CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-572

Statistical Review(s)

STATISTICAL REVIEW AND EVALUATION: 45 DAY MEETING REVIEW
(COMPLETED REVIEW FOR INTERNAL DISTRIBUTION ONLY)

NDA:	21-572
NAME OF DRUG:	CIDECIN® (Daptomycin for Injection)
APPLICANT:	Cubist Pharmaceuticals Inc.
SUBMISSION DATE:	December 19, 2002
INDICATION(S):	Complicated Skin and Skin Structure Infections (CSSSI)
NUMBER AND TYPE OF CLINICAL:	Two completed phase III studies
STATISTICAL REVIEWER:	Joel Jiang, Ph.D.
CLINICAL REVIEWER:	Susan Thompson, M.D.
PROJECT MANAGER:	LTJG Raquel Peat, M.S., M.P.H, HFD-520
45 DAY MEETING DATE:	February 13, 2003
USER FEE DATE:	June 20, 2003

I. ORGANIZATION AND DATA PRESENTATION		YES	NO	N/A
A.	Is there a comprehensive table of contents with adequate indexing and pagination?	✔		
B.	Are the original protocols, protocol amendments and proposed label provided?	✔		
C.	Adverse event listings by center and time of occurrence relative to enrollment date.	✔		
1.	Are adverse events from cited sources (foreign and domestic) provided?	✔		
D.	Is a CANDAR or an electronic submission of the data necessary?	✔		

		YES	NO	N/A
E.	If the data have been submitted electronically, has adequate documentation of the data sets been provided?		✔	
		—	—	—

Reviewer's comment: Format files are not found in sponsor's SAS data set package, which may have difficulty to reference formats or identify codes of variables in using SAS.

F.	Are inclusion/exclusion (evaluability) criteria adequately coded and described:	✔		
		—	—	—
G.	Are there discrepancies between CRF information and CANDAR/Jacket data?			✔
		—	—	—
H.	If the data have been submitted electronically, can laboratory data be easily merged across studies and indications?			✔
		—	—	—
I.	If not, can you estimate the time required to correct problems?			✔
		—	—	—

II. STATISTICAL METHODOLOGY

A.	Are all primary efficacy studies of appropriate design to meet basic approvability requirements, within current Divisional policy statements or to the extent agreed upon previously with the sponsor by the Division?	✔		
		—	—	—
B.	For each study, is there a comprehensive statistical summary of the efficacy analyses which covers the intent-to-treat population, evaluable subject population and other applicable sub populations (age, gender, race/ethnicity, etc.)?	✔		
		—	—	—
	If subset analyses were not done, was an acceptable explanation of why given?			✔
		—	—	—

		YES	NO	N/A
C.	Based on the summary analyses of each study, do you believe:			
1.	The analyses are appropriate for the type data collected, the study design, and the study objectives (based on protocol and proposed label claims)?	✔		
2.	If there are multiple endpoints, has this been adequately addressed?			✔
3.	Intent-to-treat (ITT and MITT) analyses are properly performed?	✔		
4.	Sufficient and appropriate references were included for novel statistical approaches?			✔
D.	If interim analyses were performed, were they planned in the protocol and were appropriate significance level adjustments made?			✔
E.	Are there studies which are incomplete or ongoing?		✔	
F.	Is there a comprehensive, adequate analysis of safety data as recommended in the Clinical/Statistical Guideline?	✔		
1.	Is there anything significant yet regarding safety or AE evaluations?		✔	

III. FILEABILITY CONCLUSIONS

From a statistical perspective is this submission, or indications therein, reviewable with only minor further input from the sponsor?

This submission is fileable. However the sponsor needs to clarify some issues in electronic submitted data files.

