B. Overview of Materials Consulted in Review

The following materials were consulted during the review process

- Final study reports, submitted electronically
- Case report forms
- Data sets submitted by sponsor and some additional data sets requested by FDA
- Proposed package insert
- Literature review

C. Overview of Methods Used to Evaluate Data Quality and Integrity

DSI audits were performed at two clinical trial sites for study 9801. No audits were performed for sites that enrolled patients in study 9901.There were many protocol deficiencies at both sites related mainly to eligibility determinations and laboratory assessments. Most of these deviations were considered not to impact the study significantly, hence data from these two sites were not excluded from the analyses.

A summary of audited sites is displayed in the following table.

Investigator Name (Number)	Location	Study number	Number of patients randomized
Tidman (168)	Blue Ridge, GA	9801	32
Pien (66)	Honolulu, Hawaii	9801	42

A random sample of 10% of the case report forms for both studies were reviewed by the medical officer for concurrence with the sponsor's evaluability and outcome assessments. 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.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

According to the sponsor, the protocol, informed consent form (ICF), and all other written documents provided to the investigator or subject were reviewed and approved by an Institutional Review Board (IRB) or

Independent Ethics Committee (IEC) at each site before the study was initiated. Copies of the approval letter and all other correspondence with the IRB/IEC were sent to ——— , a Contract Research Organization (CRO) located ——— All of these documents are retained in the Trial Master Files.

The sponsor and the investigators agreed to submit to the IRB/IEC any subsequent protocol amendments, reports of all serious adverse events, and any other information relevant to the safety of the subjects or the conduct of the trial.

The sponsor also stated that the study was conducted in accordance with the ethical principles articulated in the Declaration of Helsinki (Republic of South Africa, amendment October 1996), with the Harmonized Tripartite Guidelines for Good Clinical Practice (GCP) issued by the International Conference on Harmonization (ICH), and with the local laws and regulations for the use of investigational therapeutic agents. All subjects provided voluntary written informed consent. The ICF was signed and dated by both the subject and the investigator or designee. A copy of the signed ICF was provided to the study subject, and the original was retained in the source documents. Any modifications to the ICF requested by the IRB or IEC were reviewed and approved by Cubist prior to implementation.

E. Evaluation of Financial Disclosure

The sponsor (Michael Bonney, President and Chief Operating Officer, Cubist Pharmaceuticals Inc.) has submitted form FDA 3454, Certification: Financial interests and arrangements of clinical investigators. The sponsor certifies that he has not entered into any financial arrangement with the listed clinical investigators whereby the value of the compensation will be affected by the outcome of the studies as defined in CFR 54.2(a). He also certified that each listed clinical investigator was required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b), and that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Both study 9801 and 9901, comparing the use of daptomycin with comparator drugs (vancomycin/semi-synthetic penicillins), showed that daptomycin was non-inferior to the comparator drugs in the treatment of

complicated skin and skin structure infections due to Gram positive bacteria using a non-inferiority margin of 10 %. Gram positive bacteria studied include *Staphylococcus aureus* (methicillin-resistant and susceptible strains), *Streptococcus pyogenes*, *Enterococcus faecalis* (vancomycin-susceptible strains), *Streptococcus agalactiae*, and *Streptococcus dysgalactiae*.

Data submitted were not adequate to include infected diabetic ulcers in the indications and usage section. Viridans group streptococci should not be included in the list of pathogens as their role as pathogens in skin and skin structure infections is unclear, except for members of the *S. intermedius* (*milleri*) group. The number of patients with *S.intermedius* isolates was very few in both studies. As patient characteristics and clinical success rates differed significantly between the two studies, the results of the two studies should be considered separately and not included in the product label in an integrated manner as proposed by the sponsor.

B. General Approach to Review of the Efficacy of the Drug

All data in this NDA were submitted electronically and are available in the electronic document room.

DAP-SST-9801
\\CDSESUB1\N21572\N_000\2002-12-19\clinstat\dapsst9801.pdf

DAP-SST-9901
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B8B-MC-AVAE/AVAG
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C. Detailed Review of Trials by Indication

In this application, the sponsor is only seeking approval for the indication of complicated skin and skin structure infections. Results from two primary comparative studies, DAP-SST-9801 and DAP-SST-9901 were submitted in the NDA to support this indication of. Both studies had similar study design and primary endpoints. In this review, study 9801 is described in detail and the differences between the two studies are summarized in table number 3.

An additional study (B8B-MC-VAE/AVAG) was submitted as a supportive study. This study was conducted by Lilly 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

which is different from that used in the other two phase 3 clinical studies. Hence, results of this study are not included in the overall efficacy analyses and will not be discussed further in this review.
Parts of this review are excerpted from the final study reports provided by the sponsor. Comments by the medical officer are provided in Italics.

DAP-SST-9801

Objectives
The primary objective of this study was to compare the safety and efficacy of daptomycin to that of vancomycin or selected semi-synthetic penicillins in the treatment of complicated skin and skin structure infections due to Gram positive bacteria.

Design
This was a multicenter, international, investigator-blinded, randomized, Phase 3 trial.

Population and procedures
Inclusion criteria
Patients were eligible for inclusion in the study if they met all of the following criteria:
General inclusion criteria

- Age 18-85 years
- If female, the patient must have been post-menopausal for at least one year, or have had a hysterectomy or a tubal ligation or, if of child-bearing potential
  - have maintained her normal menstrual pattern for the 3 months prior to study entry and
  - have taken hormonal contraceptives for at least one month prior to study entry, or agree to use spermicide and barrier methods or be using another acceptable method of contraception and agree to continue with the same method during the study, and
  - have a negative serum pregnancy test (serum β-hCG) immediately prior to enrollment. If obtaining the serum pregnancy test result would have caused a delay in treatment, a subject could be entered on the basis of a urine pregnancy test sensitive to at least 50 mU/mL of β hCG, pending results of the serum test.
- Signed, written, informed consent must have been obtained after the nature of the study had been fully explained and before any protocol-specific procedure was performed. In the event that the subject was unable to give consent, the subject's legal representative could do so

by means approved by the investigator's Independent Ethics Committee (IEC).

Specific inclusion criteria

- A diagnosis of skin and soft tissue infection known or suspected to be due to Gram positive bacteria. *Staphylococcus epidermis* and corynebacteria were not to be considered pathogenic unless also identified in blood and deep tissue sites.
- Diagnosis of bacterial skin and soft tissue infection in the presence of some complicating factor, including infections involving deeper soft tissue or requiring significant surgical intervention. Complicating factors include a pre-existing skin lesion or some underlying condition that adversely effects either the delivery of drug to the affected area, the immunologic response, or the tissue healing response.
- At least 3 of the following clinical signs and symptoms of skin infection must have been present:
    - Temperature >38°C rectal or >37.5°C oral
    - WBC count >12 x10 ^{3} /L or with ≥10% bands
    - Pain
    - Tenderness to palpation
    - Erythema (extending at least 1 cm beyond wound edge)
    - Swelling
    - Induration
    - Pus formation
- Skin and soft tissue infections appropriate for this study included:
    - Wound infections, including wounds due to:
        - Traumatic injury
        - Surgical incision
        - Animal or human bites provided tissue damage existed
        - Foreign body (e.g., septic phlebitis associated with intravenous catheter sites)
    - Major abscesses, with or without recognized preceding trauma that required antibiotic therapy in addition to surgical incision and drainage.
    - Infected ulcers (except multiple infected ulcers) associated with diabetes, vascular insufficiency or pressure.

- Infections in immunosuppressed patients:
  - Patients known to be HIV-infected (provided CD4 counts ≥200 cells/mm ^{3})
  - Patients on chronic systemic steroids (>20 mg prednisone daily or the equivalent)
  - Patients with diabetes mellitus necessitating treatment with oral hypoglycemic agents and/or insulin.
- Patients with multiple sites of infection could be entered into the study (except multiple infected ulcers). The most severely affected site or the one most likely to yield a positive culture was chosen to follow throughout the course of evaluations.
- An appropriate specimen of the infected site was to be obtained for Gram stain and culture within 48 hours prior to initiation of study treatment. Cultures of infected ulcers should be obtained by needle aspiration of obviously purulent material or biopsy to avoid contamination with superficial, colonizing bacterial flora that may not represent the causative pathogen.

Medical Officer (MO) Comments:
According to the FDA draft guidance for industry (Uncomplicated and Complicated Skin and Skin Structure Infections, Developing Antimicrobial Drugs for Treatment, July 1998), studies in support of this indication should include infections of the deeper soft tissue, or those requiring significant surgical intervention such as infected ulcers, burns, and major abscesses or a significant underlying disease state that complicates the response to treatment.
The enrollment criteria specified by the sponsor conform to a great extent to the guidance, since the study included patients with infected ulcers, burns and major abscesses; only patients with third degree burns were excluded. Conditions such as infected ulcers, especially when associated with vascular insufficiency or diabetes mellitus, differ substantially from acute abscesses and wound infections, in their chronicity, microbiology, response to therapy and need for adjunct surgical therapy. So, the different diagnoses should be fairly well represented to support this indication.

Exclusion criteria

General exclusion criteria

Patients were not eligible for enrollment if they met any of the following criteria at baseline:

- Patients known to have bacteremia. Patients whose baseline blood cultures were positive could be continued in the trial.

- Patients with one of the following infections:
  - minor or superficial skin infections (e.g., furuncles, simple abscesses, acne, impetigo)
  - cellulitis not associated with complicating factors. Patients with cellulitis associated with more serious infection (e.g., surgical wound, diabetic ulcer, deep tissue) could be enrolled
  - perirectal abscess
  - hidradenitis suppurativa
  - myositis (with or without skin and soft tissue infection)
  - multiple infected ulcers at distant sites
  - infected third-degree burn wounds
- Conditions requiring surgery that in and of itself would cure the infection or remove the infected site (e.g., amputation)
- Conditions requiring emergent surgical intervention at the site of infection (e.g., progressive necrotizing infections)
- Diagnosis of osteomyelitis
- Infection due to an organism known to be resistant to study drug prior to study entry
- Any disorder or disease that could interfere with the evaluation in this protocol including primary muscle disorders or deep site infection, including known or suspected endocarditis and pneumonia at study entry
- Shock or hypotension (supine systolic blood pressure <80 mm Hg) unresponsive to fluids or pressors within 4 hours or oliguria (urine output <20 mL/hr)
- Any type of hemodialysis or peritoneal dialysis
- Pregnancy or nursing mothers
- Grossly underweight (≤ 40 kg)
- Previous allergic or serious reaction to daptomycin or vancomycin.

