comparator subjects in these studies. In Phase III cSSSI and CAP studies 7/989 (0.7%) daptomycin-treated patients and 7/1018 (0.7%) comparator-treated patients experienced paresthesias. New or worsening peripheral neuropathy was not diagnosed in any of these patients. In animals, effects of daptomycin on peripheral nerve were observed (see **ANIMAL PHARMACOLOGY**). Therefore, physicians should be alert to the possibility of signs and symptoms of neuropathy in patients receiving Cubicin." Since peripheral neuropathy characterized by axonal degeneration were observed in adult dogs and monkeys, this paragraph was added to provide the practitioner with all available clinical experience with neuropathy in human studies.

GERIATRIC USE

- The following sentence was added to the demographic information and efficacy data to complete the characterization of daptomycin in the geriatric population. "In addition, treatment-emergent adverse events were more common in patients ≥65 years old than in patients <65 years of age in both cSSSI studies."

ADVERSE EVENTS

- The second paragraph was modified to read "Clinical studies sponsored by Cubist enrolled 1,409 patients treated with daptomycin and 1,185 treated with comparator. Most adverse events reported in these clinical studies were described as mild or moderate in intensity. In Phase III cSSSI trials, daptomycin was discontinued in 15/534 (2.8%) patients due to an adverse event while comparator was discontinued in 17/558 (3.0%) patients." These changes were made to modify language to include AEs of severe intensity as well as to more accurately reflect the discontinuation rate due to AEs.
- The following paragraph was added in order to provide practitioners information regarding the adverse event profile of daptomycin in the treatment of CAP, as well as the cause: " In Phase III studies of community-acquired pneumonia (CAP), the death rate and rates of serious cardiorespiratory adverse events were higher in daptomycin-treated patients than in comparator-treated patients. These differences were due to lack of therapeutic effectiveness of daptomycin in the treatment of CAP in patients experiencing these adverse events (see **INDICATIONS AND USAGE**)
- The sentence [redacted] " was deleted from this section. A more complete summary of the Lilly and Cubist experience with neuropathy is now included in PRECAUTIONS.

- Under Laboratory Changes: The FDA proposed changes in the **ADVERSE EVENTS** section include the addition of a table (Table 6) showing rates of various degrees of CPK elevation in daptomycin and comparator-treated patients in cSSSI studies.

  This table provides information to prescribers on the relative rates of CPK elevation in the population of patients for whom daptomycin is indicated, and illustrates that extreme elevations of CPK consistent with myopathy occur in daptomycin-treated patients, although at a low rate In this context, it is important to note that the reported incidence of statin-associated myopathy (2.3 per 10,000 person-years [Epidemiology 2001;12:565-9] is lower than the corresponding incidence reported in Phase III trials for daptomycin (0.2%).

DOSAGE AND ADMINISTRATION

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

D. Dosing

Daptomycin exhibits concentration-dependent bactericidal activity *in vitro* against the claimed Gram-positive organisms. No formal dose response or concentration response study was performed by Cubist. The recommended daptomycin dosage regimen is based on clinical experience in the primary comparative studies, and on

microbiological and pharmacokinetic considerations. The primary comparative studies in complicated skin and skin structure infections were each performed using a daptomycin regimen of 4 mg/kg intravenously q24h for 7 to 14 days. The two studies of daptomycin in community acquired pneumonia also used a dose of 4 mg/kg q 24h for 5-14 days; this data was submitted to the NDA in support of safety.

In a multicenter Phase II trial, daptomycin (2 mg/kg q24h) was as effective as conventional therapy (oxacillin, vancomycin, penicillin, or ampicillin plus an aminoglycoside) in the treatment of Gram-positive skin and soft tissue infections. Thirty (96.8%) of 31 evaluable subjects treated with daptomycin had a favorable response, compared to 41/43 (95.3%) of the evaluable subjects who received conventional therapy. Bacteriological eradication was observed in 30/31 (96.8%) daptomycin-treated subjects, compared with 34/43 (79.1%) of subjects treated with conventional therapy. Daptomycin was effective against a variety of infecting pathogens, including *Staphylococcus aureus*, *Streptococcus pneumoniae*, other species of streptococci, and enterococci. In this study, daptomycin at 2 mg/kg q24h was less effective than conventional therapy in the treatment of bacteremia. In a subsequent Phase II trial in which daptomycin dose was increased to 3 mg/kg q12h, a successful clinical and bacteriologic outcome was seen in 21/24 (87.5%) subjects with bacteremia treated with daptomycin. This result was similar to the percentage of favorable outcomes for conventional therapy in both Phase II studies (8/9 [88.9%] in the first study and 3/4 [75.0%] in the second study).

In studies conducted to date by Lilly and Cubist, the incidence of CPK elevations does not appear to be dose-related. In Phase I and 2 clinical studies, CPK elevations did appear to be more frequent when daptomycin was dosed more frequently than once daily. In a Phase I dose-escalation study (Study B8B-MC-AVAP) conducted by Lilly, daptomycin at 4 mg/kg q12h for 14 days was administered to five normal subjects. At about Day 8 of treatment, two of the five subjects experienced muscle pain and weakness as well as rapid elevations in CPK. Study medication was discontinued and the effects resolved within a few days without sequelae. Subsequent animal studies indicated that for a given level of drug exposure the frequency and severity of skeletal muscle toxicity were decreased with once daily dosing compared with divided doses. Therefore, when Cubist acquired the drug for development, the choice was made to use only single daily dosing.

In Phase II clinical trials conducted by Eli Lilly and company and by Cubist, daptomycin was administered at 2, 4, and 6 mg/kg q24h and at 3 mg/kg q12h to 349 patients with a variety of serious infections due to Gram-positive organisms, including bacteremia, endocarditis, skin and soft tissue infection, and pneumonia. In these studies, the incidence and nature of adverse events associated with daptomycin were comparable to that seen with conventional therapy. In Cubist sponsored Phase II/III studies, 70 patients received the proposed dose of 4 mg/kg q 24h.

Conclusions

- There is adequate efficacy and safety data to recommend approval of daptomycin 4 mg/kg/day intravenously for 7-14 days, in patients 18 years of age or older, with complicated skin and skin structure infections due to Gram-positive bacteria including *Staphylococcus aureus* (methicillin-resistant and susceptible strains), *Streptococcus pyogenes*, *Enterococcus faecalis* (vancomycin-susceptible strains), *Streptococcus agalactiae*, and *Streptococcus dysgalactiae*.

- Sufficient numbers of patients with complicated skin and skin structure infections such as major abscesses, infected ulcers, wound infections, and cellulitis were included in the studies to justify inclusion in the label.

- Data were inadequate to include patients with infected diabetic ulcers.

- Gastrointestinal disorders such as nausea, constipation, diarrhea, and vomiting were the most common adverse events reported in Phase III cSSSI studies. The rates of overall adverse events, deaths, serious adverse events other than death, and adverse events leading to discontinuation were similar in both treatment groups.

- One daptomycin treated patient had biochemical and clinical evidence of myopathy while on therapy.

- There was no clinical or laboratory evidence for daptomycin cardiotoxicity in pre-clinical studies or in Phase I, II, and III data.

- There was no clinical or laboratory evidence for daptomycin hepatotoxicity in pre-clinical studies or in Phase I, II, and III data.

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/s/

Sumathi Nambiar
9/12/03 02:23:52 PM
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Susan Thompson
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CLINICAL REVIEW

Appendix A to Integrated Review of Safety and Efficacy

NDA 21-572
Cubicin (daptomycin for injection)

Original New Drug Application for marketing approval for treatment of complicated skin and skin structure infections (cSSSI) due to Gram-positive bacteria including *Staphylococcus aureus* (methicillin-resistant and susceptible strains), *Streptococcus pyogenes*, *Enterococcus faecalis* (vancomycin-susceptible strains), *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subsp. *equisimilis*

Sponsor: Cubist Pharmaceuticals, Inc.
Lexington, MA 02421

Clinical Reviewer: Sumathi Nambiar, M.D. MPH

Date of Submission: December 19, 2002

Date Assigned: December 19, 2002

Date Review Begun: December 19, 2002

Date Review to Supervisor: August 31, 2002

PDUFA Deadline: September 19, 2002

Table of Contents

Clinical Review for NDA 21-572

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Cubicin™ (daptomycin for injection; Cubist Pharmaceuticals) is the lead investigational antibiotic in a new class of drugs known as cyclic lipopeptides. Based on evidence from two randomized, active-controlled clinical trials submitted by the sponsor, there is adequate efficacy and safety data to recommend approval of daptomycin 4 mg/kg/day intravenously for 7-14 days, in patients 18-85 years of age, with complicated skin and skin structure infections (cSSSI) due to Gram-positive bacteria including *Staphylococcus aureus* (methicillin-resistant and susceptible strains), *Streptococcus pyogenes*, *Enterococcus faecalis* (vancomycin-susceptible strains), *Streptococcus agalactiae*, and *Streptococcus dysgalactiae*. In combined cSSSI studies, a total of 534 patients were treated with daptomycin. The safety database comprised data on 602 daptomycin-treated patients in Phase I studies, 349 daptomycin-treated patients in Phase II studies, and 989 patients in Phase III studies.

The two clinical studies conducted by Cubist in cSSSI were similar in trial design, but differed in certain baseline patient characteristics, such as underlying diabetes and peripheral vascular disease. Such differences in baseline characteristics may have had a significant effect on wound healing. Observed success rates were in fact quite different in the two studies. In both trials, daptomycin was demonstrated to be non-inferior to the comparator (vancomycin/semi-synthetic penicillins), using a non-inferiority margin of 10%.

Sufficient numbers of patients with complicated skin and skin structure infections such as major abscesses, infected ulcers, wound infections, and cellulitis were included in the studies to justify inclusion in the label. Data were inadequate to include patients with infected diabetic ulcers. The number of patients enrolled with infected diabetic ulcers was small, errors in classification of diabetic ulcers occurred, and the clinical success rates observed in these limited data were low.

The safety profile of daptomycin is derived from 1755 subjects exposed to daptomycin in clinical studies conducted by Cubist and Lilly; limited 120- day safety data are available for an additional 52 patients enrolled in ongoing studies, most of whom received a higher dose of daptomycin at 6 mg/kg IV given once daily. Overall, the MedDRA system organ class (SOC) with the greatest percentages of reported adverse events was gastrointestinal disorders, most

frequently nausea, constipation, diarrhea, and vomiting. The rates of overall adverse events, deaths, serious adverse events (SAEs) other than death, and adverse events (AEs) leading to discontinuation were similar in both treatment groups. Preclinical studies had predicted that the primary target of daptomycin toxicity was skeletal muscle. This prediction was confirmed in Phase 1 studies by the observed elevation of CPK with muscle-related symptoms in 2/5 subjects given 4 mg/kg IV q12h and 2/4 subjects administered daptomycin at 4 mg/kg IV q24h. In Phase 3 cSSSI trials, elevations in serum CPK were reported as clinical adverse events in 15/534 (2.8%) daptomycin-treated patients, compared to 10/58 (1.8%) comparator-treated patients. Symptoms consistent with muscle injury were observed in 1/534 (0.2%) of daptomycin- treated patients.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The Agency and Cubist have agreed that Cubist will conduct two Phase 4 studies.