APPENDIX

Table of the Studies:

Protocol	Daptomycin Regimen	Daptomycin N	Comparator Regimen	Comparator N	Type of Study
COMPLICATED SKIN AND SKIN STRUCTURE INFECTIONS (cSSSI)					
CSR-DAP-9801 3/15/99 – 8/2/01	Daptomycin: 4 mg/kg administered I.V. q.d. for 7 to 14 days	272# 265^ 256♣ 209♦ 223♥ 187▲	Vancomycin: 1 g administered I.V. BIDx7 to 14 days Or selected semi-synthetic penicillins: Nafcillin 4 to 12 g I.V. q.d. in equally divided doses for 7 to 14 days Cloxacillin 4 to 12 g I.V. q.d. in equally divided doses for 7 to 14 days Oxacillin 4 to 12 g I.V. q.d. in equally divided doses for 7 to 14 days.	275# 265^ 261♣ 212♦ 222♥ 189▲	Phase III, active-controlled, randomized (1:1 ratio), investigator-blinded, Multicenter (69)
Duration of treatment: Maximum study duration from Pre-therapy to Post-Study was to be 44 days. Study drug was to be administered for 7 to 14 days, followed by TOC and Post-Study visits conducted 7 to 12 and 21 to 28 days, respectively, after the last dose of study drug. Therapy could be extended beyond 14 days with the approval of the Medical Monitor.					
Primary efficacy: The primary outcome variable was the Sponsor-Defined Clinical Outcome, which was based on the Investigator's evaluation of Clinical Response at the TOC visit, with adjustment for specific events (e.g., removal surgery) and evaluability criteria.					
Objective: The primary objectives of this study were to compare the safety and to demonstrate the equivalent efficacy of I.V. Daptomycin to that of I.V. Vancomycin or selected I.V. semi-synthetic penicillins in the treatment of cSSSI due to Gram-positive bacteria.					
CSR-DAP-9901 3/17/00 – 12/28/00	Daptomycin: 4 mg/kg administered I.V. q.d. for 7 to 14 days	276# 269^ 270♣ 213♦ 245♥ 196▲	Vancomycin: 1 g administered I.V. BIDx7 to 14 days Or selected semi-synthetic penicillins: Oxacillin 4 to 12 g I.V. q.d. in equally divided doses for 7 to 14 days Cloxacillin 4 to 12 g I.V. q.d. in equally divided doses for 7 to 14 days Flucloxacillin 4 to 12 g I.V. q.d. in equally divided doses for 7 to 14 days.	295# 293^ 292♣ 255♦ 262♥ 231▲	Phase III, active-controlled, randomized (1:1 ratio), investigator-blinded, Multicenter (67)
Duration of treatment: see Study CSR-DAP-9801.					
Primary efficacy: see Study CSR-DAP-9801.					
Objective: see Study CSR-DAP-9801.					
# Number of all enrolled and randomized; ^ Number of safety (as treated); ♣ Number of ITT; ♦ Number of MITT; ♥ Number of clinically evaluable; ▲ Number of microbiologically evaluable					

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/s/

Joel Jiang
2/20/03 09:52:06 AM
BIOMETRICS

Daphne Lin
2/20/03 10:00:07 AM
BIOMETRICS

Sept. 12, 2003

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCE
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	21-572
Drug Name:	Cubicin™ (Daptomycin for Injection)
Indication:	Complicated Skin and Skin Structure Infections (cSSSI)
Sponsor:	Cubist Pharmaceuticals, Inc.
Dates:	Submission Date: 12/19/2002; Received Date: 12/20/2002; PDUFA Date: 9/20/2003; Review Completion Date: 9/12/2003
Review Status:	Priority Review
Biometrics Division:	Division of Biometrics III (HFD-725)
Statistical Reviewer:	Joel Jiang, Ph.D.
Concurring Reviewers:	Daphne Lin, Ph.D., Statistical Team Leader
	Mohammad Huque, Ph.D., Statistical Division Director
Medical Division:	Division of Anti-infective Drug Division (HFD-520)
Clinical Team:	Medical Officer: Sumathi Nambiar, M.D.
	Medical Officer: Susan Thompson, M.D.
	Medical team leader: David Ross, M.D.
	Medical Division Director: Janice Soreth, M.D.
Project manager:	LTJG Raquel Peat, M.S., M.P.H., HFD-520
Keywords:	NDA review, clinical studies, efficacy evaluation, statistical analysis