MO Comments:

Exclusion of patients with necrotizing fasciitis is consistent with the FDA draft guidance. Patients with infected atopic dermatitis are usually excluded as it is difficult to assess efficacy of antimicrobials due to co-existing inflammation. As patients with bacteremia were excluded from the study, this should be reflected in the product label. Exclusion of patients with osteomyelitis was based on x-ray findings alone. As x-rays have low

sensitivity in the early detection of osteomyelitis, it is possible that some patients with osteomyelitis were actually enrolled in these studies. Patients receiving concomitant HMG Coenzyme A reductase inhibitors were excluded, as skeletal muscle toxicity can be seen with daptomycin use. However, in clinical practice it is very likely that patients receiving daptomycin could also receive HMG CoA reductase inhibitor drugs. Post-marketing surveillance can provide important information about the potential for increased muscle toxicity in patients receiving both drugs.

Exclusion criteria related to medications

- Requirement for a non-study systemic antibacterial to which the target pathogen was susceptible or use of a topical antibacterial at the site of infection.
- Previous systemic antibacterial therapy for the treatment of Gram-positive skin and soft tissue infections for more than 24 hours within 48 hours prior to the day of first infusion of study drug unless:
  - the infecting Gram positive pathogen was resistant to the previous antibacterial therapy or
  - the previous antibacterial therapy was administered for 3 or more calendar days and was found to be ineffective.
- Patients admitted to the hospital for drug overdose or other conditions associated with rhabdomyolysis.
- Patients requiring intramuscular injections.
- Patients receiving HMG Coenzyme A reductase inhibitors.
- Patients who were known or suspected drug abusers.
- Previous treatment under this protocol or protocol DAP-SST-9901.
- Exposure to any investigational agent within 30 days of entry into study.

Comments:
The FDA draft guidance indicates that prior anti-infective use, even up to the day of patient enrollment would exclude a patient unless a culture is obtained showing the persistence of a pathogen. Even 24 hours of treatment with non-study antimicrobials could potentially affect outcome. In certain clinical situations, like infected ulcers or complicated cellulitis persistence of some signs of inflammation does not necessarily imply clinical failure. The use of clinical criteria alone to assess failure to prior therapy in the absence of a documented pathogen could be erroneous, leading to falsely elevated cure rates in study drugs.

Exclusion criteria related to laboratory values

- Patients were to be excluded if at the time of randomization one or more laboratory results were known to be abnormal as defined below:
  - Absolute neutrophil count $\leq 0.5 \times 10^3$ /L
  - HIV-infection with CD4 lymphocytes $\leq 0.2 \times 10^3$ /L
  - CPK >50% above upper limit of normal
  - Calculated creatinine clearance <30 mL/min

MO Comments:

As patients with creatinine clearance less than 30 ml/min were excluded, safety and efficacy information in this group of patients will be gained in post-marketing experience and in the phase 4 commitment study as described in the executive summary section I B.

Removal of patients from therapy or assessment

Patients participation could be terminated prior to completing the study for any of the following reasons:

- Adverse event
- Clinical failure
- Subject chose to withdraw from the study
- Baseline bacteriological cultures yielded a resistant pathogen

Study visits

Baseline visit: Evaluations were to be performed within 48 hours prior to the first dose of study medication. At this visit, medical history was obtained and physical examination performed. Gram stain and culture of the infection site, blood culture, X-ray (to rule out osteomyelitis), and clinical laboratory tests were also performed.

On therapy visit: Was conducted on day 3 or 4 of treatment.

End-of-Therapy (EOT) visit: Was conducted up to 3 days after the last dose of study drug or at early termination.

Post-Therapy (Test-of-Cure) visit: Was conducted 7 to 12 days post-treatment.

The EOT and TOC visits were to be performed for all patients and included the following procedures:

- Monitoring for treatment emergent adverse events, significant procedures, use of any antibacterials or concurrent medications.
- Assessment by the blinded investigator of pertinent clinical signs and symptoms of infection.

- Gram stain and culture of the infection site if a clinically significant lesion and/or drainage persisted, repeat blood cultures for patients with positive cultures at baseline or in the case of clinical deterioration, and a blood sample for clinical laboratory tests, including CPK.

Post-Study visit: Was conducted 21 to 28 days post-treatment and was to be performed only for those patients who were considered cured or improved by the blinded investigator at the TOC visit. Procedures included evaluation of pertinent clinical signs and symptoms of infection and Gram stain and culture of the infection site if a clinically significant lesion and/or drainage persisted.

MO Comments:
The FDA guidance recommends a test of cure visit at least seven days after the tissue levels of the study drug have gone lower than the minimum inhibitory concentration (MIC) of the expected pathogens, hence a test of cure visit at 7-14 days after completion of therapy is appropriate. Though these visit windows were specified in the protocol, the TOC visit for analytical purposes was 6-20 days after end of therapy.

Blinding

The protocol was conducted using an investigator-blinded design. To facilitate the investigator-blind and eliminate other sources of potential bias, the subject was also blinded to study medication. A double-blind design was deemed impractical for the following reasons:

- The dosing schedule of the investigational agent was substantially different from that of the comparator agents.
- The infusion times of the study agents were different.
- The investigational drug is active against both methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA); however, among the comparators, the agent of choice for MSSA is a semi-synthetic penicillin and for MRSA, vancomycin.
- In patients with moderately decreased renal function, vancomycin requires monitoring of drug levels and adjustment of dosing intervals.

Prior to randomization the blinded investigator was expected to:

- obtain signed informed consent from the subject,
- determine that a subject met the inclusion/exclusion criteria
- and evaluate the subject, choose the appropriate comparator agent, dose, and regimen to be used if the subject was randomized to comparator.

Following randomization, the blinded investigator was expected to:

- determine that the subject was making appropriate clinical progress,
- perform the scheduled evaluations, including assessing the subject's clinical signs and symptoms and assigning clinical outcomes,
- determine the appropriate duration of therapy,
- and assess relationship of adverse events to study therapy.

Unblinded personnel at each site were expected to do the following:

- access the centralized randomization system to enroll each subject and receive the treatment assignment,
- prepare the study medication, including cover the infusion bags with an opaque plastic cover prior to leaving the pharmacy or drug preparation station,
- and administer the study medication, review the safety variables, monitor the subject daily for adverse events, ensure that all treatment-specific procedures were performed according to the protocol and as much as possible manage the subject's routine daily care.

MO Comment:
A double-blinded study would have been ideal, but differences in dosing regimens and need for therapeutic drug monitoring and dosage modifications with vancomycin made this impractical. As responsibilities were shared between the blinded and unblinded investigator there is a potential that the blind could have been broken.

Randomization

Patients were randomized on a 1:1 basis to receive either daptomycin or the comparator. Patients were assigned to treatment groups by a computer-generated randomization schedule that was prepared prior to initiation of the study, balanced by using permuted blocks of four, and stratified by study center and by presence or absence of a diagnosis of infected diabetic ulcer. Numbers assigned to patients who withdrew before receiving study drug were not to be reused.

After a subject was determined to be eligible for the study and had given signed informed consent, the investigator was to choose, based on the subject's clinical history and condition, the comparator agent, dose, and regimen to be used in the event the subject was randomized to comparator. The agent chosen was to be recorded on the randomization form.

Treatments administered

The comparator agents selected (vancomycin, oxacillin, cloxacillin, and nafcillin) are currently approved for the treatment of complicated skin and soft tissue infections caused by susceptible pathogens in the countries in

which they were used. Vancomycin was included as treatment for patients known or suspected to be penicillin-allergic or to be infected with MRSA. Investigators could select an agent based on local availability and normal treatment practice.

Eligible patients received either daptomycin 4 mg/kg intravenously (i.v.) q24h or one of the following comparator agents:

Vancomycin 1 g i.v. q12h, or

Selected semi-synthetic penicillins:

Nafcillin 4-12 g per day i.v. in equally divided doses

Oxacillin 4-12 g per day i.v. in equally divided doses

Cloxacillin 4-12 g per day i.v. in equally divided doses

Patients assessed to have creatinine clearance of 30 to 70 ml/min were to receive daptomycin 4 mg/kg loading dose, followed by 3 mg/kg q36 hr; Patients with creatinine clearance <30 ml/min were excluded from the trial. Vancomycin dosing was to be adjusted according to a published nomogram or results of therapeutic drug monitoring.

Patients with polymicrobial infections proven or suspected to involve Gram negative or anaerobic bacteria in addition to Gram positive organisms, could receive aztreonam or metronidazole or both in addition to study therapy. Duration of therapy was to be 7 to 14 days. If a subject required more than 14 days of therapy, the duration could be extended following discussion with the medical monitor.

Patients could be switched to oral therapy if all of the following conditions were met:

- There was a compelling reason for such a switch
- There was an oral therapy to which the pathogen was susceptible
- The subject had received at least 4 days of intravenous study therapy; the signs and symptoms at the site of infection had shown clear clinical improvement as documented by an evaluation by the blinded investigator prior to the switch
- The medical monitor had given permission

MO Comments:

Semi-synthetic penicillins are approved for the treatment of infections due to penicillinase-producing strains of staphylococci. Vancomycin is approved for infections due to methicillin-resistant S.aureus. Vancomycin is an appropriate choice for the treatment of MRSA infections. However, for the treatment of infections due to MSSA, semi-synthetic penicillins are superior compared to vancomycin. Cloxacillin is not approved for use in

the United States, but is very similar to oxacillin and nafcillin in its spectrum of activity and pharmacokinetics and hence is an acceptable comparator.

