS	1 (<1%)	4 (1.5%)	
Ventricular Tachycardia	3 (1.1%)	0	
Injury and Poisoning	6 (2.3%)	10 (3.8%)	(-1.4, 4.4)
Abrasion NOS	2 (<1%)	3 (1.1%)	
Laceration	1 (<1%)	3 (1.1%)	
Surgical and Medical Procedures	5 (1.9%)	8 (3.0%)	(-1.5, 3.8)
Reproductive System and Breast Disorders	4 (1.5%)	4 (1.5%)	–
Eye Disorders	5 (1.9%)	1 (<1%)	–
Eye Irritation	3 (1.1%)	0	
Ear and Labyrinth Disorders	1 (<1%)	3 (1.1%)	–

[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

There is a slightly higher incidence of treatment-emergent AEs in the comparator arm than in the daptomycin arm. In large part, this difference is accounted for by the higher incidence of gastrointestinal and infections/infestations AEs in the

comparator arm. Examination of the AEs by SOC does not reveal disproportionate occurrence in the daptomycin arm of any AE, nor of the unusual occurrence of any AE not known to be predicted by the AEs seen in the preclinical, Phase I, and Phase II studies of daptomycin.

Adverse events by intensity - Study DAP-SST-9801

Among the 619 unique treatment-emergent AEs reported in the daptomycin arm, the majority of these events were mild 360/619 (58.3%) or moderate 202/619 (32.6%) in intensity. A total of 56/619 (9.0%) events occurring in 34/265 (12.8%) patients were judged to be severe in intensity by the investigator. In the comparator group, a total of 700 unique treatment-emergent AEs were reported of which 409/700 (58.4%) were assessed as mild and 237/700 (33.9%) as moderate. A total of 54/700 (7.7%) events occurring in 36/265 (13.6%) patients in the comparator arm were judged to be severe. In general, the frequency and distribution of severe events within each SOC were similar between the two drug exposure groups. AEs of severe intensity with incidence of ≥1% within each SOC and by preferred term are displayed in Table 35 below. The Infections and Infestations SOC included the largest number of severe AEs. These occurred in 9/265 (3.4%) patients in the daptomycin arm and 13/265 (4.9%) in the comparator arm and were most commonly related to the primary infection. The majority of severe AEs were reported in less than 1% of patients in both the daptomycin and comparator groups. Only two events, increased CPK and gangrene, were reported with incidence ≥1%. Increased CPK was reported as a severe event in 4 patients (1.5%) in the daptomycin arm. Severe gangrene was reported in 3/265 (1.1%) patients in the daptomycin group. Sixteen patients, including 10/265 (3.8%) in the daptomycin arm and 6/265 (2.3%) in the comparator arm, experienced events that were assessed as both severe in intensity and as possibly or probably related to study treatment. The only event reported as both severe and drug-related in more than two patients was increased serum CPK. Two patients, one in each arm, had severe hypersensitivity reactions reported that were assessed as drug-related. Other severe drug-related events each reported in a single patient included, in the daptomycin group, abdominal pain aggravated, constipation, diarrhea aggravated, pyrexia, weakness, myalgia, headache, fungal skin infection, abnormal liver function tests and arthralgia aggravated; and, in the comparator group, diarrhea, diarrhea aggravated, pyrexia, rigors, hypotension, increased blood creatinine, increased blood glucose, epistaxis and abnormal antibiotic levels. Laboratory abnormalities including elevations in serum CPK are discussed further in the Laboratory Analysis section.

Medical Officer Comment

It is not unexpected that elevated serum CPK is an AE associated with daptomycin in study DAP-SST-9801. It is concerning that four patients in the daptomycin arm experienced serum CPK elevations considered to be both drug-related and severe by the investigators.