- The first study will consist of a safety and efficacy study in patients with cSSSI. This study is scheduled to start in the first quarter of 2004 and has an estimated 18-month study duration. The study will be open-label, randomized, multicenter, non-comparative study. The patient population for this study will consist of 72 patients with renal insufficiency in the following categories: Clcr 30-50 mL/min an Clcr <30 mL/min. Patients in the latter category may be on hemodialysis, continuous ambulatory peritoneal dialysis, or may not be maintained on dialysis. Pharmacokinetic data will also be collected in this study.
- [redacted]

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Daptomycin [Cubicin®] is a cyclic lipopeptide antibiotic that is administered intravenously.

Phase 1, and 2 studies

The Cubist Phase I studies enrolled 240 subjects who received daptomycin. The Cubist human pharmacology studies included single- and repeat-dose pharmacokinetic studies in normal healthy subjects and in special populations. Repeat-dose studies were conducted in healthy subjects and in subjects with various degrees of renal impairment, including end-stage renal disease (ESRD). Single-dose studies were conducted in subjects with moderate hepatic impairment (Child-Pugh Classification B), in geriatric subjects, and in obese subjects, and in healthy subjects. Drug interaction studies with aztreonam, probenecid, warfarin,

and simvastatin were conducted in healthy subjects. Studies on daptomycin protein binding were conducted in healthy subjects and in subjects with various degrees of renal impairment, including ESRD. A placebo-controlled study was conducted to examine the effect of daptomycin given to healthy subjects at 6 mg/kg q24h for 14 days on cardiac repolarization (QT interval) and peripheral nerve conduction. Cubist also studied the penetration of daptomycin into inflammatory exudate from cantharides-induced skin blisters. *In vitro* studies were conducted to assess the influence of daptomycin on induction or inhibition of cytochrome P450 enzymes in human hepatocytes.

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 q 12h x 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.
Cubist conducted two Phase II studies; a third study was discontinued due to slow enrollment. DAP-BAC-9803, is an open-label, Phase II, dose-ranging trial in subjects 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 subjects with bacteremia (4 mg/kg q24h, 6 mg/kg q24h, 3 mg/kg q12h following a 6 mg/kg loading dose), complicated skin and skin structure infections (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 subjects with complicated urinary tract infections caused primarily by Gram-positive pathogens. Due to slow enrollment, this trial was terminated.

Three Phase II studies were conducted by Lilly during the years 1987 - 1990. Study B8B-MC-AVAE/B8B-EW-AVAG is described below, as it was submitted with the NDA as supportive of the cSSSI indication. The second Phase II study, B8B-MC-AVAM, was a randomized, open-label study in which subjects with endocarditis and bacteremia were given daptomycin (loading dose of 6 mg/kg followed by 3 mg/kg q 12h) for up to 42 days; pharmacodynamic data was collected in this study. The third Phase II study, B8B-EW-AVAH, was an open

label, uncontrolled study to evaluate the efficacy of daptomycin in subjects with Gram-positive skin and skin structure infections. This study was terminated after only 4 of the planned 50 subjects were enrolled due to adverse events..

One controlled study, B8B-MC-AVAE/AVAG conducted by Lilly, was submitted as a supportive study. The dose of daptomycin used in this study was 2 mg/kg q 24 hours for a total duration of five days. As the dosing regimen of daptomycin used in this study is different from that used in the two phase 3 cSSSI clinical trials, results of this study are not included in the overall efficacy analyses and will not be discussed in this review.

Phase 3 studies

Complicated skin and skin structure infections

Results of two phase 3 studies, DAP-SST-9801 and DAP-SST-9901, were included in this NDA to support the indication of complicated skin and skin structure infections. The safety and efficacy of daptomycin was compared to that of vancomycin or a semi-synthetic penicillin (cloxacillin, flucloxacillin, oxacillin, nafcillin etc) for the treatment of hospitalized patients with complicated skin and skin structure infections due to Gram-positive bacteria. The two studies were similar in design and conduct to a great extent. Both studies were randomized, active-controlled, and investigator-blinded. Study 9801 was conducted at 68 study sites, 63 in the United States and 5 in South Africa. Study 9901 was conducted at 67 study sites including Europe, South Africa, Australia, and Israel.

In the two pivotal studies, patients with complicated skin and skin structure infections including ulcers (diabetic and non-diabetic), wound infections, and major abscesses were randomized on a 1:1 basis to receive 7-14 days treatment with daptomycin 4 mg/kg intravenously as a single daily dose or a comparator agent. The comparator drug could be either vancomycin or a semi-synthetic penicillin. Investigators could select the semi-synthetic penicillin based on local availability and treatment practice. Randomization was stratified based on the presence or absence of an infected diabetic ulcer as the primary site of infection. Adjunctive treatment with aztreonam or metronidazole could be given for Gram-negative or anaerobic organisms, respectively. Ancillary surgical treatment (e.g., debridement) was permitted.

In study 9801, a total of 547 patients were randomized and 530 received at least one dose of study medication. In study 9901, a total of 571 patients were randomized and 562 received at least one dose of study medication.

Community-acquired pneumonia

Cubist conducted two controlled clinical trials, DAP-CAP-00-05 and DAP-CAP-00-08, of essentially identical design to evaluate daptomycin in the treatment of moderate to severe community-acquired pneumonia (CAP) due to *S. pneumoniae*, including penicillin-resistant strains. Each study was a randomized, multicenter,

multinational, double-blinded, parallel group, active-treatment controlled trial using a dosage of 4 mg/kg q24h. The comparator in each trial was ceftriaxone 2g q24h. At the discretion of the investigator, adjunctive treatment with aztreonam could be given for suspected Gram-negative organisms. Therapy was to be administered 5 to 14 days, followed by Test-of-Cure and Post-Study visits conducted 7 to 14 and 21 to 28 days, respectively, after the last dose of study drug. Men and women who were 18 years of age or older and had pneumonia which required hospitalization and intravenous therapy for at least 5 days were eligible for the study. The infection must have been known or suspected to be due, at least in part, to Gram-positive bacteria. Subjects previously treated with potentially effective anti-infective agents for >24 hours (or one dosing day) within 72 hours of enrollment were excluded. Protocol DAP-CAP-00-05 enrolled patients in the U.S., Europe, Canada, Australia, South America, and New Zealand. Study DAP-CAP-00-05 enrolled 355 patients in the daptomycin arm and 359 in the comparator arm and was completed in October 2000.

B. Efficacy

DAP-SST-9801 and DAP-SST-9901: Complicated skin and skin structure infections

Cubist has provided sufficient data to support granting the indication of complicated skin and skin structure infections. Intravenous daptomycin 4 mg/kg/day as a single dose was demonstrated to be non-inferior to comparator (semi-synthetic penicillins or vancomycin). The 95% confidence intervals around the difference in clinical cure rates demonstrated that the two treatment regimens were equivalent using a non-inferiority margin of 10%.

Patients 18 years of age and older with complicated skin and skin structure infections including wound infections, major abscess, cellulitis, or infected ulcer (diabetic and non-diabetic) were enrolled in the studies. Patients with bacteremia, osteomyelitis, patients on hemodialysis or peritoneal dialysis, those receiving HMG-CoA reductase inhibitors, and those with creatinine clearance < 30 ml/min were excluded.

The primary efficacy endpoint was sponsor-defined clinical outcome at the test of cure (TOC) visit, 6-20 days after the end of therapy. The sponsor defined clinical outcome took into account the length of therapy in addition to the investigator's clinical response. The patient must have received ≥ 4 calendar days of study medication to be classified as a cure or > 2 days to be classified as a failure. Investigator response of either improved/cure at the TOC visit was considered a clinical success.

Study 9801 was conducted at sites in the United States and South Africa, while study 9901 was conducted entirely outside the Unites States, mainly in South Africa and Europe. Both studies were similar in design, but differed significantly in patient baseline characteristics that potentially impact the overall cure rates.

Patients in study 9801 tended to be sicker, with more co-morbid conditions, required concomitant antibiotics for Gram-negative/anaerobic coverage more commonly, and needed concomitant surgical procedures more often. Patients in study 9901 were less sick, had fewer complicating medical illnesses, and the need for concomitant antibiotics for Gram-negative/anaerobic coverage or concomitant surgical procedures was also less frequent. Efficacy estimates differed significantly in the two studies in both the daptomycin and comparator arms. Results of the two studies will thus be presented separately rather than in an integrated manner.

In both cSSSI studies, daptomycin was non-inferior to the comparator drugs using a non-inferiority margin of 10 %. Results of sponsor's and FDA analyses were comparable. In the FDA analyses, 95% confidence intervals (CI) around the difference in success rates (daptomycin-comparator) were calculated, while the sponsor calculated the 95% CI for difference in success rates between comparator and daptomycin. Hence, using a non-inferiority margin of 10 %, non-inferiority is established if the value of the lower bound of the 95% CI is less than 10 % in the FDA analyses and a value of the upper bound of the 95% CI is less than 10 % in the sponsor's analyses.

The primary efficacy populations were the Intent To Treat (ITT) and Clinically Evaluable (CE) populations. Clinical success rates using the sponsor defined clinical outcome for the ITT and CE populations for both studies are presented below. Sponsor's results are presented first, followed by the FDA results.

Sponsor's Results

Table ES1:Sponsor-defined clinical outcome (Population: ITT)

Clinical Response	Daptomycin N = 256	Comparator N = 261	95% CI*
Clinical success	167 (65%)	166 (64%)	-9.9, 6.6
Cure	110 (43%)	100 (38%)	
Clinical improvement	57 (22%)	66 (25%)	
Clinical failure	89 (35%)	95 (36%)	
Failure	56 (22%)	56 (21.5%)	
Unable to evaluate	33 (13%)	39 (15%)	

Source: Table 14.2.1.1, final study report

*95% confidence interval around the difference in success rates (comparator-daptomycin)

Table ES2: Sponsor-defined clinical outcome (Population: CE)

Clinical Response	Daptomycin N = 223	Comparator N = 222	95% CI*
Clinical success	167 (75%)	166 (75%)	-8.2, 8.0
Cure	110 (49%)	100 (45%)	
Clinical improvement	57 (26%)	66 (30%)	
Clinical failure	56 (25%)	56 (25%)	
Failure	56 (25%)	56 (25%)	

Source: Sponsor table 11-7, final study report
*95% confidence interval around the difference in success rates (comparator-daptomycin)

FDA Results

Table ES3: Sponsor-defined clinical outcome (Population: ITT)

Clinical Response	Daptomycin (N=264)	Comparator (N=266)
Clinical Success	165 (62.5%)	162 (61%)
Clinical Failure	99 (37.5%)	104 (39%)
Difference in Success Rate : Daptomycin vs. Comparator	1.6%, 95% C.I.: -7.1%, 10.3%	

Table ES4: Sponsor-defined clinical outcome (Population: CE)

Clinical Response	Daptomycin (N=208)	Comparator (N=206)
Clinical Success	158 (76%)	158 (77%)
Clinical Failure	50 (24%)	48 (23%)
Difference in Success Rate: Daptomycin vs. Comparator	-0.7%, 95% C.I.: -9.4%, 7.9%	