Prior and concomitant therapy

The use of HMG Coenzyme A reductase inhibitors was to be avoided throughout the study period. The use of topical antiseptics (e.g., Betadine, iodine, povidone, peroxide, alcohol) and topical antimicrobial agents were prohibited. Wound care including the use of wet to dry dressings and adjunctive surgical treatment (e.g., debridement, incision and drainage) was allowed. Amputation or en bloc excision of the primary infection was a criterion for clinical failure.

Administration of non-study systemic antibacterial agents active against Gram positive pathogens for treatment of the primary infection was considered evidence of lack of efficacy of the study drug and was a criterion for clinical failure. Administration of such agents for other reasons for more than two days was a criterion for a non-evaluable outcome.

MO Comments:

Adjunctive surgical treatment in itself can be curative in certain patients with complicated skin infections especially those with abscesses and hence could confound assessment of the role of antimicrobials in clinical cure. Surgical procedures alone may be curative in some patients with diabetic ulcers.[1]

Treatment compliance

Measures taken to assure compliance included recording date and time of each dose, recording of receipt and dispensing of study drug and, at the completion of the study, verifying the accuracy of the accounting of study drug.

Evaluation of clinical response

At each visit following the end of study therapy, the blinded investigator was to determine the subject's clinical response to treatment by comparing the subject's signs and symptoms at the visit to those observed and recorded at baseline.

The following definitions for clinical response applied to the EOT and TOC evaluations:

Cure: Resolution of clinically significant signs and symptoms associated with the skin infection present at baseline.

[1] 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.

Improved: Partial resolution of clinical signs and symptoms of the skin infection so that no further antibiotic therapy was required.

Failure: Inadequate response to therapy.

Unable to Evaluate: Unable to determine response because subject was lost to follow-up.

The following definitions for clinical response applied to the Post-Study visit:

Cure: Continued absence of clinically significant signs and symptoms associated with the skin infection present at baseline.

Clinical Relapse/New Infection: Recurrence of clinically significant signs and symptoms associated with the skin infection that was present at baseline so that antibiotic therapy was warranted.

Unable to Evaluate: Unable to determine response because the subject was lost to follow-up.

Microbiologic methods

A specimen for Gram stain and aerobic culture was to be obtained from the infected area at the baseline visit. Culture specimens of debrided tissue or pure pus were preferred to swabs or aspirates of non-purulent material. Cultures of infected ulcers were to be obtained by needle aspiration of obviously purulent material or biopsy to avoid contamination with superficial, colonizing bacterial flora that might not represent the causative pathogen. Gram stain results were to include a description of the bacteria seen and the number of polymorphonuclear leukocytes per low power field. All Gram positive pathogens were to be identified to the level of genus and species and susceptibility testing was to be performed. Patients from whom a specimen could not be obtained were not to be enrolled.

Patients were to be discontinued prematurely if baseline cultures yielded only Gram negative organisms and/or yeasts. However, patients who were improving clinically at the time such results became available could at the discretion of the investigator continue in the study.

Blood cultures

At least two sets of blood cultures from separate venipuncture sites were to be obtained using aseptic technique within 48 hours prior to the first infusion of study drug. If necessary, one of the two specimens could be drawn from an indwelling intravascular catheter. If baseline blood cultures were positive, blood cultures were to be repeated at the on-therapy, EOT and TOC visits, or whenever the subject's condition deteriorated raising suspicion of bacteremia.

Susceptibility testing of Gram positive pathogens

The local microbiology laboratory was to perform susceptibility testing of all Gram positive pathogens to daptomycin, vancomycin, and a semi-synthetic penicillin using Kirby-Bauer (K-B) disk diffusion methods performed according to the guidelines of the National Committee for Clinical Laboratory Standards (NCCLS).

At the central microbiology reference laboratory, all Gram positive pathogens were also to be identified to the level of genus and species. Discordant identifications were to be resolved by the local laboratory sending the frozen duplicate aliquot of the isolate. The central microbiology laboratory was to perform susceptibility testing for each isolate by both K-B and microdilution MIC methods.

Radiological assessments

Patients with a diagnosis of infected ulcer were to have an X-ray of bone adjacent to the site of infection. If the X-ray results were consistent with osteomyelitis, the subject was not to be enrolled. Patients in whom osteomyelitis was diagnosed during study treatment were to be prematurely terminated.

MO Comments:

Radiologic changes of osteomyelitis like osteopenia, osteolytic lesions or periosteal reaction may not be detected by a plain x-ray for 10-14 days after the onset of symptoms. It is thus possible that some patients with osteomyelitis will be enrolled in the study based on a negative x-ray. Other imaging modalities like radionuclide scanning or magnetic resonance imaging can identify bony involvement earlier than conventional x-ray.

Clinical laboratory assessments

Laboratory tests, including hematology, clinical chemistry and urinalysis, were to be obtained at the baseline and EOT visits. Hematology was to be repeated at the TOC visit; clinical chemistries and urinalysis were also to be obtained at this visit if they had not been obtained at the EOT visit, or if warranted by the subject's condition or previous abnormalities.

Monitoring of Creatine Phosphokinase (CPK)

Blood samples for serum chemistries, including CPK, were to be obtained prior to the first dose of study medication, every two days up to Day 7, and then daily thereafter while on study medication. These samples were to be sent to the central laboratory; the investigator could also have additional CPK tests performed at the local laboratory.

If CPK levels exceeded twice the upper limit of normal (>2xULN) at any time during the trial, blood samples for CPK and serum chemistries were to be obtained on a daily basis and sent to the local and central laboratories. If CPK levels subsequently declined to within the normal range, samples could be obtained according to the original schedule.

If CPK levels exceeded 500 U/L, the investigator was to contact the medical monitor. A decision to discontinue or continue study treatment was to be made jointly based on the risks and benefits to the subject. If the subject was continued in the trial and CPK levels increased another twofold (i.e., to >4x ULN) the subject was to be withdrawn from the study, and urine and blood samples sent to the central laboratory for CPK isoenzymes, serum myoglobin, and urine myoglobin.

For all samples with CPK values >2xULN, the central laboratory was to automatically evaluate CPK isoenzymes (MM, MB, and BB isoenzymes).

Statistical Methods

Determination of sample size

The sample size was calculated to provide sufficient patients to conclude that daptomycin was at least as effective as the comparator. With 201 clinically evaluable patients in each treatment group, there would be 80% power to test the above hypothesis assuming an 85% success rate for comparator therapy and an 85% success rate for daptomycin using a significance level of 0.025. With an estimated evaluability rate of 80%, a total of approximately 500 patients would need to be enrolled. The 95% confidence interval was to be calculated based on the normal approximation to the binomial distribution. The protocol was amended to decrease the acceptable upper limit of the 95% CI for the difference in success rates (comparator-daptomycin) from 15 % to 10%.

MO Comments:

Using a delta of 10% rather than 15% provides stronger evidence of non-inferiority of daptomycin compared to comparator drug. A smaller delta also reflects greater treatment effect over a putative placebo arm.

Populations for analysis

Patients were to be analyzed for efficacy according to randomization, regardless of treatment administered. Safety analyses were to be performed on all patients who received at least one dose of study medication, according to treatment actually received. Patients who were randomized but never received any study drug were to be excluded from all efficacy and safety analyses. Sponsor and FDA defined populations differed in some respects as described below.

Sponsor-defined populations

Intent to Treat population

The Intent to Treat (ITT) population was to include all enrolled patients who had a complicated skin and soft tissue infection and received at least one dose of study medication. However, patients who received one or more doses of study medication but, based on the Sponsor's review, did not have a complicated skin and soft tissue infection were excluded from all efficacy populations.

Modified Intent to Treat population

The Modified Intent to Treat (MITT) population was to include all patients in the ITT population who had an infecting Gram positive pathogen isolated at baseline.

Clinically Evaluable population

The Clinically Evaluable (CE) population was to comprise all patients in the ITT population who met the following specific criteria:

- Met the clinical criteria for the study infection.
- Received the correct study drug, as randomized and for an appropriate duration and intensity.
- Had the necessary clinical evaluations performed.
- Did not receive potentially confounding non-study antibiotics.

The specific criteria used for evaluability by the sponsor are included in Appendix 1.

Microbiologically evaluable population

The Microbiologically Evaluable (ME) population was to include all patients in the CE population who had an infecting Gram positive pathogen at baseline.

Comments:

The ITT population should include all patients who were randomized and who received at least one dose of study medication. Patients who were excluded from the sponsor's ITT population after randomization and receipt of one or more doses of study medication as they did not have appropriate infections were included in the FDA-defined ITT population. They were, however, excluded from the FDA CE population.

FDA-defined populations

ITT population

All enrolled patients who had a complicated skin and soft tissue infection and received at least one dose of study medication were included.

MITT population

All patients in the ITT population who had an infecting Gram positive pathogen isolated at baseline were included.

Clinically Evaluable population

In addition to the criteria used by the sponsor to define the CE population, patients meeting the following criteria were excluded from the FDA CE population:

- All patients with missing TOC visits.
- Patients who received potentially effective non-study antibiotics from day 2 till the TOC visit, irrespective of the duration of therapy. These patients were excluded as any concomitant antibiotic could potentially confound assessments.

Microbiologically Evaluable population

The ME population was to include all patients in the CE population who had an infecting Gram positive pathogen at baseline.

Differences between the sponsor-defined populations and the FDA-defined populations are presented in Appendix 2.

The following time points and visit windows were used for analysis:

Table 1: Evaluation time points and visit windows

Evaluation	Protocol-specified interval	Interval for analysis
Baseline	Day 2 to Day 1	Day 3 to Day 1
End-of-Therapy	Day 1P to Day 3P	Day 0P to Day 5P
Test-of-Cure	Day 7P to Day 12P	Day 6P to Day 20P
Post-Study	Day 21P to Day 28P	Day 21P to Day 35P

Efficacy Analyses

Primary efficacy variable

The Sponsor-Defined Clinical Outcome (SDCO) was defined as the primary efficacy variable. The outcomes were to be based primarily on the investigator's assessment of clinical response at the TOC evaluation.

The following outcomes were designed to be hierarchical and mutually exclusive.