TABLE OF CONTENTS

Reviewer's Note: Throughout the review, the following terms are abbreviated and referred to as:
AE = adverse event; BID = twice daily; CE = clinically evaluable; Comparator = Vancomycin or semi-synthetic Penicillins; Daptomycin = Cubicin™ (Daptomycin for Injection) (ciprofloxacin 0.3% and dexamethasone 0.1% otic suspension); cSSSI = complicated skin and skin structure infections; EOT = end of treatment; ITT = intent-to-treat; I.V. = intravenous; ME = microbiologically evaluable; MITT = modified intent-to-treat; MO = Medical Officer, QD = once daily; TOC = test of cure; SOC = system organ class.
Confidence intervals for differences in outcome rates (Daptomycin minus control) are reported as $_{n1,n2}(l, u)_{p1,p2}$, *where* n_1 *is the number of Daptomycin subjects,* n_2 *is the number of control subjects, l and u are the lower and upper bounds of the 95% confidence interval, respectively,* p_1 *is the response rate in Daptomycin subjects, and* p_2 *is the response rate in control subjects.*

1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

This NDA submission supported by two pivotal studies was to evaluate the efficacy and safety of Daptomycin in the treatment of cSSSI.

Both studies 9801 and 9901 showed therapeutic non-inferiority to the approved comparator. These studies support approval of Daptomycin (4 mg/kg I.V. QD x 7 to 14 days) for the cSSSI indication.

In addition, both pivotal studies demonstrated that Daptomycin and its comparator provided substantially comparable safety profiles.

Based on the above findings, it is the opinion of this reviewer to conclude that the accessible data from two pivotal studies of this submission supported the use of Daptomycin with proposed treatment regimen in the treatment of cSSSI and the trial provided sufficient evidence to confirm that Daptomycin as an effective and safe medicine in this indication.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

The sponsor submitted this NDA in order to obtain approval to market its Daptomycin (4 mg/kg I.V. QD x 7 to 14 days) for thetreatment of cSSSI. Daptomycin is a novel cyclic lipopeptide antibiotic being developed for treatment of serious and life-threatening Gram-positive infections, and it is claimed to be rapidly bactericidal in vitro against most clinically significant Gram-positive pathogens, including drug-resistant strains such as Methicillin-resistant staphylococci. Daptomycin is said to be effective against clinical isolates in several different animal models of infection and the data from Phase II clinical trials also suggested that Daptomycin might be effective in treating such infection. This Phase III clinical trial was designed to compare the safety and efficacy of Daptomycin with that of current conventional therapy in the treatment of cSSSI.

The two studies were multicenter, investigator-blinded, randomized, comparative, Phase III trials to compare I.V. Daptomycin (4 mg/kg I.V. QD) with either I.V. Vancomycin (1 g I.V. BID) or selected I.V. semi-synthetic Penicillin in the treatment of cSSSI known or suspected to be due to Gram-positive bacteria. Study 9801 was conducted primarily in the United States and South Africa, and Study 9901 was conducted in non-US sites only. Both studies were similar in design, but differed in subject characteristics including history of diabetes and peripheral vascular disease.

Adult subjects with a diagnosis of cSSSI who met all of the inclusion criteria and none of the exclusion criteria could be enrolled in the study. Baseline evaluations were performed within 48 hours prior to the first dose of study medication. Eligible subjects who gave informed consent were randomized on a 1:1 basis to receive either Daptomycin or comparator (Vancomycin or semi-synthetic Penicillins). During the treatment phase, subjects were monitored daily for treatment-emergent adverse events and concurrent medications. At Day 3 or 4 of treatment the blinded investigator conducted an on-therapy evaluation. Duration of therapy for both regimens was 7 to 14 days as clinically indicated. It was anticipated that most subjects would receive I.V. study therapy for the duration of their treatment. However, subjects could be switched to oral therapy if certain conditions were met and the medical monitor had given permission. Post-treatment visits included an EOT visit conducted up to 3 days after the last dose of study drug (or at early termination); a TOC visit conducted 7 to 20 days post-treatment; and a Post-Study visit conducted 21 to 28 days post-treatment. For subjects who received both I.V. study medication and oral therapy administered per protocol, the last day of oral therapy was defined as the end of treatment. The EOT and TOC visits were performed for all subjects. The Post-Study visit was performed only for those subjects who were considered cured or improved by the blinded investigator at the TOC visit.