Study 9901

Sponsor's Results

Table ES5: Sponsor-defined clinical outcome (Population: ITT)

Clinical Response	Daptomycin N = 270	Comparator N= 292	95% CI
Clinical Success	218 (81%)	237 (81%)	-6.1, 6.9
Cure	103 (38%)	123 (42%)	
Clinical Improvement	115 (43%)	114 (39%)	
Clinical Failure	52 (19%)	55 (19%)	
Failure	28 (10%)	27 (9%)	
Unable to Evaluate	24 (9%)	28 (10%)	

Source: Table 14.2.1.1, final study report
*95% confidence interval around the difference in success rates (comparator-daptomycin)

Table ES6: Sponsor-defined clinical outcome (Population: CE)

Clinical Response	Daptomycin N = 245	Comparator N = 262	95% CI*
Clinical Success	217 (89%)	235 (90%)	-4.3, 6.5
Cure	103 (42%)	122 (47%)	
Clinical Improvement	114 (46.5%)	113 (43%)	
Clinical Failure	28 (11%)	27 (10%)	
Failure	28 (11%)	27 (10%)	

Source: Sponsor table 11-7, final study report
*95% confidence interval around the difference in success rates (comparator-daptomycin)

FDA Results

Table ES7: Sponsor-defined clinical outcome (Population: ITT)

Clinical Response	Daptomycin (N=270)	Comparator (N=292)
Clinical Success	217 (80%)	235 (80.5%)
Clinical Failure	53 (20%)	57 (19.5%)
Difference in Success Rate: Daptomycin vs. Comparator	-0.1%, 95% C.I.: -7.0%, 6.8%	

Table ES8: Sponsor-defined clinical outcome (Population: CE)

Clinical Response	Daptomycin (N=238)	Comparator (N=250)
Clinical Success	214 (90%)	226 (90%)
Clinical Failure	24 (10%)	24 (10%)
Difference in Success Rate: Daptomycin vs. Comparator	-0.5%, 95% C.I.: -6.2%, 5.2%	

C. Safety

The safety database comprised data on 602 daptomycin-treated patients in Phase I studies, 349 daptomycin-treated patients in Phase II studies, and 989 patients in Phase III studies.

Adverse events in Phase 1 studies

A total of 240 subjects received daptomycin in the Phase 1 studies: 19 human pharmacology studies were conducted by Lilly (9 single-dose Phase 1 in the U.S., 3 repeat-dose in the U.S., 3 single dose in Japan, and 4 repeat dose in Japan). Cubist conducted 22 human pharmacology studies (7 single dose and 5 repeat dose). In Lilly-sponsored Phase 1 studies, 102 subjects were administered single-dose daptomycin at doses ranging from 5 mg to 6.0 mg/kg; Phase 1 repeat-dose studies assessed doses of 1 mg/kg q 24h in a total of 25 subjects. In the Cubist-sponsored Phase 1 studies there were 240 daptomycin-treated patients and 109 comparator treated patients. The greatest number of subjects in the Cubist-

sponsored phase 1 trials were exposed to daptomycin for less than or equal to one day, or to a single dose and received a dose of daptomycin <1g. Eighty-six subjects received a total dose of daptomycin >4g in multiple dose studies.

No deaths occurred in clinical pharmacology studies conducted by either sponsor. Three serious adverse events (SAEs) in daptomycin-treated subjects were reported in the Cubist-sponsored Phase 1 studies. Two subjects had gastrointestinal symptoms considered "probably related" to study drug, and one subject had Bell's palsy considered by the investigator to be unrelated to study drug. One subject in the Lilly-sponsored Phase 1 trials developed the SAE of anemia, described as unrelated to study drug.

In the Cubist-sponsored clinical pharmacology studies, seven subjects discontinued study medication due to adverse events (AEs): 5 of 240 (2.1%) in the daptomycin group and 2 of 109 (1.8%) in the comparator group. The most common reason for discontinuation was elevation of CPK, with three subjects in the daptomycin group and one in the comparator group being discontinued for this reason. The three subjects with elevation in CPK (maximum of 1940/1593/4490 with MM isoenzymes, all asymptomatic) were considered to have a drug-related AE; AEs of facial palsy and diarrhea were also considered drug related in the daptomycin group. In the comparator group 1/2 AEs was drug-related, a rash with pruritis. In the Lilly-sponsored Phase 1 studies, 2/5 subjects in one study given 4 mg/kg IV q12h discontinued daptomycin due to symptomatic CPK elevations to a maximum of 20,812 and >10,000 with a MM isoenzyme pattern. CPK returned to normal in both subjects.

During the Cubist-sponsored Phase 1 studies, similar proportions of subjects in the daptomycin and comparator arms experienced at least one adverse event (daptomycin, 62/240 (25.8%); comparator, 32/109 (29.4%)). In Cubist-sponsored multiple dose studies, 37% (44/119) of subjects experienced one or more adverse events; the most commonly occurring adverse events (>5%) were injection site pain (5.9%, 7/119), injection site edema (5%, 6/119), increased blood creatine phosphokinase (5%, 6/119), and headache (5%, 6/119). In single-dose Cubist-sponsored Phase 1 trials, no adverse event occurred in more than 5% of subjects. Adverse events seen in 19/102 (18.6%) of subjects in the Lilly-sponsored Phase 1 studies included headache, abdominal pain, and pain and bruising at the venipuncture site.

The frequency of probably or possibly drug-related AEs in daptomycin-treated subjects was 12.1% (29/240) in the Cubist-sponsored Phase 1 studies.

Adverse events in Phase 2 studies

Three Phase 2 studies were conducted by Lilly. In study B8B-MC-AVAE/B8B-EW-AVAG, daptomycin was given at 2 mg/kg q24h for up to 25 days in 81 patients with various Gram-positive infections. The groups were well matched with respect to age; there were more males than females. In the daptomycin group, 7 subjects (8.7%) died and 6 subjects (7.4%) in the comparator group died. Causes of death included cardiac arrest, cerebral hemorrhage, lung cancer, renal failure,

respiratory failure, sepsis, shock and sudden death. None of these deaths were attributed to study drug by the investigator or reviewing Medical Officer.

SAEs were reported in 6/80 (7.5%) of daptomycin-treated subjects and 6/81 (7.4%) of subjects in the comparator group. These SAEs included angina, urinary tract infection, cerebral hemorrhage, pancreatitis, decreased nerve conduction velocity (NCV), renal failure, aortic valve replacement, myocardial infarction, pulmonary embolism, edema, labial pain and neutropenia. None of these SAEs were attributed to study drug by the investigator or reviewing Medical Officer.

Overall, 166 adverse events were reported in this study by 53 of 80 (66.3%) patients treated with daptomycin and 53 of 81 (65.4%) treated with comparator. The most commonly occurring AEs across both treatment groups were (daptomycin/comparator) nausea (4%/9%), vomiting ((0/2%), pruritis (1%/5%), diarrhea (6%/5%), headache (2%/4%), rash (4%/3%), and phlebitis (6%/8%).

In the second Phase 2 study, B8B-MC-AVAM, 89 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 and 35 patients received comparator. The groups were well matched with respect to age; there were more males than females.

In this study, 13 daptomycin-treated patients (14.6%) and 6 comparator-treated patients (17.1%) died. Causes of death included abscess, cardiac arrest, cirrhosis of the liver, congestive heart failure, 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 or reviewing Medical Officer to daptomycin administration. The relatively high death rate in this study is due to the severity of the presenting illnesses and underlying conditions.

SAEs were reported in 6/89 (6.7%) of patients in the daptomycin group including 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 group. None of these SAEs were attributed to daptomycin administration by the reviewing Medical Officer.

Overall AEs occurred in 52/89 (58.4%) of the 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 adverse event. The most commonly reported adverse events occurring in >10% of subjects across both treatment groups included cardiovascular disorder, constipation, nausea, edema, pain, insomnia, vaginitis, rash and surgical procedure.

The third Lilly-sponsored Phase 2 study, B8B-EW-AVAH, was an open label, uncontrolled study to evaluate the efficacy of daptomycin in subjects with Gram-positive skin and skin structure infections. This study was terminated after only 4 of the planned 50 patients were enrolled. One of the four patients enrolled in study B8B-EW-AVAH was discontinued due to the SAE of a 50% decrease in NCV

amplitude after a 1 mg dose of daptomycin. The study was put on hold due to the SAE, and no further enrollment occurred.

Cubist-sponsored Phase 2 studies

Cubist conducted two Phase 2 studies; a third study was discontinued due to slow enrollment, and is included here for purposes of this safety review. DAP-BAC-9803 included 74 daptomycin patients and 24 comparator 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. The majority of patients were treated for at least 14 days.

Ten daptomycin patients and two comparator patients died. Death occurred in patients as follows: three of 24 (12.5%) in the daptomycin 4 mg/kg q24h group, four of 26 (15.4%) in the daptomycin 6 mg/kg q24h group, three of 24 (12.5%) in the daptomycin 3 mg/kg q12h group, and in two of 24 (8.3%) in the comparator group. The death of one patient- with a history of cardiac dysrhythmias and congestive heart failure who received daptomycin 3 mg/kg q 12 h for a complicated UTI who developed complete heart block on day 3 and died- was considered possibly related to study drug. This death appears unlikely to be related to the study drug, in the reviewing Medical Officer's opinion.

A total of 66 (89.2%) patients in the daptomycin group and 19 (79.2%) in the comparator group reported at least one AE during the study. The most frequently reported AEs were nausea, reported in 14 patients (18.9%) in the daptomycin group and constipation, reported in seven patients (29.2%) in the comparator group. A total of 32 subjects experienced one or more SAEs, including 25 of 74 (33.8%) in the daptomycin group and seven of 24 (29.2%) in the comparator group. There was a higher incidence of SAEs reported in the 6 mg/kg q24h daptomycin group (46.2%, 12/26) than in the 4 mg/kg q24h (20.8%, 5/24) or the 3 mg/kg q12h (33.3%, 8/24) groups; however, no system organ class was represented disproportionately in the 6 mg/kg q24h group.

The second Phase 2 study, DAP-RRC-9804, used three dose regimens of daptomycin in 72 hospitalized subjects with bacteremia (4 mg/kg q24h, 6 mg/kg q24h, 3 mg/kg q12h following a 6 mg/kg loading dose), complicated skin and skin structure infections (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. This study also included a "dialysis group" consisting of six patients on hemodialysis with dose modification based on decreased creatinine clearance. Note that six patients received seven "treatment periods" in this hemodialysis group. This study was terminated due to slow enrollment. The majority of patients received daptomycin treatment for at least fourteen days.

Death occurred in six of 23 (26.1%) in the 4 mg/kg q24h group, 10 of 33 (30.3%) in the 6 mg/kg q24h group, five of 10 (50.0%) in the 3 mg/kg q12h group, and four

of six (66.7%) in the dialysis group. None of the deaths in this study were considered by the investigator to be related to study drug; the Medical Officer agrees with this assessment. The relatively high mortality rate in study DAP-RRC-9804 reflects the serious underlying illnesses in this patient population; there was no comparator arm in this study.