Failure: Patients who received the i.v. study drug as assigned by randomization on >2 calendar days and met one or more of the following criteria:

- Patient was judged a "Clinical Failure" by the investigator at any time from Day 3 up to the TOC evaluation or
- Patient received a potentially effective non-study antibiotic as treatment for the primary infection for lack of efficacy at any time from Day 3 up to the TOC evaluation or
- Patient's primary site of infection was removed by surgical amputation or en bloc excision at any time from Day 3 up to the TOC evaluation or
- Patient had no evaluation by the investigator at any time from the EOT visit through the end of the TOC visit.

Clinical Success: Patients who were not in the above category and who fulfilled the following exclusion and inclusion criteria:

Exclusion criteria:

- Patient received a potentially effective non-study antibiotic on >2 calendar days in the interval from Day –3 to Day 1 inclusive, and had no infecting Gram-positive pathogen isolated at baseline or
- Patient received a potentially effective non-study drug on >2 calendar days in the interval from Day 1 to TOC evaluation inclusive, for reason other than lack of efficacy for the primary infection.

Inclusion criteria:

- Patient was judged Cure or Clinical Improvement by the investigator at the TOC evaluation and
- Patient received i.v. study drug as assigned by randomization for a duration of ≥ 4 calendar days.

Non-evaluable: Patients not in either of the above categories.

MO comments:

Patients who received > 2 days therapy and had missing TOC visit, were classified as evaluable failures by the sponsor, but were excluded from the FDA CE population. Prior to breaking the blind, the sponsor reviewed computer-derived assignments for sponsor-defined clinical outcome, pathogen-specific microbiologic response, and subject's microbiologic response. Based on sponsor's review of the data, alternate assignments were made to outcome and or evaluability assessments for some patients. In the FDA analyses, outcome assessments were based purely on the algorithm described above and hence overrides were not handled differently from that dictated by the algorithm.

Additional efficacy analyses

Subgroup Analyses

The success rates for the MITT and CE populations were to be compared for the following subgroups: gender, age (< 65 years, ≥65 years), race, presence or absence of severe infection, therapeutic surgical intervention at the primary site of infection, ancillary antibiotic treatment, and switch to oral therapy. Two-sided 95% confidence intervals around the differences in success rates were to be determined for subsets comprising >10% of the ITT population.

Stratification analyses

The 95% confidence intervals around the difference in success rates were also to be calculated adjusting for each of the following factors (one factor at a time): Diabetic ulcer stratification as assigned by the investigator, diagnostic group and study center. This analysis was to be done for the MITT and CE populations. Since the number of study centers was large (60 to 70) and the number of patients per center could be small, centers were to be defined using a pooling process. The method was to be applied prior to unblinding.

Secondary Efficacy Variables and Analyses

The following secondary efficacy analyses were to be performed, including calculation of two-sided 95% confidence intervals.

- Clinical success rates in the ITT and ME populations based on the SDCO.
- Microbiological response for the infecting Gram positive pathogen(s) isolated at the baseline evaluation was to be determined only for patients in the ME population with a SDCO of clinical success. Microbiological responses at TOC visit were documented eradication, presumed eradication, persistence, and missing data. For purposes of analysis, documented and presumed eradication were to be combined into a single outcome (microbiologic success); similarly, persistence and missing data were to be combined (microbiologic failure).
- Pathogen-specific microbiologic response rates were to be determined by treatment group for the following pathogens, provided there were >5% of patients in the ITT population with the pathogen for each treatment response group: *S. aureus*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae/equisimilis*, viridans streptococci, and *Enterococcus faecalis*.
- Pathogen-specific clinical response rates were to be calculated using the SDCO for patients in the MITT and ME subpopulations. Pathogen-specific clinical response rates were to be calculated for *S. aureus* isolates based on methicillin susceptibility as determined by the central laboratory.

- Subject's microbiological response at the TOC evaluation were to be determined as follows for patients with one or more infecting Gram positive pathogens isolated at baseline and a SDCO of success:
    - Microbiologic Success: All infecting Gram positive pathogens isolated at baseline were eradicated or presumed eradicated at the TOC evaluation and a superinfecting pathogen was not isolated up to that time.
    - Microbiological Failure: Persistence of one or more infecting Gram positive pathogens or isolation of a superinfecting pathogen prior to or at the TOC evaluation.
- The success rates using the patients' overall therapeutic response at the TOC evaluation was to be compared by treatment group as follows:
    - Therapeutic Success: Patients who were a clinical success and also a microbiologic success.
    - Therapeutic Failure: Patients were either a clinical failure or a microbiologic failure.
    - Therapeutic Non-Evaluable: Patients who had a non-evaluable clinical outcome.
- Investigator's clinical response at the TOC evaluation: As determined by the blinded investigator and recorded in the CRF. Clinical responses were specified as cure, improved, failure and unable to evaluate.
- Investigator's Post-Study clinical response: Analyzed only for patients with a successful SDCO. The Investigator's Post-Study clinical responses were cure, clinical relapse / new infection, and unable to evaluate.
- Resolution of clinical signs and symptoms at TOC evaluation: The Signs Scores at the TOC evaluation was to be compared between treatment groups using a one-way ANOVA fixed effects model with factor for treatment group. The Signs Score is based on the blinded investigator's clinical examinations. The clinical signs and symptoms included 8 standard physical signs (tenderness, erythema, edema, purulent discharge, fluctuance, induration, ulceration, necrotic tissue) to be assessed as none, mild, moderate, severe. Those assessments were scored as 0, 1, 2, 3, respectively and the sum designated as the Signs Score for that evaluation. If assessments were missing for >2 of 8 signs, the entire evaluation was to be considered missing; if assessments were missing for 1 or 2 signs, those signs were to be scored as 0.

17 pages redacted from this section of the approval package consisted of draft labeling

- Time to defervescence: For patients who were febrile at baseline [temperature of ≥37.8°C (by any method) on either day -1 or day 1], defervescence was defined as 2 consecutive calendar days after day 1 with no observed temperatures >37.2°C. Time to defervescence was defined as the number of days from day 1 to the first day of defervescence. The median time to defervescence was to be analyzed using the log-rank test in the context of a Kaplan-Meier analysis. Patients who discontinued or completed the study prior to defervescence were to be censored in the analysis.

MO Comments:

Microbiologic endpoints were defined differently in the two studies. Microbiologic response by pathogen and by subject for study 9801 were only assessed in patients with a clinical outcome of success, while for study 9901 the results were assessed irrespective of the clinical outcome. In this review, microbiologic endpoints for both studies are presented for all patients in the MITT and ME population irrespective of their clinical outcome.

Changes in the conduct of the study

The original study protocol was dated 21 December 1998. There were three amendments; amendments 1 and 3 were administrative in nature and amendment 2 related to changes in the target enrollment and statistical analysis.

Table 2: Protocol amendments

No.	Date	Country	Summary of Amendment
1	01/05/00	All	Modified contact information for reporting of serious adverse events.
2	07/26/00	All	Expanded enrollment from ~400 to ~500 patients to ensure 400 clinically evaluable patients (200 in each treatment group). The acceptable upper limit of the 95% CI for the difference in success rates between treatment groups decreased from 15% to 10%.
3	01/19/01	South Africa	Added cloxacillin as a semi-synthetic penicillin comparator agent. Prohibited the enrollment of patients previously treated with daptomycin in study DAP-SST-9901. Modified medical monitor contact information.

MO Comments:

These amendments were of a minor nature and did not significantly affect the overall outcome of the study.

APPEARS THIS WAY
ON ORIGINAL

DAP-SST-9901

The conduct and design of this study was essentially similar to study 9801. Flucloxacillin is not approved for use in the Unites States. However, it is comparable in spectrum of activity and pharmacokinetics to approved semisynthetic penicillins, like nafcillin and oxacillin and is hence an acceptable comparator. Significant differences between the two studies are summarized in the table 3.

Table 3: Differences between studies 9801 and 9901

Characteristic	9801	9901
Study sites	USA and South Africa	All non-US sites
Study period	3/15/99-08/02/01	3/17/00-12/28/00
Inclusion criteria		
CD4 counts	≥ 200 x 10^3/mm^3	≥ 500 x 10^3/mm^3 for South Africa only
Age	18-85 years	18-65 years in South Africa, 18-85 years at other sites
Additional exclusion criteria (9901) • Concomitant gangrene • Systemic antibacterial(s) known to be active in vitro against Gram positive cocci administered > than 24 hours within the 48 hours prior to the first infusion of study drug as treatment for **another** site of infection or as surgical prophylaxis, unless the skin and soft tissue infection developed during this treatment. • Treatment with i.v. vancomycin within the past 48 hours, unless given for less than 24 hours or dosed inadequately as indicated by vancomycin serum levels.		
Treatment administered (9901) • Flucloxacillin used as comparator instead of nafcillin. • Patients empirically given vancomycin could be switched to a semi-synthetic penicillin if the infecting pathogens were susceptible. • If infection was due to glycopeptide intermediate *S.aureus*, vancomycin dose could be increased to 1 gram q6h		

RESULTS

Study 9801

Disposition of patients

A total of 547 patients were randomized to study treatment, 272 were randomized to receive daptomycin and 275 were randomized to receive comparator. Seventeen randomized patients discontinued from the study prior to receiving any study treatment. Among the 530 patients who received at least one dose of study drug, 264 were randomized to the daptomycin arm and 266 to the comparator arm. One subject (0169100044) was randomized to receive comparator but was administered one dose of daptomycin in error on day 2 of a 10-day course of vancomycin. This subject is referred to as being misrandomized. Table 4 lists patient disposition and reasons for prematurely discontinuing therapy.

Table 4 (Sponsor table 10-1): Subject Disposition

Population	Daptomycin	Comparator
Randomized	272	275
Randomized but not treated	8	9
Treated population (as randomized)	264	266
Misrandomized	0	1
Safety population (as treated)	265 (100.0%)	265 (100.0%)
Completed therapy	219 (82.6%)	220 (83.0%)
Prematurely discontinued therapy	46 (17.4%)	45 (17.0%)
Adverse event	9 (3.4%)	12 (4.5%)
Elevated CPK	1 (0.4%)	0 (0.0%)
Clinical (Symptomatic) failure	15 (5.7%)	16 (6.0%)
Subject' s decision	4 (1.5%)	4 (1.5%)
Protocol violation	2 (0.8%)	0 (0.0%)
Lost to follow-up	2 (0.8%)	5 (1.9%)
Death	1 (0.4%)	0 (0.0%)
Other	13 (4.9%)	8 (3.0%)

Of the 265 patients treated with comparator drugs, 153 (57.7%) received vancomycin as study drug, 97 (36.6%) received semisynthetic penicillins (46 received cloxacillin, 39 received nafcillin, 12 received oxacillin), and 15 (5.7 %) received vancomycin in combination with nafcillin or oxacillin.

