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 I 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

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