AEs were most commonly reported in the system organ class of gastrointestinal disorders. The most frequently reported AEs were nausea (16.7%), diarrhea (15.3%), and vomiting (15.3%). A total of 45/72 (62.5%) patients experienced a total of 86 SAEs including 13/23 (56.5%) in the 4 mg/kg q24h group, 19/33 (54.3%) in the 6 mg/kg q24h group, 7/10 (63.6%) in the 3 mg/kg q12h group, and 6/7 (85.7%) in the dialysis group.

Study DAP-00-03 was an open-label Phase 3 study comparing daptomycin at a dosage of 4 mg/kg q24h (34 patients) with ciprofloxacin 400 mg (34 patients) in patients with complicated urinary tract infections caused primarily by Gram-positive pathogens. Due to slow enrollment, this trial was terminated early. The majority of patients were treated for 2 to 14 days. No deaths occurred in study DAP-00-03. In Study DAP-00-03, 2/68 (2.9%) patients (1/34 daptomycin - 2.9%, 1/34 comparator - 2.9%) experienced a total of 3 SAEs: arrhythmia and paralytic ileus in a daptomycin subject, and deep venous thrombosis in a comparator patient. A total of 4 (11.8%) patients in the daptomycin group and 13 (38.2%) in the ciprofloxacin group reported at least one AE during the study. The most frequently reported AE was diarrhea occurring in 5 patients (14.7%) in the ciprofloxacin group and no patients in the daptomycin group.

Overall, in the three Cubist-sponsored Phase 2/3 studies, six subjects in the daptomycin group had a total of six SAEs assessed as possibly or probably related to study treatment. These SAEs included cholecystitis, leucopenia, pericardial effusion, complete atrioventricular block, acute renal failure, and thrombocytopenia. The patients in studies DAP-BAC-9803 and DAP-RRC-9804 had severe presenting illness and underlying medical conditions, and the relatively high mortality rate reflects these factors. There was not a disproportionate mortality rate in the daptomycin arm in the comparative study, and the deaths did not appear to be related to study drug. The death rate appeared 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.

Adverse events in Phase 3 studies

Complicated Skin and Skin Structure Infections - Studies 9801 and 9901
For details of the study protocols, please see the clinical efficacy review by Dr. Sumathi Nambiar. A total of 1092 patients were treated during the cSSSI studies; 534 received daptomycin 4 mg/kg q24 hours for 7-14 days and 558 received comparator: vancomycin, nafcillin, oxacillin, flucloxicillin or cloxacillin, as designated by the investigator prior to randomization. There were no apparent differences between the treatment groups in either study or in the pooled results in

the proportion of patients who discontinued I.V. drug therapy prematurely or in the reasons for discontinuation. One patient in the daptomycin arm and no patients in the comparator arm of study 9801, and no patients in either arm in study 9901 discontinued therapy due to an elevated CPK. The treatment groups were well-balanced in terms of demographic characteristics. Overall, 381 of 534 patients (71.3%) in the daptomycin group and 401 of 558 patients (71.9%) in the comparator group received 7 to 14 days of I.V. study therapy.

A total of 16 patients (8 (1.5%) daptomycin, 8 (1.4%) comparator) died during the cSSSI studies. All of the deaths appeared to be directly related to pre-existing underlying conditions and were assessed by the investigator as unrelated to study treatment; the MO reviewed these cases and agrees with this assessment.

A total of 107 patients, 58/534 (10.9%) in the daptomycin group and 49/558 (8.8%) in the comparator group, experienced one or more SAEs. There was little difference between the drug exposure groups for the overall incidence of any individual SAE. The only SAEs with a reported incidence of $\geq$1% of patients in either arm of the two studies were cellulitis and urosepsis, occurring in 7 (1.3%) patients and 3 (0.6%) patients, respectively, in the daptomycin group of the combined studies. All other serious events were reported in <1% of subjects in both drug exposure groups. Five patients, including 3 in the daptomycin group and one in the comparator group, experienced serious drug-related events. These included a hypersensitivity reaction, diarrhea (aggravated) and eosinophil count increased in the daptomycin group; and hypersensitivity reaction and pruritic rash in the comparator group. Five patients, including 3 patients in the daptomycin group and one in the comparator group, experienced serious drug-related events.

The proportions of patients in the daptomycin and comparator treatment groups that experienced at least one AE in the cSSSI studies (51.3% daptomycin, 52.5% comparator) were similar. There was no statistically significant difference between the treatment groups in the number of AEs in any SOC with the exception of Diagnostic Investigations where 15 daptomycin patients (12.2%) and ten comparator patients (9.0%) reported AEs (95% CI, -6.3, 0.0). The rates of the most common reported AEs, organized by MedDRA System Organ Class (SOC), are shown in Table ES1. The MedDRA SOC with the greatest numbers of reported AEs was gastrointestinal disorders; 103 of 534 daptomycin patients (19.3%) and 123 of 558 comparator patients (22.0%) reported AEs in this SOC. The most commonly reported AEs in this SOC included nausea and constipation.

The majority of events were assessed as unrelated to treatment by the investigators. A somewhat higher percentage of patients in comparator group than in the daptomycin group experienced at least one AE that was considered possibly or probably related to study treatment (17.6% of daptomycin patients, 21.1% of comparator patients). For the daptomycin group the Diagnostic Investigations SOC had the most drug-related AEs (36 patients), and for the comparator group, Gastrointestinal Disorders SOC had the most drug-related AEs (41 patients). The most frequently reported drug-related AEs were nausea (12

daptomycin, 19 comparator) and blood creatine phosphokinase increased (11 daptomycin, 8 comparator).

Because of the preclinical data suggesting skeletal muscle and peripheral nerves as target organs for daptomycin toxicity, adverse events involving these systems were analyzed in further detail. Increased blood CPK (as a clinical adverse event, as opposed to a laboratory change) was seen in 15 of 534 (2.8%) patients in the daptomycin group and 10 of 558 (1.8%) patients in the comparator group. The MedDRA SOC of Musculoskeletal, Connective Tissue, and Bone Disorders (comprised of the SOC terms reported in >1% of patients, of pain in limb, arthralgia, back pain, myalgia, muscle cramps) were reported in 7 of 534 (2.6%) daptomycin treated and 5/558 (0.9%) comparator-treated patients. Paresthesias were reported in 1 of 534 (0.2%) and 2 of 558 patients (0.4%).

Eleven patients in the daptomycin arm (2.1%) and 8 patients in the comparator arm (1.4%) had an increase in CPK considered to be drug-related. Drug-related AEs in the MedDRA SOC of Musculoskeletal, Connective Tissue, and Bone Disorders were reported in 3 of 534 (0.6%) daptomycin-treated and 0/558 (0.0%) comparator-treated patients. Drug-related paresthesias were reported in 0 of 534 and 1 of 558 comparator-treated patients (0.2%).

Table ES9. Incidence of Adverse Events that Occurred in ≥ 2% of Patients in Phase 3 cSSSI Studies		
Adverse Event	**Daptomycin (N=534)**	**Comparator* (N=558)**
Any adverse event	51.3%	52.5%
Gastrointestinal disorders	19.3%	22.0%
Constipation	6.2%	6.8%
Nausea	5.8%	9.5%
Diarrhea	5.2%	4.3%
Vomiting	3.2%	3.8%
Dyspepsia	0.9%	2.5%
General disorders	13.9%	15.1%
Injection site reactions	5.8%	7.7%
Fever	1.9%	2.5%
Nervous system disorders	13.9%	13.4%
Headache	5.4%	5.4%
Insomnia	4.5%	5.4%
Dizziness	2.2%	2.0%
Skin/subcutaneous disorders	11.2%	11.8%
Rash	4.3%	3.8%
Pruritus	2.8%	3.8%
Diagnostic investigations	12.2%	9.0%
Abnormal liver function tests	3.0%	1.6%
Elevated CPK	2.8%	1.8%
Infections	12.4%	13.4%
Fungal Infections	2.6%	3.2%
Urinary Tract Infections	2.4%	0.5%
Vascular disorders	5.4%	5.6%
Hypotension	2.4%	1.4%
Hypertension	1.1%	2.0%
Renal/urinary disorders	3.2%	3.2%
Renal failure	2.2%	2.7%
Blood/lymphatic disorders	2.8%	3.2%
Anemia	2.1%	2.3%
Respiratory disorders	6.7%	5.6%
Dyspnea	2.1%	1.6%
Musculoskeletal disorders	6.2%	6.3%
Limb pain	1.5%	2.0%
Arthralgia	0.9%	2.2%

* vancomycin/semi-synthetic penicillin

Community-acquired pneumonia – Studies DAP-CAP-00-05 and DAP-CAP-00-08

For details of the clinical protocols of these studies, see section IIA of this review (Brief overview of Clinical Program). Cubist conducted two controlled clinical trials (DAP-CAP-00-05 and DAP-CAP-00-08) of essentially identical design to evaluate daptomycin at a dosage of 4 mg/kg q24h versus ceftriaxone 2 g q24h in the treatment of moderate to severe CAP due to *S. pneumoniae*, including penicillin-resistant strains. Study DAP-CAP-00-05 enrolled 355 patients in the daptomycin arm and 359 in the comparator arm and was completed in October, 2000. After completion of the study, the sponsor's analysis indicated that daptomycin did not meet the predetermined criteria for non-inferiority (which specified that the upper bound of the 95% CI for the difference in clinical success between the comparator, ceftriaxone, and daptomycin be <10%) in any of the populations analyzed. At that time the second study DAP-CAP-00-08 (which had enrolled 100 patients in the daptomycin arm and 101 patients in the comparator arm) was discontinued. Safety data from these two studies was submitted to the NDA, and a summary of the data from the combined studies is presented here.

Overall, the treatment groups were well-balanced in terms of demographic characteristics. A total of 177 subjects in the daptomycin group and 168 subjects in the comparator group were age 65 or older. In study DAP-CAP-00-08, there were more 18-39 and >65-year-old patients in the daptomycin arm than in the comparator arm; conversely, there were fewer 40-65-year-old patients in the daptomycin arm than in the comparator arm. These differences are evened out somewhat when the two studies are combined. However, since differences in daptomycin adverse event rates were found by age group (≥65 years of age versus <65 years; see below) these differences between study arms are worthy of note.

Overall, 265 of 455 patients (58.2%) in the daptomycin group and 279 of 460 patients (60.7%) in the comparator group received 7 to 14 days of intravenous study therapy. It is of interest that when the combined CAP studies are examined, more patients in the daptomycin arm (14/455; 3.1%) than in the comparator arm (7/460; 1.5%) received more than 14 days of therapy. Although the numbers are small, it is may be that longer durations of therapy in these patients were necessary due to slow clinical response. Most subjects in both treatment groups completed the planned treatment course of intravenous treatment; however, more daptomycin- treated patients (23.3%) than comparator patients (14.1%) prematurely discontinued therapy. The most common reason for premature discontinuation in both treatment groups was "Clinical Failure" (9.7% and 5.0% of patients in the daptomycin and comparator groups, respectively).