The frequency of premature discontinuations was similar in the two arms. The most common reasons for premature discontinuation in both treatment arms were clinical failures and adverse events. One subject (0131100041) in the daptomycin group discontinued study treatment due to an elevation in CPK. One additional subject (0169100002) in the daptomycin group was switched to oral antibiotics due to an elevation in CPK. In 21 patients, the reason for discontinuation was "other". Review of these patients revealed that nine had osteomyelitis, four had culture results that were

considered inappropriate for continued inclusion (e.g., only Gram-negative pathogen), three had intercurrent procedures or other infections, two had technical problems, two were clinical failures and one had resolution of infection.

Protocol Deviations

Among patients in the ITT population one or more eligibility deviations were reported for 54 (21.1%) patients in the daptomycin treatment group and 82 (31.4%) patients in the comparator group. Deviations that were reported by an investigator for two or more of the treated patients are tabulated below.

Table 5 (Sponsor table 10-2): Eligibility Deviations Reported in ≥ 2 patients (Population: ITT)

Deviation	Daptomycin N = 256	Comparator N = 261
CPK >50% above ULN; require i.m. injections; rhabdomyolysis; receiving statins	10 (3.9%)	25 (9.6%)
Previous systemic antimicrobial Rx >24h in 48h prior to first dose	7 (2.7%)	11 (4.2%)
Diagnosis of Gram positive skin infection with complicating factor	7 (2.7%)	10 (3.8%)
Age <18 or > 85 years	5 (2.0%)	11 (4.2%)
No specimen available for Gram stain/culture < 48 hr	6 (2.3%)	9 (3.4%)
Known or suspected drug abuser	6 (2.3%)	3 (1.1%)
Known or suspected osteomyelitis	3 (1.2%)	5 (1.9%)
Calculated creatinine clearance < 30 mL/min	2 (0.8%)	6 (2.3%)
Subject has bacteremia	3 (1.2%)	4 (1.5%)
Infection known to be resistant to any study drug prior to entry	1 (0.4%)	5 (1.9%)
Multiple infected ulcers at distant sites	1 (0.4%)	4 (1.5%)
Subject grossly underweight	3 (1.2%)	0 (0.0%)
Female non-child bearing age or using appropriate contraception	0 (0.0%)	3 (1.1%)
Muscle disorder; deep site infection; endocarditis; pneumonia	1 (0.4%)	1 (0.4%)
Perirectal abscess or hidradenitis suppurativa	1 (0.4%)	1 (0.4%)
Previous allergic /serious reaction to daptomycin or vancomycin	2 (0.8%)	0 (0.0%)

The most commonly reported deviation was exclusion #11 which included serum CPK >50% above ULN at baseline, requirement for intramuscular injections; conditions associated with rhabdomyolysis, or receipt of HMG coenzyme A reductase inhibitors. This deviation was reported in 3.9% and 9.6% of patients in the daptomycin and comparator groups, respectively. Among these 35 patients, 22 (63%) had CPK elevations that were considered by the investigator as related to their primary skin and skin structure infection and not related to any underlying primary muscle pathology. All other deviations were reported in <5% of patients in either treatment group.

Twelve (4.7%) patients in the daptomycin group and 13 (5.0%) in the comparator group were excluded from the CE population as they received potentially effective non-study antibiotics post-baseline for intercurrent problems other than the primary infection. Six (2.3%) patients in the daptomycin arm and seven (2.7%) in the comparator arm were excluded from the CE population as they received inadequate length of therapy. For 16 patients, 6 (2.3%) in the daptomycin group and 10 (3.8%) in the comparator group, the sole reason for exclusion from the CE population was missing TOC evaluation. For two patients, both in the daptomycin arm, the investigator indicated that study medication was discontinued due to protocol violation.

Comments:
Eligibility deviations were similar in both groups, with a slightly higher number in the comparator arm and are unlikely to have a significant impact on the overall results. Enrollment of patients with elevated CPK or those receiving HMG coenzyme A reductase inhibitors could impact safety assessments.

EFFICACY EVALUATION

Data sets analyzed

Based on the sponsor's review while blinded, 13 treated patients were found not to have complicated skin and skin structure infection and were therefore designated as rejected and were excluded from the ITT population. Twelve of these patients had osteomyelitis that was diagnosed after the enrollment evaluation and 1 had an infected foreign body that was not removed as per protocol. One patient who was misrandomized was included as randomized in all efficacy analyses and was assigned an outcome of non-evaluable.

Table 6 presents the subject populations used by the sponsor for efficacy analyses. The two treatment groups were comparable with regard to the proportion of patients included in each study population.

Table 6 (Sponsor table 11-1): Subject populations for efficacy analyses

Population	Daptomycin	Comparator
Randomized	272	275
Randomized But Not Treated	8	9
Rejected	8	5
Intent-to-Treat	256 (100.0%)	261 (100.0%)
Modified Intent-to-Treat	209 (81.6%)	212 (81.2%)
No Baseline Pathogen	47 (18.4%)	49 (18.8%)
Clinically Evaluable	223 (87.1%)	222 (85.1%)
Not Clinically Evaluable*	33 (12.9%)	39 (14.9%)
No Evaluation in the Test-of-Cure Window	19 (7.4%)	17 (6.5%)
Duration Compliance	6 (2.3%)	7 (2.7%)
Post-baseline Effective Antibiotic	12 (4.7%)	13 (5.0%)
Prior Effective Antibiotic	6 (2.3%)	9 (3.4%)
Sponsor Override	3 (1.2%)	1 (0.4%)
Misrandomized	0 (0.0%)	1 (0.4%)
Microbiologically Evaluable	187 (73.0%)	189 (72.4%)
Not Microbiologically Evaluable	69 (27.0%)	72 (27.6%)

* Patients could have more than one reason for exclusion from CE population

MO Comments:

The ITT population should include all randomized patients who receive one or more doses of study medication. For the FDA efficacy analyses, the 13 patients classified as rejected by the sponsor were included in the FDA-defined ITT population.

Demographics

The distribution of patients by country, presence or absence of diabetic ulcer and by treatment group is displayed in the following table. Of the 517 patients in the ITT population, 421 (81.4%) were enrolled in the U.S. and 96 (18.6%) were enrolled in South Africa.

Table 7: Distribution of patients by country

Country	Sites	Daptomycin			Comparator		
		Diabetic ulcer	Non-diabetic	Total	Diabetic ulcer	Non-diabetic	Total
South Africa	5	1	47	48	0	48	48
USA	63	36	172	208	42	171	213
Total	68	37	219	256	42	219	261

Source: Table 14.1.2, Section 14.1

The two treatment groups were comparable with regard to all demographic characteristics. The majority of the patients in both treatment groups were male (>53%) and Caucasian (>62%). Mean age of the patients was 55 years in both treatment groups, 34% in the daptomycin group and 31% in

the comparator group were ≥65 years old. Demographic characteristics are summarized in table 8.

Table 8 (Sponsor table 11-2): Demographic characteristics (Population: ITT)

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

Baseline Disease Characteristics

Primary Diagnosis

The distribution of diagnoses was similar in both treatment groups. Wound infection was the most common diagnosis reported. The sponsor reviewed the 71 patients designated as having "Other" infections, 37 had specific diagnoses, primarily wound infections or abscesses. All of the remaining 34 infections had complicating factors; 9 required adjunctive surgery, 11 were in patients with significant co-morbidity (e.g., diabetes), and 13 were severe infections and one was assessed as complicated by the investigator (e.g., involved deeper tissues). Table 9 summarizes the primary diagnoses reported by the investigators at study entry. The sponsor-determined final diagnosis is shown in Table 10.

Table 9 (Sponsor table 11-3): Investigator's Primary Diagnosis (Population: ITT)

Primary Diagnosis	Daptomycin N = 256	Comparator N = 261	p-value
Wound Infection	97 (37.9%)	114 (43.7%)	0.421
Major Abscess	55 (21.5%)	43 (16.5%)	
Infected Diabetic Ulcer	33 (12.9%)	38 (14.6%)	
Infected Ulcer (non-diabetic)	32 (12.5%)	34 (13.0%)	
Other Infection	39 (15.2%)	32 (12.3%)	

Table 10 (Sponsor table 11-4): Sponsor determined final diagnosis (Population: ITT)

Primary Diagnosis	Daptomycin N = 256	Comparator N = 261
Wound Infection	107 (41.8%)	130 (49.8%)
Major Abscess	60 (23.4%)	45 (17.2%)
Infected Diabetic Ulcer	33 (12.9%)	38 (14.6%)
Infected Ulcer (non-diabetic)	35 (13.7%)	35 (13.4%)
Other Infection	21 (8.2%)	13 (5.0%)

Stratification by diagnosis of infected diabetic ulcer

At the time of randomization, 37 (14.4%) patients in the daptomycin arm and 42 (16.1%) in the comparator arm were assigned to the diabetic ulcer stratum by the investigator.

The sponsor reviewed the primary diagnosis and the description of the infection for each patient and compared these data with the stratum assigned by the study site at the time of randomization. Seven patients in the daptomycin arm who were stratified as having diabetic ulcer, had a primary diagnosis other than diabetic ulcer. In addition, 3 patients with a primary diagnosis of diabetic ulcer were not assigned to that stratum. In the comparator arm, 13 patients had diagnosis other than diabetic ulcer. In addition, nine patients with a primary diagnosis of diabetic ulcer were not assigned to that stratum. Efficacy results were similar when data were analyzed using either stratum or final diagnosis.