The primary objectives were to compare the safety and to demonstrate equivalent efficacy of Daptomycin to that of Vancomycin or selected semi-synthetic Penicillin in the treatment of cSSSI.

Efficacy was assessed for clinical response based on evaluations of the clinical signs and symptoms of the infection at baseline, during treatment, and in the post-treatment period; and for microbiologic response by cultures conducted concurrently. Efficacy analyses were conducted on 4 subject populations defined as ITT, MITT, CE, and ME.

Safety was assessed by monitoring for treatment-emergent adverse events and use of concomitant medications, and by assessing changes from baseline in vital signs and clinical laboratory test results. All subjects who received at least one dose of study medication were included in the safety population.

1.3 STATISTICAL ISSUES AND FINDINGS

The comparisons of statistical interest in this study were conducted between Daptomycin and its comparator. The reviewer employed the following methodologies in primary statistical analyses of efficacy and safety for two pivotal studies.

The variable in statistical evaluation of efficacy was the success rate of clinical or microbiologic outcomes.

A two-sided 95% confidence interval was constructed for the difference in proportions of clinical or microbiologic outcomes between Daptomycin's group and its comparator's group. The confidence intervals were computed using a normal approximation to the binomial, and included a continuity correction. The evaluation of whether non-inferior in efficacy was declared was judged based upon the lower confidence limit for the difference in proportion (Daptomycin – its comparator) and the delta value. With respect to this indication, the delta value 0.1 is considered a clinically acceptable non-inferiority margin. The assessment of clinical response was primarily performed on CE and ITT populations, and microbiologic response on ME and MITT populations. Subgroup analyses by demographic, baseline, prognostic and geographic characteristics were also performed for primary efficacy variables. Homogeneity of treatment effect was evaluated by Breslow-Day's test.

Safety evaluation was primarily conducted on the following variables: the rates as per at least one AE, treatment related AEs, severe AEs, serious AEs, died, discontinuation due to AE, discontinuation due to treatment related AEs. Fisher's exact test was employed to compare the safety variables between the two treatment groups.

Prior to performing efficacy analyses, this reviewer assessed the comparability of the treatment groups with respect to pretreatment characteristics of randomized subjects. Quantitative variables were assessed using the t-test, and qualitative variables were assessed using chi-square test.

All tests were two-sided and used a 5% level of significance. A 15% level of significance was applied to the test of homogeneity.

Study 9801

For CE population, a total of 158/208 (76.0%) Daptomycin subjects were considered clinical success, while 158/206 (76.7%) comparator subjects were considered clinical success. The efficacy results demonstrated therapeutic non-inferiority of Daptomycin to its comparator (-0.7%, 95%CI: -9.4%, 7.9%).

For ITT population, a total of 165/264 (62.5%) Daptomycin subjects were considered clinical success, while 162/266 (60.9%) comparator subjects were considered clinical success. The efficacy results demonstrated therapeutic non-inferiority of Daptomycin to its comparator (1.6%, 95% CI: -7.1%, 10.3%).

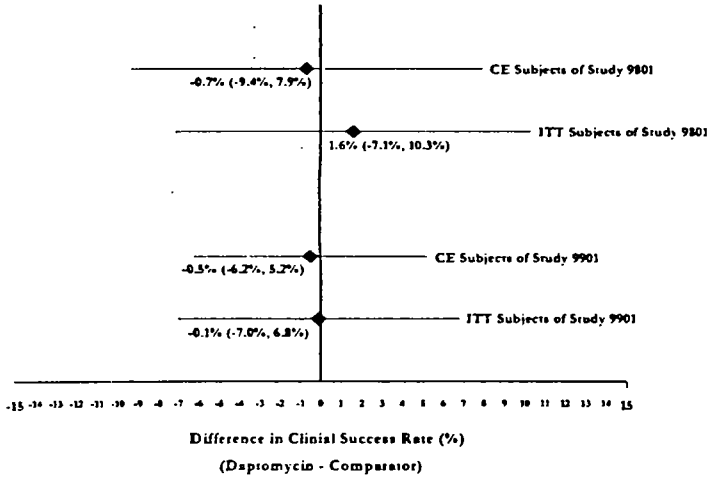
Study 9901

For CE population, a total of 214/238 (89.9%) Daptomycin subjects were considered clinical success, while 226/250 (90.4%) comparator subjects were considered clinical success. The efficacy results demonstrated therapeutic non-inferiority of Daptomycin to its comparator (-0.5%, 95%CI: -6.2%, 5.2%).