Table ES2 shows the incidence of death, serious adverse events, and common adverse events in the CAP studies. A total of 33 patients (21 daptomycin - 4.6%, 12 comparator - 2.6%) died during the CAP studies. All of the deaths appeared to be directly related to pre-existing underlying conditions and/or the presenting condition of CAP, and all were assessed by the investigator as unrelated to study treatment. Among the 33 patients who died, 18 were male and 15 were female;

21 were ≥ 65 years of age and 12 were <65 years of age. Twenty-two (16 daptomycin, 6 comparator) of the 33 deaths occurred while patients were on study drug or up to three days after study drug had been stopped. The other 11 (5 daptomycin, 6 comparator) deaths occurred four to 51 days after treatment with study drug had stopped. According to the sponsor's assessment, in study DAP-CAP-00-05, in 10 (67%) of the 15 deaths in the daptomycin group, the cause of death was potentially related to lack of efficacy; in study DAP-CAP-00-08, 2 of the 6 deaths in the daptomycin group were potentially related to lack of efficacy. The MO reviewed these cases in detail, and agrees with these assessments. In study DAP-CAP-00-05, 60% of patients who died had severe underlying cardiac or respiratory conditions; all except one of the remaining patients had other serious preexisting underlying conditions. The patients who died also tended to enter the study with more serious CAP: 10 (67%) of the daptomycin patients who died and 4 (40%) of ceftriaxone patients entered the study with Fine Score Grades IV or V. In study DAP-CAP-00-08, all 6 of the patients who died entered the study with Fine Score Grade IV. Four of these six patients had serious underlying cardiac or respiratory preexisting conditions.

A total of 100 patients, 62 (13.6%) in the daptomycin group and 38 (8.3%) in the comparator group, experienced one or more SAEs in CAP studies DAP-CAP-00-05 or DAP-CAP-00-08. The only SAEs by preferred term with a reported incidence of ≥1% of patients in either of the two studies were pneumonia aggravated, chronic obstructive airways disease exacerbated, and respiratory failure, occurring in 6 (1.3%), 5 (1.1%) and 7 (1.5%) of patients, respectively, in the daptomycin group, and 2 (0.4%), 1 (0.2%) and 1 (0.2%) of patients, respectively in the comparator group. All other serious events were reported in <1% of patients in both drug exposure groups. When SAEs were examined by SOC, differences between the daptomycin arm and the comparator arm were seen in Cardiac Disorders (16/455; 3.5% versus 6/460; 1.3%, respectively) and Respiratory, Thoracic and Mediastinal disorders (15/455; 3.3% versus 3/460; 0.7%). In four of the 100 patients with serious adverse events, three in the daptomycin group and one in the comparator group, the serious adverse events were considered drug-related. These included coma, tachyarrhythmia, and respiratory failure in the daptomycin group, and neutropenia in the comparator group. Review by the MO of the narratives and case report forms for these four patients indicated agreement with each assessment except that of respiratory failure, which in the opinion of the Medical Officer was not related to study drug. No SAE appeared to be reflective of myopathy or neuropathy.

The differences between daptomycin and comparator arms in the occurrence of the SAEs pneumonia, exacerbation of chronic obstructive airways disease, and respiratory failure, as well as Cardiac Disorders, is most likely attributable to the inferior efficacy of daptomycin relative to ceftriaxone in this population with significant co-morbidity and/or severe baseline infections.

Significantly more patients in the daptomycin arm than in the comparator arm experienced at least one AE (reported in ≥2% of patients within a study and in either study arm) in the CAP studies (57.4% of daptomycin patients, 49.8% of comparator patients). SOCs where significantly more daptomycin patients reported AEs were General Disorders and Administration Site Conditions and Infections and Infestations. In the Nervous System Disorders SOC, significantly more comparator patients than daptomycin patients reported AEs. The MedDRA SOC with the greatest numbers of reported AEs was Gastrointestinal Disorders; 86 of 455 daptomycin patients (18.9%) and 86 of 460 comparator patients (18.7%) reported AEs in this SOC. Increased blood CPK was seen in 6 of 455 (1.3%) patients in the daptomycin group and 6 of 460 (1.3%) patients in the comparator group. The MedDRA SOC of Musculoskeletal, Connective Tissue, and Bone Disorders (comprised of the SOC term reported in >1% of patients of arthralgia) was reported in 21 of 455 (4.6%) daptomycin-treated and 32/460 (7.0%) comparator-treated patients; the corresponding rates in all treated patients were 4.6% and 7.1%, respectively. Paresthesias were reported in 2 of 455 (0.4%) of daptomycin-treated patients and 2 of 460 comparator-treated patients (0.4%); neuritis was reported in 1 of 455 (0.2%) daptomycin-treated patients and none of 460 comparator treated patients.

The majority of AEs in the two CAP studies were assessed as unrelated to study drug by the investigators. A higher percentage of patients in the comparator groups than in the daptomycin groups experienced at least one AE that was considered possibly or probably related to study treatment (20.2% daptomycin, 18.3% comparator). The Gastrointestinal Disorders SOC had the most drug-related AEs (27 daptomycin and 30 comparator patients). Blood creatine phosphokinase assessed as drug-related was increased in 6 (1.3%) daptomycin-treated patients and 2 (0.4%) comparator-treated patients. Drug-related Musculoskeletal, Connective Tissue and Bone Disorders were seen in 7 (1.5%) daptomycin-treated and 4 (0.9%) comparator-treated patients. Drug-related paresthesias were seen in 2 (0.4%) of daptomycin-treated patients and no comparator-treated patients.

In the two CAP studies a total of 34 patients, 19 (4.2%) of 455 in the daptomycin group and 15 (3.3%) of 460 in the comparator group, were discontinued from study drug due to AEs. The events leading to discontinuation were reported as possibly or probably related to study treatment for three of the 19 daptomycin-treated and three of the 15 comparator-treated patients. In study DAP-CAP-00-05, four patients (2 daptomycin, 2 comparator) discontinued due to adverse events reported as possibly or probably related to study treatment. The AEs in the daptomycin arm were acute respiratory insufficiency leading to coma in one patient and increased cardiac enzymes in a second patient. The drug-related AEs resulting in study discontinuation in the comparator group were neutropenia in one patient and a drug-related allergic reaction in the second. In study DAP-CAP-00-08, a daptomycin-treated patient discontinued study drug due to severe respiratory failure assessed as possibly related to treatment. In the comparator

group of that study, one patient discontinued from treatment due to drug-related severe urticaria. Case report forms and narratives from the three patients in the daptomycin arm who had AEs resulting in discontinuation either possibly or probably attributable to daptomycin were reviewed. In the opinion of the MO, these three events are unrelated to daptomycin administration.

Table ES10. Incidence of Death, Serious Adverse Events, and Cardiac and Respiratory SOC Adverse Events in CAP Studies

	Daptomycin (N=455)	Comparator* (N=460)
Death	4.6%	2.6%
Any Serious Adverse Event	13.6%	8.3
Cardiac SOC SAE	3.5%	1.3%
Respiratory SOC SAE	3.3%	0.7%

* Ceftriaxone 2 g q 24 hr

Correlation of preclinical cardiac effects with cardiac toxicity in clinical trials

Preclinical Studies of Cardiac Muscle Function and Cardiac Conduction

In vivo and *in vitro* data demonstrated that daptomycin had no adverse effect on the cardiovascular system. No effect on cardiac muscle function was seen *in vitro* at concentrations 20-25-fold higher than peak plasma concentrations of unbound drug at the intended clinical dose of 4 mg/kg q 24h. Daptomycin also had no effect on hERG channel exposed to concentrations of unbound drug up to 100 times the clinical plasma concentration of daptomycin.

Exposure of dogs to daptomycin for periods of up to 6 months did not show any histopathologic effect of daptomycin on cardiac muscle. A study in anesthetized dogs did not reveal any effect of daptomycin on cardiac repolarization at a dose of 50 mg/kg.

Phase 1 Studies

Cubist conducted a study of the effects of daptomycin on cardiac repolarization. Study DAP-QTNC-01-06 included 120 healthy volunteers: 60 in the daptomycin group and 60 in the placebo group. No clinically significant changes in ECG results were seen in either treatment group. The mean values for QTcB and the associated standard deviations were similar across all time points and both treatment groups. For the daptomycin group, the mean values of QTcB ranged from 417.1 to 431.5 msec; for the normal saline group the range was 415.4 to 430.0 msec. Standard deviations were all between 19 and 27 msec. There were no statistically significant or clinically meaningful differences in the mean QTcB values at any time point. There were no statistically significant differences in mean QTcB changes from baseline between the treatment groups. On Day 1 and Day 7, the proportion of subjects with increases of 30 to 60 msec was low in both

treatment groups (5.9% in the daptomycin group, ≤10.5% in the NS group), with no statistically significant differences between the treatment groups at any time point on Day 1 and Day 7. On Day 14, 2 subjects in the daptomycin group (3.9%) and eleven subjects in the NS group (19.3%) and had an increase in QTcB of 30 to 60 msec. This difference was statistically significant ($p < 0.037$). There were only 3 increases in QTcB >60 msec observed during the study, one in the daptomycin group (Day 1, 2 hrs) and two in the NS group (Day 7, pre-dose and Day 7, 12 hrs). QTcB values classified as prolonged (males >450 msec, females >470 msec) occurred in both treatment groups (0 to 9.8% in the daptomycin group; 0 to 10.5% in the NS group). The highest value among daptomycin treated subjects was QtcB of 493 msec on Day 1 (2 hrs post dose) and among normal saline treated subjects was QtcB of 499 msec on Day 1 (30 minutes post dose). No values in either group exceeded 500 msec. There was no apparent temporal relationship between the frequency of prolonged QTcB and the time or study day of the measurement.

In other Cubist Phase 1 studies, one daptomycin-treated subject experienced a cardiac AE of tachycardia, which was assessed as unrelated to study drug. No cardiac adverse events were reported in any Lilly Phase 1 single dose clinical study.

Phase 2 Studies

Cubist studies

Cubist conducted two Phase 2 studies (DAP-BAC-9803 – a controlled trial of daptomycin in bacteremia, and DAP-RRC-9804, an uncontrolled study of daptomycin in the treatment of infections due to resistant Gram-positive pathogens) which enrolled 146 daptomycin-treated subjects and 24 comparator-treated subjects. Daptomycin was dosed in these studies at 4 mg/kg q24h, 6 mg/kg q24h, or 3 mg/kg q12h. Subjects in both studies generally had serious bacterial infections such as pneumonia or intra-abdominal infection and had multiple co-morbidities.

In these studies, which enrolled seriously ill patients, the mortality rate was 35/146 (24.0%) in daptomycin patients and 2/24 (12.5%). The majority of deaths occurred in the uncontrolled study (DAP-RRC-9804). Most fatal events were due to the underlying infection or co-morbid conditions. One death, in Study DAP-BAC-9803, was caused by a third degree heart block and was considered by the investigator to be possibly related to daptomycin treatment. However, the reviewing Medical Officer did not feel that this death was causally related to daptomycin.

In Cubist Phase 2 studies, the incidence of serious cardiac AEs was 8.2% in daptomycin-treated subjects and 12.5% in comparator-treated subjects. There were no serious arrhythmic events in these studies.