MO Comments:

In both arms, the number of patients with infected diabetic ulcer was small. Prior drug applications for the indication of diabetic foot infections have had larger number of patients (Linezolid-241 patients, Trovafloxacin -183 patients). Additionally, several patients were classified as having diabetic foot infections by the investigator while in fact they were diabetic patients with skin and skin structure infections only at body sites other than the lower extremities. Since the number of patients with infected diabetic ulcer was insufficient to support labeling for diabetic ulcers, no additional analyses of the subpopulation of patients with diabetic ulcers were performed. These patients were however included in the overall analyses. Sponsor's and FDA analyses based on randomization strata will be presented in this review. Success rates in the FDA-defined populations based on the final diagnosis will also be presented later in the review.

Baseline pathogens

Distribution of pathogens was similar in both treatment arms. The most common pathogen was *Staphylococcus aureus*, which was isolated from 71.8% and 69.3% of patients in the daptomycin and comparator arms, respectively. *Streptococcus pyogenes* and *Streptococcus agalactiae* were isolated from ~25% of patients in both groups. Dual infection with both *S.*

aureus and β-hemolytic streptococci was present in 13.1% of patients. Table 11 presents the infecting Gram positive pathogens isolated from the primary site of infection at baseline in the MITT population.

Table 11 (Sponsor table 11-5): Infecting Gram positive pathogens (Population: MITT)

Pathogen	Daptomycin N = 209	Comparator N = 212
S. aureus	150 (71.8%)	147 (69.3%)
S. pyogenes	33 (15.8%)	35 (16.5%)
S. agalactiae	17 (8.1%)	21 (9.9%)
Viridans group Streptococcus	11 (5.3%)	16 (7.5%)
Enterococcus faecalis	25 (12.0%)	33 (15.6%)

MO Comments:
The role of viridans group streptococci as etiologic agents in skin infections is unclear, except for members of the Streptococcus intermedius (milleri) *group. This group includes* S.constellatus, S.anginosus, *and* S.intermedius. *In addition to causing deep infections like brain abscess, intrabdominal abscesses etc. these organisms have been reported to cause skin and soft tissue infections.*[2]

Signs and symptoms of infection
Signs (tenderness, erythema, edema, purulent drainage, fluctuance, induration, ulceration, and necrotic tissue) and symptoms (localized pain, swelling, drainage, redness, chills and fever) of infection were assessed at each evaluation. The two treatment groups were clinically and statistically comparable for all these baseline factors. At the baseline visit, moderate to severe tenderness, erythema, edema, and induration were present at the infection site in >60% of patients, localized pain, swelling, or redness in 88%, and moderate to severe purulent drainage in 47 % of patients in both treatment groups.

Severity of infection
Patients were characterized as having severe infection at baseline if they met one or more of the following criteria:
- had positive blood cultures at baseline
- fulfilled the published definition for Systemic Inflammatory Response Syndrome (SIRS) by having 2 or more of the following findings: temperature >38° C or < 36° C, heart rate >90 beats/minute,

[2] 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.

respiration rate >20 breaths /minute, or WBC ≥12 x 10^3 /L or < 4 x 10^3 /L or >10% bands)
- Investigator assessed at least 3 of 8 physical signs at the primary site of infection as severe

A total of 128 (50.0%) patients in the daptomycin arm and 138 (52.9%) in the comparator arm were classified as having severe infection. Over 40% of the patients in each treatment group had SIRS. Bacteremia was diagnosed at baseline in 6 patients in each treatment arm.

Baseline medical history, vital signs, and physical examination
There were no statistically significant differences between the treatment groups in the history of co-morbid illnesses, including diabetes, peripheral vascular disease, or immunosuppression. A history of diabetes was reported in 40.6% and 46.4% of patients in the daptomycin and comparator groups respectively and a history of peripheral vascular disease was reported in 26.2% and 30.3%, respectively. In both treatment groups, 3-4% of patients were reported to be immunocompromised at study entry. Proportion of patients that were reported to be chronically bedridden was similar in the two treatment arms (3.5% in the daptomycin arm and 2.3% in the comparator arm). There were no statistically significant differences between the treatment groups for any vital signs assessments at baseline.

Baseline laboratory evaluations
There were no statistically significant differences observed between the treatment arms for hematology parameters or clinical chemistry assessments at baseline. Mean CPK at baseline was 108.7 U/L (SEM 9.38) and 124.5 U/L (SEM 12.65) in the daptomycin and comparator groups, respectively ($p = 0.320$). The range of CPK values were 18-1221 U/L in the daptomycin arm, and 18-1487 U/L in the comparator arm.

Measurements of treatment compliance
Study treatment
Of the 256 patients in the ITT population treated with daptomycin, 215 (84%) received 4 mg/kg for their entire course and 41 (16%) had their regimen adjusted for renal function. In the daptomycin arm, 167 patients (63.0%) received treatment for 7 to 14 days, compared to 171 (64.5%) in the comparator arm, while 39 (14.7%) in the daptomycin arm and 43 (16.2%) in the comparator arm received treatment for >14 days. Table 12 presents a summary of duration of exposure to daptomycin and the comparator agents. Switch to oral therapy occurred in 22 patients (8.6%) in the daptomycin arm and in 32 (12.3%) in the comparator arm. The primary reason for switching to oral therapy was clinical improvement.

Table 12 (Sponsor table 12-1): Summary of duration of exposure

Duration of IV therapy	Daptomycin N = 265	Comparator N = 265
Mean ± SD	10.1 ± 5.7	10.2 ± 5.1
Median	8.0	8.0
Minimum, Maximum		
< 7 days	59 (22.3%)	51 (19.2%)
7 to 14 days	167 (63.0%)	171 (64.5%)
>14 days	39 (14.7%)	43 (16.2%)

Dosing in patients with renal insufficiency

Patients with creatinine clearance between 30-70 ml/min were to receive a modified dosing regimen for daptomycin (loading dose 4mg/kg, followed by 3mg/kg q 36 hrs). However, based on data subsequently submitted by the sponsor, it was noted that, only 25/51 (49.0%) patients with creatinine clearance between 30-70 ml/min actually received a modified regimen. These results are summarized in Table 13.

Table 13: Dose modification in renal insufficiency

Creatinine Clearance ml/min	Dose Adjusted	No Dose Adjustment	Total
30-50*	8	7	15
50-70	17	19	36
Total	25	26	51

*includes 2 patients with CrCL < 30ml/min

Concomitant antibiotic therapy and concurrent procedures

Overall, 81 patients (31.6%) in the daptomycin arm and 83 (31.8%) in the comparator arm received aztreonam and or metronidazole during the study. Nine patients (3.5%) in the daptomycin arm and 8 (3.1%) in the comparator arm were designated as failures based on treatment for lack of efficacy. Twelve (4.7%) patients in the daptomycin arm and 13 (5%) in the comparator arm were excluded from the sponsor's CE population because they were administered potentially effective antibiotics for >2 days for reasons other than lack of efficacy.

A total of 102 (39.8%) patients in the daptomycin arm and 103 (39.5%) in the comparator arm underwent a surgical procedure related to the infection site during the study. The most commonly performed procedures were incision and drainage, and wound debridement. One subject required amputation of the 4th and 5th toes due to ongoing infection.

Efficacy results

Primary Efficacy Analysis

The sponsor has presented clinical outcomes in the MITT and CE populations in the main body of the final study report. Results for the ITT and ME populations were provided in additional tables included in the study report. Sponsor's analyses of the ITT, MITT, CE, and ME populations using the sponsor defined clinical outcome (SDCO) are included in this review.

MO Comments:

In complicated skin infections such as cellulitis, isolation of a bacterial pathogen may not always be feasible. Thus, a negative microbiologic result does not necessarily exclude a bacterial etiology. Also, the role of non-bacterial pathogens in complicated skin infections is limited. Thus, empiric therapy is frequently used, based on the known microbiology of these infections. The ITT population thus provides an appropriate population for assessment of clinical response. Therefore, the ITT and CE populations were the primary populations used for assessment of clinical outcomes in the FDA analyses. FDA analyses in the MITT and ME populations will also be presented in this review.

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 sponsor's results for the ITT and CE populations, and the FDA results for the FDA-defined ITT and CE populations for SDCO are presented in the following tables:

Sponsor's Results

Table 14: Sponsor-defined clinical outcome (Population: ITT)

Clinical Response	Daptomycin N = 256	Comparator N = 261	95% CI*
Clinical success	167 (65.2%)	166 (63.6%)	-9.9, 6.6
Cure	110 (43.0%)	100 (38.3%)	
Clinical improvement	57 (22.3%)	66 (25.3%)	
Clinical failure	89 (34.8%)	95 (36.4%)	
Failure	56 (21.9%)	56 (21.5%)	
Unable to evaluate	33 (12.9%)	39 (14.9%)	

Source: Table 14.2.1.1

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

Table 15 (Sponsor table 11-7): Sponsor-defined clinical outcome (Population: CE)

Clinical Response	Daptomycin N = 223	Comparator N = 222	95% CI*
Clinical success	167 (74.9%)	166 (74.8%)	-8.2, 8.0
Cure	110 (49.3%)	100 (45.0%)	
Clinical improvement	57 (25.6%)	66 (29.7%)	
Clinical failure	56 (25.1%)	56 (25.2%)	
Failure	56 (25.1%)	56 (25.2%)	

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

FDA Results

Table 16: Sponsor-defined clinical outcome (Population: ITT)

Clinical Response	Daptomycin (N=264)	Comparator (N=266)
Clinical Success	165 (62.5%)	162 (60.9%)
Clinical Failure	99 (37.5%)	104 (39.1%)
Difference in Success Rate Daptomycin vs. Comparator:	1.6%, 95% C.I.: -7.1%, 10.3%	

Table 17: Sponsor-defined clinical outcome (Population: CE)

Clinical Response	Daptomycin (N=208)	Comparator (N=206)
Clinical Success	158 (76.0%)	158 (76.7%)
Clinical Failure	50 (24.0%)	48 (23.3%)
Difference in Success Rate Daptomycin vs. Comparator:	-0.7%, 95% C.I.: -9.4%, 7.9%	

MO Comments:

Patients rejected by the sponsor were not excluded from the FDA ITT population, hence there are 13 more patients in the FDA ITT population. Point estimates for success rates in the FDA-defined populations were slightly lower than those of the sponsor in the ITT population and slightly higher than those of the sponsor in the CE population.