Table 35: Treatment-Emergent Severe 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 Severe AEs	34 (12.8%)	36 (13.6%)
Infections and Infestations	9 (3.4%)	13 (4.9%)
Investigations (Laboratory)	7 (2.6%)	2 (<1%)
Blood Creatine Phosphokinase Increased	4 (1.5%)	0
Gastrointestinal Disorders	3 (1.1%)	5 (1.9%)
Respiratory, Thoracic and Mediastinal Disorders	4 (1.5%)	3 (1.1%)
Vascular Disorders	5 (1.9%)	2 (<1%)
Gangrene	3 (1.1%)	0
General Disorders and Administration Site Conditions	4 (1.5%)	2 (<1%)
Musculoskeletal, Connective Tissue and Bone Disorders	4 (1.5%)	2 (<1%)
Renal and Urinary Disorders	2 (<1%)	4 (1.5%)
Nervous System Disorders	3 (1.1%)	3 (1.1%)
Cardiac Disorders	3 (1.1%)	2 (<1%)
Skin & Subcutaneous Tissue Disorders	3 (1.1%)	1 (<1%)
Surgical and Medical Procedures	0	3 (1.1%)

Adverse events by subgroups - Study DAP-SST-9801

Table 36 below presents the overall incidence of treatment-emergent AEs for demographic subgroups. For several subgroups the frequency of AEs was significantly greater in the comparator arm than in the daptomycin arm. These subgroups include female patients, patients <65 years of age, Black patients, and patients whose race is given as "Other". AE rates were higher in the daptomycin arm (74/91; 81.3%) than in the comparator arm (63/83; 75.9%) for patients ≥65 years of age. AE rates were similar between the two arms for males and Caucasian patients.

Table 36: Incidence of Adverse Events by Demographic Characteristics in Study DAP-SST-9801 (Population: Safety)

Demographic Characteristic	Patients with AEs in Subgroup N (%)		95% CI[1]
	Daptomycin	Comparator	
	N = 265	N = 265	
Sex			
Male	95/144 (66.0%)	98/147 (66.7%)	(-10.2, 11.6)
Female	76/121 (62.8%)	95/118 (80.5%)	(6.5, 28.9)
Age			
< 65 years	97/174 (55.7%)	130/182 (71.4%)	(5.8, 25.6)
≥ 65 years	74/ 91 (81.3%)	63/ 83 (75.9%)	(-17.6, 6.8)
Race			
Caucasian	138/178 (77.5%)	128/166 (77.1%)	(-9.3, 8.4)
Black	15/ 50 (30.0%)	37/ 60 (61.7%)	(14.0, 49.3)
Other	18/ 37 (48.6%)	28/ 39 (71.8%)	(1.7, 44.6)

[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

It is notable that the AE rate is slightly higher in males (95/144; 66.0%) than in females (76/121; 62.8%) in the daptomycin arm. AEs were also more common in the daptomycin arm in patients ≥65 years of age (74/91; 81.3%) compared with patients less than 65 years of age (97/174; 55.7%). The latter difference is of special concern since there was a lower efficacy rate in the daptomycin group than in the comparator group in the ≥65 year old population (see Dr. Nambiar's Appendix A for further details). Pharmacokinetic studies did not indicate that daptomycin dose adjustment is necessary in the geriatric population (see Dr. Bonapace's Pharmacokinetic review for details).

Drug related adverse events - Study DAP-SST-9801

Treatment-emergent drug-related AEs occurring in ≥1% of patients in study DAP-SST-9801 are shown in Table 37. The majority of AEs were assessed as unrelated to treatment by the investigators. In the daptomycin group 64/265 (24.2%) patients and 90/265 (34.0%) patients in the comparator group experienced at least one AE that was considered possibly or probably related to study treatment. For 21/265 (7.9%) patients in the daptomycin group and 30/265 (11.3%) patients in the comparator group gastrointestinal events were assessed as drug-related, most commonly nausea, diarrhea, vomiting and constipation. In 5 patients, including 3/265 (1.1.%) patients in the daptomycin group and 2/265 (<1%) patients in the comparator group, the drug-related gastrointestinal events were assessed as severe in intensity; these events included diarrhea (including aggravated) (3 patients), aggravated abdominal pain, and constipation. Drug-related nervous system disorders were reported in 9/265 (3.4%) and 7/265 (2.6%) of patients in the daptomycin and comparator groups, respectively. Only one drug-related event (headache reported in the daptomycin group) was considered severe in intensity. For ~6% of patients in both treatment groups AEs in the General Disorders/Administration Site Conditions SOC were assessed as drug-