In these two studies, the rate of cardiac AEs was 32/146 (21.9%) in the daptomycin group and 8/24 (33.3%) in the comparator group. In daptomycin

treated patients, 9/146 (6.2%) had a dysrhythmia versus 2/24 (8.3%) in the comparator group; five of the events in the daptomycin group were tachycardias. There were no reports of torsades de pointes. The rates of congestive heart failure were 2/146 (1.4%) for daptomycin-treated patients and 3/24 (12.5%) for comparator patients. None of these were assessed as related to study drug by the investigator or reviewing Medical Officer.

Lilly Studies

In the Phase 2 studies B8B-MC-AVAE/B8B-EW AVAG, causation was not assessed. There were no cardiac AEs resulting in discontinuation thought to be secondary to daptomycin. SAEs reported in daptomycin treated patients included angina, aortic valve replacement, and myocardial infarction; from the information available, these do not appear to be related to study drug. The seven deaths in this study do not appear to be related to daptomycin, and were not attributed to cardiac events.

In Study B8B-MC-AVAM, there were 9 daptomycin treated subjects (9/89, 10.1%) and 3 (3/35, 8.6%) comparator treated subjects who developed treatment emergent cardiac SAEs and one cardiac related death in each group (1.1% and 2.9%, respectively). Of the three cardiac deaths that occurred in all the studies combined, 2 occurred in comparator treated subjects and one in a daptomycin treated subject (attributed to mechanical failure of a prosthetic aortic valve).

Phase 3 Studies

In the comparative studies of cSSSI (Study 9801 and Study 9901), there were two cardiac deaths in the daptomycin group (one due to cardiopulmonary insufficiency and one to myocardial infarction) and one in the comparator group (heart failure). None of these was assessed as being drug-related. The incidence of cardiac AEs was 18/534 (3.4%) in daptomycin treated patients and 18/558 (3.2%) in comparator-treated subjects. The incidence of serious cardiac AEs was 5/534 (0.9%) daptomycin-treated patients and 6/558 (1.1%) in comparator-treated patients. The incidence of cardiac AEs that represented dysrhythmic events was 12/534 (2.2%) in daptomycin-treated subjects and 10/558 (1.8%) in comparator-treated subjects. Two events in the daptomycin group (atrial flutter and nodal arrhythmia) and one in the comparator group (tachycardia NOS) were assessed as being related to study drug.

In the CAP studies (DAP-CAP-00-05 and DAP-CAP-00-08), the mortality rates were 21/455 (4.6%) for daptomycin-treated patients and 12/460 (2.6%) for comparator-treated patients. There were six cardiac deaths in daptomycin-treated patients and two in comparator-treated patients. No death was attributed to study drug by either the investigator or the reviewing Medical Officer. The difference in mortality rates between treatment arms is attributable to the differences in efficacy in the treatment of CAP between treatment arms. The rates of serious cardiac adverse events were 3.5% in the daptomycin arm and 1.3% in the comparator arm.

Overall, in the CAP studies, the rates of cardiac adverse events were 8.8% in daptomycin-treated patients and 5.4% in comparator-treated patients; of note, this difference has a nominal p-value <0.05. The rates of dysrhythmias were 2.9% in daptomycin patients and 2.3% in comparator patients. The rates of congestive heart failure were 0.4% in the daptomycin group and 0.6% in the comparator group. The rates of drug-related cardiac adverse events were 1.3% in daptomycin-treated patients and 0.2% in comparator-treated patients; however, none of these included congestive heart failure or ventricular tachycardia. There were no reports of torsades de pointes in these studies.

In general, the differences in cardiac deaths, serious cardiac AEs, and cardiac AEs in these studies reflected complications resulting from the lower efficacy of daptomycin relative to comparator in the treatment of CAP.

In a Phase 3 study of daptomycin in the treatment of complicated urinary tract infections at a dose of 4 mg/kg q24h, which enrolled 34 daptomycin-treated patients and 34 comparator-treated patients (DAP-00-03), there were no deaths. There was one cardiac adverse event in a daptomycin-treated patient, designated as serious and described as arrhythmia NOS; this event was not attributed to daptomycin.

In conclusion, in vivo and in vivo preclinical data suggest that myocardial tissue and conductive systems are not targets for daptomycin toxicity. The safety database from Phase 1, 2, and 3 trials do not show clinical evidence for a cardiotoxic effect of daptomycin, manifested either as dysrhythmias or congestive heart failure. This consistent body of scientific data supports the conclusion that daptomycin is not cardiotoxic

Laboratory Analyses in Phase 3 Studies

Measures of central tendency

Complicated skin/skin structure (cSSSI) studies

In the pooled safety database for the two cSSSI studies (9801 and 9901) measures of central tendency (mean, standard deviation, median, and interquartile range) were similar between daptomycin and comparator at baseline and for all on-therapy and post-therapy hematologic parameters (hematocrit, white blood cell count, and platelets), chemistry parameters (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, and calcium), hepatobiliary function tests (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin). Analysis of creatinine phosphokinase (CPK ,a marker for muscle injury) showed an on-therapy mean of 120.3 ± 410.8 U/L for daptomycin-treated patients and 93.2 ± 130.9 U/L for comparator-treated patients, reflecting the presence of a number of daptomycin-treated patients with significant elevations in CPK on-therapy (see below under Outlier Analysis). Although not statistically significant, this difference persisted for post-therapy CPK values (124.0 ± 289.2 U/L for daptomycin-treated patients and 98.9 ± 112.6 U/L for comparator-treated patients). Stratification of these analyses by

demographic subgroups (age ≥ 65, sex, race) gave similar results. On-therapy differences in mean CPK, although not statistically significant, occurred primarily in individuals younger than 65 years (140.1 ± 484.9 U/L for daptomycin-treated patients and 104.6 ± 148.0 U/L for comparator-treated patients) and women (109.3 ± 579.3 U/L for daptomycin-treated patients and 66.0 ± 78.8 U/L for comparator-treated patients).

Community-acquired pneumonia studies

In the pooled safety database for the two CAP studies (DAP-05 and DAP-08), measures of central tendency (mean, standard deviation, median, and interquartile range) were similar between daptomycin and comparator at baseline and for all on-therapy and post-therapy hematologic parameters (hematocrit, white blood cell count, and platelets), chemistry parameters (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, and calcium), hepatobiliary function tests (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin), and myopathy markers (creatinine phosphokinase and lactate dehydrogenase). Stratification of these analyses by demographic subgroup did not reveal any differences.

Outlier analysis

In the cSSSI studies, there were similar proportions of patients with on-therapy outlier values and similar on-therapy maximum values for all laboratory parameters between treatment arms except for CPK. Table ES4 shows the incidence of CPK elevations from baseline values for patients in the pooled cSSSI database. Although there were 534 daptomycin-treated patients and 558 comparator-treated patients in cSSSI trials, not all patients had valid baseline or on-therapy CPK assessments. The upper limit of normal for CPK was 200 U/L.

Table ES11. Incidence of patients with elevations of CPK from baseline in cSSSI studies

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

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

Three daptomycin-treated patients with CPK elevations had clinical events described by terms relevant to the musculoskeletal system. All of these events

resolved after discontinuation of therapy. One patient, described below, had a clinical and laboratory course consistent with myopathy induced by daptomycin.

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

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

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

CPK elevations in the CAP studies did not show significant differences between daptomycin and comparator-treated patients overall (Table ES5); however; there was a slight excess of higher CPK elevations in daptomycin-treated patients.

Table ES12: Incidence of patients with elevations of CPK from baseline in CAP studies				
Increase in CPK	All patients		Patients with normal CPK at baseline	
	Daptomycin (N=344)	Comparator (N=358)	Daptomycin (N=277)	Comparator (N=305)
	n %	n %	n %	n %
>1x ULN	32 (9.3%)	27 (7.5%)	20 (7.2%)	26 (8.5%)
>2x ULN	15 (4.4%)	12 (3.4%)	7 (2.5%)	8 (2.6%)
>4x ULN	7 (2.0%)	5 (1.4%)	3 (1.1%)	2 (0.7%)
>5x ULN	6 (1.7%)	3 (0.8%)	3 (1.1%)	1 (0.3%)
>10x ULN	2 (0.6%)	1 (0.2%)	1 (0.3%)	0 (0.0%)

In summary, the incidence of daptomycin-associated on-therapy CPK elevations beyond those seen in the comparator group was approximately 1.1% in patients with normal values at baseline. The maximum elevation in this group was approximately 51.5x ULN. Given the relatively few cases of extreme elevations, it is difficult to draw definitive conclusions regarding risk factors for CPK elevations. The latency of CPK elevation appeared to range from 5-11 days in those daptomycin-treated patients with values greater than those in the comparator group. In most but not all cases, elevations of CPK completely resolved following daptomycin discontinuation. In the daptomycin-treated patient with the most extreme elevation of CPK value, the laboratory event was associated with clinically evident signs of muscle injury and led to drug discontinuation. There were no significant sequelae noted as a result of CPK elevations in the NDA patient population. Many of the cases were asymptomatic and symptoms resolved after drug discontinuation after daptomycin discontinuation. When follow-up information was available, elevated CPK had either returned to normal after daptomycin discontinuation or was declining. No patient had further complications due to elevated CPK.

D. Dosing

Daptomycin exhibits concentration-dependent bactericidal activity *in vitro* against the claimed Gram-positive organisms. No formal dose response or concentration response study was performed by Cubist. The recommended daptomycin dosage regimen is based on clinical experience in the primary comparative studies, and on microbiological and pharmacokinetic considerations. The primary comparative studies in complicated skin and skin structure infections were each performed using a daptomycin regimen of 4 mg/kg intravenously q24h for 7 to 14 days. The two studies of daptomycin in community acquired pneumonia also used a dose of 4 mg/kg q 24h for 5-14 days; this data was submitted to the NDA in support of safety.

In a multicenter Phase II trial, daptomycin (2 mg/kg q24h) was as effective as conventional therapy (oxacillin, vancomycin, penicillin, or ampicillin plus an aminoglycoside) in the treatment of Gram-positive skin and soft tissue infections. Thirty (96.8%) of 31 evaluable subjects treated with daptomycin had a favorable response, compared to 41/43 (95.3%) of the evaluable subjects who received conventional therapy. Bacteriological eradication was observed in 30/31 (96.8%) daptomycin-treated subjects, compared with 34/43 (79.1%) of subjects treated with conventional therapy. Daptomycin was effective against a variety of infecting pathogens, including *Staphylococcus aureus*, *Streptococcus pneumoniae*, other species of streptococci, and enterococci. In this study, daptomycin at 2 mg/kg q24h was less effective than conventional therapy in the treatment of bacteremia. In a subsequent Phase II trial in which daptomycin dose was increased to 3 mg/kg q12h, a successful clinical and bacteriologic outcome was seen in 21/24 (87.5%) subjects with bacteremia treated with daptomycin. This result was similar to the percentage of favorable outcomes for conventional therapy in both Phase II studies (8/9 [88.9%] in the first study and 3/4 [75.0%] in the second study).