Success rates were comparable in the two treatment groups using a non-inferiority margin of 10 %. The lower bound of the 95% CI around the difference in success rates was less than 10 % in the FDA analyses and the value of the upper bound of the 95 % CI did not exceed 10 % in the sponsor's analyses. Also, the 95 % CI includes the value of zero consistent with non-inferiority.

The sponsor's results in the MITT and ME populations, and the results in the FDA defined MITT and ME populations for sponsor-defined clinical outcomes are presented in the following tables:

Sponsor's Results

Table 18 (Sponsor table 11-6): Sponsor-defined clinical outcome (Population: MITT)

Clinical Response	Daptomycin N = 209	Comparator N = 212	95% CI*
Clinical success	140 (67.0%)	142 (67.0%)	-9.0, 9.0
Cure	91 (43.5%)	85 (40.1%)	
Clinical improvement	49 (23.4%)	57 (26.9%)	
Clinical failure	69 (33.0%)	70 (33.0%)	
Failure	47 (22.5%)	47 (22.2%)	
Unable to evaluate	22 (10.5%)	23 (10.8%)	

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

Table 19: Sponsor-defined clinical outcome (Population: ME)

Clinical Response	Daptomycin N = 187	Comparator N = 189	95% CI*
Clinical success	140 (74.9%)	142 (75.1%)	-8.5, 9.0
Cure	91 (48.7%)	85 (45.0%)	
Clinical improvement	49 (26.2%)	57 (30.2%)	
Clinical failure	47 (25.1%)	47 (24.9%)	

Source: Table 14.2.1.4

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

FDA Results

Table 20: Sponsor-defined clinical outcome (Population: MITT)

Clinical Response	Daptomycin (N=215)	Comparator (N=216)
Clinical Success	140 (65.1%)	140 (64.8%)
Clinical Failure	75 (34.9%)	76 (35.2%)
Difference in Success Rate Daptomycin vs. Comparator:	0.3%, 95% C.I.: -9.2%, 9.8%	

Table 21: Sponsor-defined clinical outcome (Population: ME)

Clinical Response	Daptomycin (N=174)	Comparator (N=176)
Clinical Success	133 (76.4%)	137 (77.8%)
Clinical Failure	41 (23.6%)	39 (22.2%)
Difference in Success Rate Daptomycin vs. Comparator:	-1.4%, 95% C.I.: -10.8%, 8.0%	

MO Comments:

Of the 13 patients rejected by the sponsor from the ITT population but included in the FDA analyses, 10 had Gram positive pathogens identified at baseline. Hence, there were 10 more patients in the FDA MITT population compared to the sponsor's MITT population.

Point estimates for success rates in the FDA defined MITT population were slightly lower than that seen in the sponsor's analysis. Success rates were comparable in the two treatment groups using a non-inferiority margin of 10 %. The lower bound of the 95% CI around the difference in success rates was less than 10 % in the FDA analysis and the upper bound of the 95% CI was less than 10 % in the sponsor's analysis. Also, the 95% CI included the value of zero consistent with non-inferiority.

Point estimates for success rates in the FDA-defined ME population were slightly higher than that seen in the sponsor's analysis. In the FDA-defined ME population, the lower bound of the 95% CI around the difference in success rates was marginally greater than 10 %, thus failing to establish non-inferiority using a non-inferiority margin of 10 %. A smaller sample size in the ME population may account for the wider confidence intervals and for an indication such as complicated skin infections, is a clinically acceptable difference.

Secondary analyses

In the final study report, microbiologic response rates by pathogen and by subject (ME population) and clinical response rates by pathogen (MITT population) were provided by the sponsor. However, efficacy in the ME population was only determined in patients with a SDCO of success. The following tables are adapted from tables in the integrated summary of efficacy (ISE) where the success rates were determined for all patients in the ME population irrespective of their clinical outcome. Analyses that were performed using FDA determined populations are also included in this review.

Sponsor's Results

Sponsor-Defined Clinical Outcome by infecting pathogen

Clinical success rates using the SDCO were comparable in the two treatment arms for the commonly isolated pathogens.

Table 22 (Sponsor table 11-8): SDCO by infecting pathogen (Population: MITT)

Infecting Pathogen	Daptomycin	Comparator	95% CI
Staphylococcus aureus	100/150 (66.7%)	96/147 (65.3%)	-12.1, 9.4
Streptococcus pyogenes	27/ 33 (81.8%)	25/ 35 (71.4%)	-30.3, 9.5
Streptococcus agalactiae	13/ 17 (76.5%)	14/ 21 (66.7%)	--
Viridans group Streptococcus	4/ 11 (36.4%)	13/ 16 (81.3%)	--
Enterococcus faecalis	13/ 25 (52.0%)	19/ 33 (57.6%)	-20.3, 31.4

For patients infected with *S. aureus*, the clinical success rates were also evaluated by oxacillin susceptibility of the baseline isolate in the MITT and ME populations. These analyses were restricted to isolates that were tested by the central laboratory. In the MITT population, clinical success rates in patients with oxacillin-susceptible isolates were 70.9% (73/103) for daptomycin and 68.0% (66/97) for comparator; for oxacillin-resistant isolates, the success rates were 50.0% (17/34) for the daptomycin arm and 51.4% (18/35) for the comparator.

Table 23: Sponsor defined clinical success rates by oxacillin susceptibility*

Oxacillin susceptibility	Daptomycin	Comparator
MITT	**N = 137**	**N = 132**
Susceptible	73 / 103 (70.9%)	66 / 97 (68.0%)
Resistant	17 / 34 (50.0%)	18 / 35 (51.4%)
ME	**N= 120**	**N= 118**
Susceptible	73/94 (77.7%)	66/88 (75.0%)
Resistant	17/26 (65.4%)	18/30 (60.0%)

Source: Appendix 2 and Appendix 3, ISE

* Only isolates tested at central laboratory

MO Comments:

The number of MRSA isolates was rather small in both arms. Clinical and microbiologic cure rates were similar in the two treatment arms. It is interesting to note that the clinical cure rates in the comparator arm were also low (~50%). Six patients in the comparator arm were treated with semi-synthetic penicillin and not vancomycin. Four of these patients were classified as clinical success. This raises a question about the role of MRSA isolated at baseline as a colonizer versus a true pathogen. Hospitalized patients can often have MRSA colonization on the skin. During the review of case report forms it was noted that in some patients with ulcers, swab specimens were used for culture instead of an aspirate

or tissue as specified in the protocol hence making it to difficult to differentiate surface colonization from true infection.

Microbiologic response by pathogen

Pathogen-specific microbiologic response rates for the more common infecting Gram positive pathogens is summarized in the following table for the ME population followed by microbiologic success rates in the ME population in table 25.

Table 24: Microbiologic response by pathogen (Population: ME)

Pathogen	Daptomycin n/N (%)	Comparator n/N (%)
Staphylococcus aureus (all)	85/132 (64.4)	84/130 (64.6)
Staphylococcus aureus (MSSA)	64/94 (68.1)	58/88 (65.9)
Staphylococcus aureus (MRSA)	12/26 (46.2)	15/30 (50.0)
Streptococcus pyogenes	26/32 (81.3)	22/31 (71.0)
Streptococcus agalactiae	12/16 (75.0)	12/18 (66.7)
Streptococcus dysgalactiae equisimilis	7/7 (100.0)	3/5 (60.0)
Viridans Streptococci Group	4/11 (36.4)	13/20 (65.0)
Enterococcus faecalis (all)	12/21 (57.1)	17/29 (58.6)
Enterococcus faecalis (VSE)	12/20 (60.0)	16/28 (57.1)

Source: Appendix 5, ISE
MSSA: Methicillin-susceptible *S.aureus*
MRSA: Methicillin-resistant *S.aureus*

Table 25: Microbiologic response by subject (Population: ME)

Response	Daptomycin N=187	Comparator N=189	95% CI
Microbiological Success	123 (65.8%)	123 (65.1%)	-10.3. 8.9
Microbiological Failure	64 (34.2%)	66 (34.9%)	

Source: Table 9-17, ISE

FDA Results

Results of FDA analyses are presented in the following tables. Viridans group streptococci were not considered significant pathogens and hence are not included in the following tables.

Table 26: Clinical success by pathogen (Population: MITT)

Baseline Pathogen	Daptomycin	Comparator
MSSA	73/107 (68.2%)	65/99 (65.7%)
MRSA	17/35 (48.6%)	17/36 (47.2%)
Streptococcus pyogenes	27/33 (81.8%)	25/35 (71.4%)
Streptococcus agalactiae	13/17 (76.5%)	14/23 (60.9%)
Enterococcus faecalis	13/25 (52.0%)	19/33 (57.6%)
Streptococcus dysgalactiae	7/8 (87.5%)	3/6 (50.0%)

Table 27: Microbiologic success by pathogen (Population: ME)

Baseline Pathogen	Daptomycin	Comparator
MSSA	59/87 (67.8%)	56/84 (66.7%)
MRSA	12/24 (50.0%)	13/27 (48.1%)
Streptococcus pyogenes	25/29 (86.2%)	22/29 (75.9%)
Streptococcus agalactiae	11/15 (73.3%)	12/16 (75.0%)
Enterococcus faecalis	12/21 (57.1%)	17/29 (58.6%)
Streptococcus dysgalactiae	6/6 (100.0%)	3/5 (60.0%)

Table 28: Microbiologic response by subject (Population: ME)

Microbiologic Response	Daptomycin (N=174)	Comparator (N=176)
Microbiologic Success	118 (67.8%)	121 (68.8%)
Microbiologic Failure	56 (32.2%)	55 (31.3%)
Difference in Success Rate Daptomycin vs. Comparator:	-0.9%, 95% C.I.: -11.3%, 9.4%	

MO Comments:

Microbiologic eradication rates by pathogen and by subject and clinical success rate by pathogen were essentially similar in the two treatment arms in both the FDA and sponsor's analyses. As expected with complicated skin and skin structure infections, S.aureus *and* S.pyogenes *were the two most common pathogens isolated.*

<u>Analyses by diabetic ulcer stratification</u>

At the time of randomization, patients were stratified based on the presence or absence of diabetic ulcer. Sponsor's results for the SDCO based on stratification by diabetic ulcer are summarized in table 29, followed by the FDA results in table 30.

Table 29: Sponsor-defined clinical outcome by randomization stratification (Population: MITT)

Randomization stratum	Clinical Response	Daptomycin	Comparator	95% CI
Diabetic Ulcer	No of patients	29	34	-8.9, 9.1
	Clinical Success	17 (58.6%)	23 (67.6%)	
	Cure	10 (34.5%)	7 (20.6%)	
	Clinical Improvement	7 (24.1%)	16 (47.1%)	
	Clinical Failure	12 (41.4%)	11 (32.4%)	
	Failure	10 (34.5%)	8 (23.5%)	
	Unable to Evaluate	2 (6.9%)	3 (8.8%)	
Other stratum	No of patients	180	178	
	Clinical Success	123 (68.3%)	119 (66.9%)	
	Cure	81 (45.0%)	78 (43.8%)	
	Clinical Improvement	42 (23.3%)	41 (23.0%)	
	Clinical Failure	57 (31.7%)	59 (33.1%)	
	Failure	37 (20.6%)	39 (21.9%)	
	Unable to Evaluate	20 (11.1%)	20 (11.2%)	

Source: Table 14.2.1.27

FDA results

Table 30: Clinical success rates by randomization stratification (Population: CE)

Diabetic Ulcer	Daptomycin (N=208)	Comparator (N=206)	95% C.I.	P-value
Yes	18/31 (58.1%)	21/32 (65.6%)	(-34.7%, 19.5%)	0.5559
No	140/177 (79.1%)	137/174 (78.7%)	(-8.7%, 9.5%)	

MO Comments:

Success rates in patients randomized to the diabetic ulcer stratum were lower than in those in the other stratum in both sponsor's and FDA analysis. The difference in success rates between the two strata was more marked in the daptomycin arm. Altered tissue distribution of daptomycin in patients with diabetic ulcers is a plausible explanation for this difference.

Subgroup analyses

A. Enrollment sites

Five South African sites that participated in study 9801 had previously participated in study 9901. To exclude the possibility of bias introduced by these five sites, success rates in the MITT and CE populations were recalculated by the sponsor after excluding all patients enrolled in South Africa and are shown in table 31. This analysis showed that after

excluding the South African sites, cure rates in the daptomycin arm were significantly lower than in the comparator arm. The decrease in success rates after excluding sites in South Africa was more marked in the daptomycin arm than the comparator arm.

Table 31 (Sponsor table 8-3): Success Rates excluding South African sites (Population: MITT and CE)

Population	Daptomycin n/N (%)	Comparator n/N (%)	95% CI*
MITT	100/168 (59.5%)	111/172 (64.5%)	-5.3, 15.3
CE	121/177 (68.4%)	128/180 (71.1%)	-6.8, 12.3

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

Table 32: FDA Analysis comparing South African and US sites (Population: ITT)

Country	Daptomycin (N=264)	Comparator (N=266)	95% C.I.	P-value
South Africa	46/49 (93.9%)	38/48 (79.2%)	-0.7%, 30.1%	0.0339
USA	119/215 (55.4%)	124/218 (56.9%)	-11.3%, 8.3%	

MO comments:

In both the sponsor's and FDA analyses, success rates in South African sites were much higher than that in United States, especially in the daptomycin arm. This is probably a reflection of the differences in the patient characteristics enrolled in the two countries, but it is unclear why the effect is more pronounced in the daptomycin arm. Patients enrolled in South Africa tended to be younger, less sick and had less co-morbid conditions, similar to the nature of patients enrolled in study 9901.

B. Demographic and baseline characteristics

Clinical success rates by treatment group for the MITT population subdivided by gender, age and race and by baseline disease characteristics are presented in tables 33 and 34 respectively. Success rate for daptomycin was greater than comparator for subgroups defined by age <65 years, black race, or absence of surgical intervention and less than comparator for subgroups defined by age ≥65 years, presence of adjunct surgical treatment, or bacteremia at baseline. Cure rates in patients ≥65 years and older was significantly lower in the daptomycin arm compared to the comparator arm (52.8% versus 74.2%, 95% CI 5.6, 37.3). Results of the FDA analyses by demographic characteristics are presented in table 35.

Table 33 (Sponsor table 11-15): SDCO by demographic characteristics (Population: MITT)

Demographic Subgroup	Daptomycin N = 209	Comparator N = 212	95% CI
Age			
< 65 years	102/137 (74.5%)	96/150 (64.0%)	21.1, 0.1
≥ 65 years	38/.72 (52.8%)	46/ 62 (74.2%)	5.6, 37.3
Gender			
Male	77/119 (64.7%)	75/120 (62.5%)	-14.4, 10.0
Female	63/ 90 (70.0%)	67/ 92 (72.8%)	-10.3, 16.0
Race			
Caucasian	85/138 (61.6%)	83/128 (64.8%)	-8.3, 14.8
Black	34/ 38 (89.5%)	40/ 52 (76.9%)	-27.6, 2.5
Other	21/ 33 (63.6%)	19/ 32 (59.4%)	-27.9, 19.4

Table 34 (Sponsor table 11-16): SDCO by baseline disease (Population: MITT)

Baseline Characteristic	Daptomycin N = 209	Comparator N = 212	95% CI
Severity of Infection			
Severe	70/107 (65.4%)	68/111 (61.3%)	-16.9, 8.6
Not Severe	70/102 (68.6%)	74/101 (73.3%)	-7.8, 17.1
SIRS			
Yes	58/89 (65.2%)	60/97 (61.9%)	-17.1, 10.5
No	82/120 (68.3%)	82/115 (71.3%)	-8.8, 14.7
Surgical Intervention			
Yes	25/44 (56.8%)	34/47 (72.3%)	-3.9, 35.0
No	115/165 (69.7%)	108/165 (65.5%)	-14.3, 5.8
Bacteremic Status			
Yes	1/4 (25.0%)	4/6 (66.7%)	–
No	139/205 (67.8%)	138/206 (67.0%)	-9.9, 8.2

Table 35: FDA efficacy analyses by demographic characteristics (Population: ITT)

Subgroup	Daptomycin (N=264)	Comparator (N=266)	95% C.I.
Age			
< 65 years	119/173 (68.8%)	112/183 (61.2%)	(-2.9%, 18.0%)
≥ 65 years	46/91 (50.5%)	50/83 (60.2%)	(-25.6%, 6.2%)
Gender			
Male	86/143 (60.1%)	87/148 (58.8%)	(-10.6%, 13.3%)
Female	79/121 (65.3%)	75/118 (63.6%)	(-11.2%, 14.7%)
Race			
White	101/177 (57.1%)	93/167 (55.7%)	(-9.7%, 12.4%)
Black	42/50 (84.0%)	47/60 (78.3%)	(-10.7%, 22.1%)
Other	22/37 (59.5%)	22/39 (56.4%)	(-21.8%, 27.9%)

MO Comments:

In the FDA-defined ITT population, success rates in patients ≥ 65 years of age were lower than in patients < 65 years of age in the daptomycin arm. Success rates were comparable in the two age group categories in the comparator arm. In the sponsor's analysis in the MITT population, success rates in patients ≥ 65 years of age were lower in both arms, however the difference was more pronounced in the daptomycin arm. Altered tissue distribution due to reduction in vascular perfusion with increasing age or the higher likelihood of co-morbid conditions in older patients may account for some reduction in success rates. However, it is unclear why the difference is more marked in the daptomycin arm.

Very few patients with bacteremia were included in the study, as documented bacteremia prior to enrollment was an exclusion criterion. The efficacy of daptomycin is thus unknown in patients with complicated skin and skin structure infections with concurrent bacteremia and this should be reflected in the product label. Only patients with surgical intervention at baseline are represented in this table. A larger number of patients had adjunctive procedures during the study and results of an analysis based on concomitant surgical procedures are presented later (table 38).

C. Primary Diagnosis

Table 36: FDA efficacy analysis by primary diagnosis (ITT)

Primary Diagnosis	Daptomycin (N=264)	Comparator (N=266)	95% C.I.	P-Value
Wound Infection	66/99 (66.7%)	74/116 (63.8%)	(-10.8%, 16.6%)	0.5962
Major Abscess	43/55 (78.2%)	29/43 (67.4%)	(-9.1%, 30.6%)	
Infected diabetic ulcer	20/38 (52.6%)	21/41 (51.2%)	(-23.2%, 26.0%)	
Infected Ulcer (non-diabetic)	15/33 (45.5%)	20/34 (58.8%)	(-40.1%, 13.3%)	
Other Infection	21/39 (53.8%)	18/32 (56.3%)	(-28.5%, 23.7%)	

D. Renal insufficiency

In study 9801, in both arms, success rates were lower in patients with creatinine clearance between 30-70 ml/minute compared to those with creatinine clearance > 70 ml/minute. However the difference was more pronounced in the daptomycin arm. Sponsor's results stratifying patients based on creatinine clearance (30-70ml/min versus > 70 ml/min) are presented in the table 37.

Table 37: SDCO in patients based on creatinine clearance (Population: ITT)

Clinical Response	Daptomycin	Comparator	95% CI
Clearance 30-70ml/min	**N=46**	**N=52**	-10.2, 28.9
Clinical Success	24 (52.2%)	32 (61.5%)	
Clinical Failure	22 (47.8%)	20 (38.5%)	
Clearance >70ml/min	**N=197**	**N=193**	-21.5, 16.0
Clinical Success	133 (67.5%)	125 (64.8%)	
Clinical Failure	64 (32.5%)	68 (35.2%)	

Source: TableA3 and A4, sponsor's submission 8/8/03

E. History of diabetes

Table 38: FDA efficacy analysis by history of diabetes (Population: ITT)

History of Diabetes	Daptomycin (N=264)	Comparator (N=266)	95% C.I.	P-Value
Yes	69/110 (62.7%)	67/126 (53.2%)	(-3.9%, 23.0%)	0.0784
No	96/154 (62.3%)	95/140 (67.9%)	(-17.1%, 6.0%)	