In studies conducted to date by Lilly and Cubist, the incidence of CPK elevations does not appear to be dose-related. In Phase 1 and 2 clinical studies, CPK elevations did appear to be more frequent when daptomycin was dosed more frequently than once daily. In a Phase 1 dose-escalation study (Study B8B-MC-AVAP) conducted by Lilly, daptomycin at 4 mg/kg q12h for 14 days was administered to five normal subjects. At about Day 8 of treatment, two of the five subjects experienced muscle pain and weakness as well as rapid elevations in CPK. Study medication was discontinued and the effects resolved within a few days without sequelae. Subsequent animal studies indicated that for a given level of drug exposure the frequency and severity of skeletal muscle toxicity were decreased with once daily dosing compared with divided doses. Therefore, when Cubist acquired the drug for development, the choice was made to use only single daily dosing.

In Phase II clinical trials conducted by Eli Lilly and company and by Cubist, daptomycin was administered at 2, 4, and 6 mg/kg q24h and at 3 mg/kg q12h to 349 patients with a variety of serious infections due to Gram-positive organisms, including bacteremia, endocarditis, skin and soft tissue infection, and pneumonia. In these studies, the incidence and nature of adverse events associated with daptomycin were comparable to that seen with conventional therapy. In Cubist sponsored Phase II/III studies, 70 patients received the proposed dose of 4 mg/kg q 24h.

E. Special Populations

Demographic Characteristics

The number of male patients enrolled in both studies was slightly higher (~55%) than that of female patients (~45%). Distribution of patients by gender was comparable between the two treatment arms. The protocol specified age groups to be enrolled in the two cSSSI studies were patients from 18-85 years of age, except in South Africa, where the upper age limit for enrollment was 65 years. A few patients < 18 years/ >85 years were also enrolled. Overall, patients in study 9801 were slightly older, with a mean age ~55 years versus ~48 years in study 9901. The majority of patients in both studies were between 40-64 years of age. Patients in the age group category of ≥ 65 years were more common in study 9801, while those in the 18-39 years age category were more common in study 9901. In both studies, distribution of patients by age group was comparable in the two treatment arms. In study 9801, over 60 % of patients were Caucasian, ~ 20% were blacks and the remainder were Asian/others. In study 9901 ~50% of patients were Caucasian, over a third were blacks, and the remainder were Asian/others. The following two tables summarize the demographic characteristics of patients in study 9801 and 9901 respectively.

Study 9801

Table ES13: Demographic characteristics (Population: ITT)

Characteristic	Daptomycin (N=264)	Comparator (N=266)	P-Value
Age (yrs.)			
Range (Min, Max)	(18, 91)	(18, 94)	
Mean ± SD	55.2 ± 17.6	55.5 ± 17.7	*0.8455
Distribution			
< 65 years	173 (65.5%)	183 (68.8%)	0.4233
≥ 65 years	91 (34.5%)	83 (31.2%)	
Gender			
Male	143 (54.2%)	148 (55.6%)	0.7334
Female	121 (45.8%)	118 (44.4%)	
Race			
White	177 (67.1%)	167 (62.8%)	0.5366
Black	50 (18.9%)	60 (22.6%)	
Other	37 (14.0%)	39 (14.7%)	
Weight (kg)			
Range (Min, Max)	(36, 274)	(44, 193)	
Mean ± SD	87.6 ± 33.5	87.0 ± 27.7	*0.8417

* Using t-test; others using chi-square test

Study 9901

Table ES14: Demographic characteristics (Population: ITT)

Characteristic	Daptomycin (N=270)	Comparator (N=292)	P-Value
Age (yrs.)			
Range (Min, Max)	(18, 87)	(17, 85)	*0.6284
Mean ± SD	47.9 ± 17.2	48.6 ± 16.7	
Distribution			
< 65 years	216 (80.0%)	236 (80.8%)	0.8062
≥ 65 years	54 (20.0%)	56 (19.2%)	
Gender			
Male	150 (55.6%)	160 (54.8%)	0.8562
Female	120 (44.4%)	132 (45.2%)	
Race			
White	136 (50.4%)	146 (50.0%)	0.3156
Black	95 (35.2%)	91 (31.2%)	
Other	39 (14.4%)	55 (18.8%)	
Weight (kg)			
Range (Min, Max)	(40, 165)	(40, 130)	
Mean ± SD	73.5 ± 19.8	72.7 ± 17.4	*0.6244

* Using t-test; others using chi-square test

Efficacy

In study 9801, clinical success rates were slightly higher in females in both treatment arms. In study 9901, slightly higher success rates were seen in females in the comparator arm, and in males in the daptomycin arm. In the daptomycin arm, success rates were lower in patients ≥ 65 years of age in both studies. In the comparator arm, success rates were comparable in the two age group categories in study 9801, while they were slightly lower in patients ≥ 65 years of age in study 9901. In study 9901, the reduction in success rates in patients ≥ 65 years was more pronounced in the daptomycin arm. In study 9801, slightly higher success rates were seen in black patients compared to Caucasian and others. In study 9901, slightly higher success rates were seen in patients of black/other race compared to Caucasian.

Clinical success rates by demographic characteristics in the ITT population in the two studies are presented below:

Study 9801

Table ES15: FDA efficacy analyses by demographic characteristics (Population: ITT)

Subgroup	Daptomycin (N=264)	Comparator (N=266)	95% C.I.
Age			
< 65 years	119/173 (69%)	112/183 (61%)	(-2.9%, 18.0%)
≥ 65 years	46/91 (50.5%)	50/83 (60%)	(-25.6%, 6.2%)
Gender			
Male	86/143 (60%)	87/148 (59%)	(-10.6%, 13.3%)
Female	79/121 (65%)	75/118 (64%)	(-11.2%, 14.7%)
Race			
White	101/177 (57%)	93/167 (56%)	(-9.7%, 12.4%)
Black	42/50 (84%)	47/60 (78%)	(-10.7%, 22.1%)
Other	22/37 (59.5%)	22/39 (56%)	(-21.8%, 27.9%)

Study 9901

Table ES16: FDA efficacy analyses by demographic characteristics (Population: ITT)

Subgroup	Daptomycin (N=270)	Comparator (N=292)	95% C.I.
Age			
< 65	181/216 (83.8%)	194/236 (82.3%)	(-5.8%, 9.0%)
≥ 65	36/54 (66.7%)	41/56 (73.2%)	(-25.5%, 12.4%)
Gender			
Male	122/150 (81.3%)	125/160 (78.1%)	(-6.4%, 12.8%)
Female	95/120 (79.2%)	110/132 (83.3%)	(-14.6%, 6.3%)
Race			
White	107/136 (78.7%)	111/146 (76.0%)	(-7.8%, 13.1%)
Black	78/95 (82.1%)	75/91 (82.4%)	(-12.4%, 11.7%)
Other	32/39 (82.1%)	49/55 (89.1%)	(-23.8%, 9.7%)

Safety

Adverse events by demographic group in the phase 3 studies are shown in Table ES3.

Community acquired pneumonia

The incidence of adverse events in CAP patients was higher in all age groups in the daptomycin arm than in the comparator arm; this difference was largest in the <65 year old age group (54.3% versus 45.4%, daptomycin versus comparator, respectively). There was no difference in adverse events reported by gender in the daptomycin arm; in the comparator arm, AE's were more frequent in females (278/522; 53.3%) than in males (309/663; 46.6%). In both arms, patients in the

racial group described as "Other" had higher rates than other racial groups; the difference between arms, however, was small.

Complicated skin and skin structure infections

Adverse event rates were similar between treatment groups when stratified by gender and race; however, overall adverse event rates were higher in daptomycin-treated patients than in comparator-treated patients in patients 65 years of age and older. The higher adverse event rates in the ≥65 years age group likely reflects the higher rate of underlying medical conditions in this age group, since this same differential in adverse events by age is also present in the comparator group. Pharmacokinetic data in the geriatric population do not support a need for a change in dose in this age group.

Table ES17. Adverse event rates by demographic groups in Phase 3 (cSSSI and CAP) studies

Demographic Characteristic	Daptomycin			Comparator		
	CSSSI (N=534) n/N (%)	CAP (N=455) n/N (%)	All Studies (N=1409) n/N (%)	cSSSI (N=558) n/N (%)	CAP (N=460) n/N (%)	All Studies (N=1185) n/N (%)
Gender						
Male	148/294 (50.3)	153/262 (58.4)	417/793 (52.6)	151/307 (49.2)	126/266 (47.4)	309/663 (46.6)
Female	126/240 (52.5)	108/193 (56.5)	320/616 (51.9)	142/251 (56.6)	104/194 (53.6)	278/522 (53.3)
Age						
< 65 years	176/390 (45.1)	152/278 (54.3)	472/991 (47.6)	208/418 (49.8)	132/291 (45.4)	389/846 (46.0)
≥ 65 years	98/144 (68.1)	111/177 (62.7)	261/411 (63.5)	85/140 (60.7)	98/168 (58.3)	198/338 (58.6)
≥ 75 years	46/66 (69.7)	49/75 (65.3)	117/180 (65.0)	43/67 (64.2)	54/86 (62.8)	103/166 (62.0)
Race						
Caucasian	196/313 (62.6)	211/378 (55.8)	540/938 (57.6)	184/313 (58.8)	177/375 (47.2)	407/811 (50.2)
Black	45/145 (31.0)	21/35 (60.0)	102/254 (40.2)	59/151 (39.1)	19/40 (47.5)	83/205 (40.5)
Other*	33/76 (43.4)	30/42 (71.4)	95/217 (43.8)	50/94 (53.2)	34/45 (75.6)	97/169 (57.4)

*includes Other + Asian

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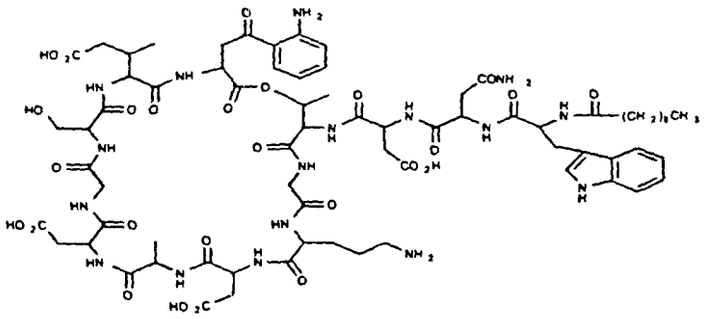
ON ORIGINAL

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Group

Pharmacologic name: Daptomycin
Trade name: Cubicin®
Drug class: Lipopeptide
Proposed indication: Treatment of complicated skin and skin structure infections
Dose: 4 mg/kg intravenously, once a day
Age groups: ≥18 years of age
Structure:



B. State of Armamentarium for Indication(s)

Several drugs have been approved for the treatment of complicated skin and skin structure infections in adults including linezolid (Zyvox™), ertapenem (Invanz™) quinupristin-dalfopristin (Syncercid®), and extended-spectrum penicillins like piperacillin-tazobactam (Zosyn®).

B. Important Milestones in Product Development

Development by Eli Lilly and Company

Daptomycin entered clinical trials for the treatment of Gram-positive infections, including endocarditis, in March 1986 under IND # 27,627. The compound was evaluated in 19 Phase 1 and two Phase 2 studies. In June 1987, a Phase 2 clinical trial (B8B-MC-AVAE/B8B-EW-AVAG) was initiated by Lilly to evaluate the efficacy of daptomycin at a dose of 2 mg/kg q24h. This dose regimen appeared to be effective in skin and skin structure infections, but not against bacteremia and deep-seated infections. A second Phase 2 trial (B8B-MC-AVAM),

initiated in June, 1989, demonstrated that daptomycin at 3 mg/kg q12h was potentially effective in bacteremia, but was less effective than conventional therapy for staphylococcal endocarditis. A further Phase 1 study evaluated the safety of 4 mg/kg q12h over 14 days. This study was discontinued when 2/5 patients experienced muscle-related adverse events (forearm weakness, myalgia, and elevated CPK).

On March 8, 1991, Eli Lilly informed the FDA that it had voluntarily suspended further evaluations of daptomycin. On April 3, 1991, FDA put the daptomycin IND on clinical hold. In 1997, Cubist Pharmaceuticals, Inc., decided to license daptomycin and resumed development of the drug under Cubist's own IND #57,693.

The pre-clinical and clinical data previously generated by Lilly was used to support Cubist's initial Phase 2 and 3 trials. In addition, Lilly authorized Cubist to cross-reference its daptomycin IND #27,627. Cubist modified the dosing-regimen to once-daily dose based on preclinical studies and modeling that showed once-daily dosing maximized antibacterial efficacy and minimized skeletal muscle adverse effects.

Development by Cubist

The following table summarizes some important milestones in the development of daptomycin by Cubist. This table was excerpted from a table provided by the sponsor in the integrated summary of efficacy (Table 3-1).

Date	Event
December 15, 1997	Teleconference with FDA to discuss re-opening of daptomycin IND previously held by Eli Lilly.
February 2, 1998	Teleconference between FDA and Cubist. FDA recommended that Cubist submit their own IND while cross referencing the Lilly IND.
April 29, 1998	Teleconference with FDA to discuss Agency's internal review of Cubist's pre-IND package. It was agreed that Lilly's clinical hold will not apply to Cubist's new IND.
December 2, 1998	Pre-IND meeting of Cubist/FDA to present details of proposed clinical development program for daptomycin.
December 31, 1998	IND application submitted for daptomycin in the
July 12, 2000	End of Phase 2 meeting to discuss the daptomycin Phase 3 clinical trial for community-acquired Pneumonia (CAP) and the overall NDA development plan for daptomycin. Agreement was reached on the protocol for the Phase 3 CAP study, which included modifying the delta from Also, the Agency agreed to the general overall NDA plan for the SSSI and CAP indications as long as Cubist undertakes an appropriately designed second CAP study.
August 23, 2000	Amendment to cSSSI protocols DAP-SST-9801 and DAP-SST-9901 to recalculate the sample size using a 10% delta.
November 9, 2001	Pre-NDA meeting to discuss general, pre-clinical and clinical questions related to the daptomycin NDA. Overall, the Agency agreed that the data Cubist planned to submit for the NDA was adequate to support the proposed indications. FDA and Cubist agreed upon an approach to presenting an integrated safety analysis in the ISS that addresses both Cubist and Lilly-sponsored trials. The Agency requested the addition of a Phase 1 study in geriatric patients to differentiate between age and renal function. No decision was reached as to priority review status, pending review of the data submitted.
December 3, 2001	Pre-NDA CMC Meeting between Cubist and FDA.
January 16, 2002	Submission of the primary efficacy results of Study DAP-CAP-00-05. Cubist voluntarily suspended enrollment of Study DAP-CAP-00-08 until further analysis of the data from the first trial.
March 4, 2002	Correspondence from FDA that an NDA for daptomycin could be filed with a single indication of cSSSI with the CAP studies providing additional safety data to support the NDA.

D. Other Relevant Information

Daptomycin is not currently approved for use in any foreign country or in the United States.

E. Important Issues with Pharmacologically Related Agents

Daptomycin is the first drug in the class of cyclic lipopeptides.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Animal Pharmacology and Toxicology
The major target organs of toxicity in rat, dog and monkey were muscle and peripheral nerves. Muscle damage consisted of muscle degeneration/regeneration and usually resolved within 1 month of cessation of treatment. Muscle changes were sometime accompanied by increases in CPK. Peripheral nerve damage occurred at higher doses and included loss of patellar/gag reflexes, loss of pain perception, decreases in nerve conduction velocity, and axonal degeneration. Recovery was dependent on dose, and was incomplete after a 3-month period. In the rat, renal toxicity was also observed. The NOEL levels from the animal toxicity studies, when expressed as either AUC or doses on a body surface area basis, were less than those at the proposed human dose of 4 mg/kg. Similar toxicities were noted in the 1, 3 and 6 month toxicity studies.
Daptomycin was negative in the Segment I, II and III reproductive toxicity studies. Daptomycin was neither mutagenic nor clastogenic in a series of in vitro and in vivo genotoxicity tests. 3

For details please refer to the review by Dr. Wendelyn J. Schmidt, Ph.D.

Microbiology
Daptomycin acts by binding to bacterial membranes and causes a rapid depolarization of membrane potential. The loss of membrane potential leads to inhibition of protein, DNA, and RNA synthesis, which results in bacterial cell death. Activity of daptomycin has been shown against isolates of the following microorganisms both in vitro and in clinical infections
Enterococcus faecalis (vancomycin-susceptible strains only)
Staphylococcus aureus (including methicillin-resistant strains)
Streptococcus agalactiae
Streptococcus dysgalactiae subsp. equisimilis
Streptococcus pyogenes

The following table summarizes the susceptibility interpretive criteria for daptomycin as included in the package insert.

Pathogen	Minimal inhibitory concentration (µg/mL)			Disk diffusion zone Diameter (mm)		
	S	I	R	S	I	R
Staphylococcus aureus (methicillin-susceptible and methicillin-resistant)	≤1	(c)	(c)	≥16	(c)	(c)
Streptococcus pyogenes, *Streptococcus agalactiae*, and *Streptococcus dysgalactiae* subsp. *Equisimilis*	≤0.5	(c)	(c)	≥16	(c)	(c)
Enterococcus faecalis (vancomycin–susceptible only)	≤4	(c)	(c)	≥11	(c)	(c)

For details of the microbiology review, please see the review by Dr. Peter Coderre Ph.D.

Biostatistics

Analyses by the statistical reviewer Dr. Joel Jiang Ph.D. and the medical officer were done in conjunction. The overall conclusions of Dr. Jiang are in concurrence with those of the medical officer. For details of the biostatistics review, please see the review by Dr. Jiang Ph.D.

Chemistry

The manufacturing process for daptomycin is difficult including [redacted] procedures. The expiration date is within 24 months of manufacture. No other major clinically relevant chemistry issues were noted in the application. For details please refer to the review by Dr. Zi-Qiang Gu Ph.D.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Daptomycin pharmacokinetics are nearly linear and time-independent at doses up to 6 mg/kg administered once daily for 7 days. Steady-state concentrations are achieved by the third daily dose. Daptomycin is reversibly bound to human plasma proteins, primarily to serum albumin, in a concentration-independent manner. The mean serum protein binding of daptomycin was approximately 92% in healthy adults after the administration of 4 mg/kg. In vitro studies with human hepatocytes indicate that daptomycin does not inhibit or induce the activities of

the following human cytochrome (CYP) P450 isoforms: 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4. Daptomycin is excreted primarily by the kidney. Because renal excretion is the primary route of elimination, dosage adjustment is necessary in patients with severe renal insufficiency (CL_{CR} < 30 mL/min)
The pharmacokinetics of daptomycin is not altered in subjects with moderate hepatic impairment. No dosage adjustment is warranted when administering daptomycin to patients with mild to moderate hepatic impairment. The pharmacokinetics of daptomycin in patients with severe hepatic insufficiency have not been evaluated. No clinically significant gender-related differences in daptomycin pharmacokinetics have been observed between healthy male and female subjects. No dosage adjustment is warranted based on gender when administering daptomycin. No dosage adjustment is warranted for elderly patients with normal (for age) renal function. The pharmacokinetics of daptomycin in pediatric populations (<18 years of age) have not been established.

For details of the review please refer to by Charles R. Bonapace, Pharm.D.

B. Pharmacodynamics

The exposure-response relationship of daptomycin has been evaluated using in vitro time-kill studies and in vivo animal models of infection. Pharmacodynamic investigations have been conducted using various animal models. In these studies, the PK/PD parameters that were most associated with efficacy were the AUC/MIC and C_{max}/MIC, whereas the percentage of the dosing interval that plasma concentrations exceeded the MIC (T>MIC) was associated with efficacy but not to the extent of the AUC/MIC and C_{max}/MIC. These findings are consistent with the concentration-dependent bactericidal activity of daptomycin demonstrated with *in vitro* time-kill studies.

For details of the review please refer to by Charles R. Bonapace, Pharm.D.

IV. Description of Clinical Data and Sources

A. Overall Data

Study reports and data sets submitted by the sponsor in the NDA were used as the sources of data for this review.

C. Tables Listing the Clinical Trials

Name	Phase	Number randomized	Indication
DAP-SST-9801	3	547	cSSSI
DAP-SST-9901	3	571	cSSSI

C. Postmarketing Experience

Cidecin® (Daptomycin) has never been marketed in any country.

D. Literature Review

The sponsor has provided an adequate list of references. The following additional references were consulted for this review:

1. Clinically significant infections with organisms of the Streptococcus milleri group. Belko J, Goldmann DA, Macone A, Zaidi, A. Pediatr Infect Dis 2002;21(8):715-723.
2. Chantelau E, Tanudjaja T, Altenhöfer, et al. Antibiotic treatment for uncomplicated neuropathic foot ulcers in diabetes: A controlled trial. Diabetic Medicine 1996; 13: 156-159.
3. Cabrera H, Skoczdopole L, Marini M, et al. Necrotizing gangrene of the genitalia and perineum. Int J Dermatol. 2002 Dec;41(12):847-51.
4. Edson RS, Osmon DR, Berry DJ. Septic arthritis due to Streptococcus sanguis. Mayo Clin Proc. 2002 Jul;77(7):709-10.

V. Clinical Review Methods

A. How the Review was Conducted

The two phase 3 studies submitted in this application to support the indication of complicated skin and skin structure infections, DAP-SST-9801 and DAP-SST-9901 were reviewed in detail. One controlled study, B8B-MC-VAE/AVAG was submitted as a supportive study. It was conducted by Lilly at 22 sites in North America and 2 sites in Europe and was a multi-indication supportive protocol that included patients with skin and skin structure infections due to susceptible Gram positive bacteria. The dose of daptomycin used in this study was 2 mg/kg q 24h for a total duration of 5 days. As the dosing regimen of daptomycin used in this study is different from that used in the other two phase 3 clinical trials, results of this study are not included in the overall efficacy analyses and will not be discussed in this review.

For the efficacy analyses in complicated skin and skin structure infections, the medical officer reviewed case report forms of 10% of the study population in study 9801 and 9901 in a blinded manner. Overall, no major inconsistencies were seen in the evaluability or outcome assessments. Hence, this sample was considered to be adequately representative of the quality of data and the sponsor's data were used for FDA analyses. In addition to the sponsor's analyses of data, FDA analyses were performed using FDA defined patient populations and FDA defined clinical end points for both studies. Differences between the sponsor defined and FDA defined populations are described in the review.