For ITT population, a total of 217/270 (80.4%) Daptomycin subjects were considered clinical success, while 235/292 (80.5%) comparator subjects were considered clinical success.

The efficacy results demonstrated therapeutic non-inferiority of Daptomycin to its comparator (-0.1%, 95% CI: -7.0%, 6.8%).

It is noteworthy that Study 9901 (international study without site in the United States) had always better efficacy outcomes than Study 9801 (79.2% in CE subjects and 81.7% in ITT subjects from the Unites States sites). Divergence in the pretreatment status and baseline characteristics of enrolled subjects could cause the differences in efficacy outcome between the two studies.



2 INTRODUCTION

2.1 OVERVIEW

The sponsor submits this NDA in order to obtain approval to market Daptomycin for the treatment of cSSSI. Two pivotal phase III controlled studies were completed and presented as evidence to support that Daptomycin was safe and efficacious for the indication when compared with its comparator. Statistical review focuses on these comparative clinical trials which formed the basis of this application.

Study 9801

Primary Objectives

The primary objective of this study was to compare the safety and to demonstrate the equivalent efficacy of I.V. Daptomycin to that of I.V. Vancomycin or selected I.V. semi-synthetic Penicillin in the treatment of cSSSI due to Gram-positive bacteria.

Study Design

This was a multicenter, multinational, investigator-blinded study of cSSSI known or suspected to be due to Gram-positive bacteria. Subjects were randomized on a 1:1 basis to receive Daptomycin 4 mg/kg QD or a comparator agent (Vancomycin, Nafcillin, Cloxacillin or Oxacillin). Baseline evaluations were performed within 48 hours prior to treatment start. An On-Therapy evaluation of pertinent clinical signs and symptoms of infection was conducted on Study Day 3 or 4. Post treatment visits included an EOT visit conducted up to 3 days after the last dose of study drug (whether per protocol or due to early termination); a TOC visit conducted 7 to 20 days post treatment; and a Post-Study visit conducted 21 to 28 days post treatment. Subjects previously assessed as clinical failure were not required to attend the Post-Study visit.

The study was conducted at 69 study sites in the United States (64 sites) and South Africa (5 sites). It was initiated on March 15, 1999 and completed on August 2, 2001.

Five hundred subjects were enrolled into this study to ensure 400 subjects (200 in each treatment group) were clinically evaluable. Subjects were stratified by presence or absence of a diagnosis of infected diabetic ulcer. A total of 547 subjects were randomized into the study and 530 received at least one dose of study medication.

Study 9901

Primary Objectives

The primary objectives of this study were to compare the safety and to demonstrate the equivalent efficacy of I.V. Daptomycin to that of I.V. Vancomycin or selected I.V. semi-synthetic Penicillin in the treatment of cSSSI due to Gram-positive bacteria.

Study Design

This was a multicenter, international, investigator-blinded study of cSSSI known or suspected to be due to Gram-positive bacteria. Subjects were randomized on a 1:1 basis to receive Daptomycin 4 mg/kg QD or a comparator agent (Vancomycin or semi-synthetic Penicillin). Baseline evaluations were performed within 48 hours prior to treatment start. An On-Therapy evaluation of pertinent clinical signs and symptoms of infection was conducted on Study Day 3 or 4. Post treatment visits included an EOT visit conducted up to 3 days after the last dose of study drug (or at early termination); a TOC visit conducted 7 to 20 days post treatment; and a Post-Study visit conducted 21 to 28 days post treatment. Subjects previously assessed as clinical failure were not required to attend the Post-Study visit.

The study was conducted at 67 study sites in Europe (42 sites), South Africa (20 sites), and Australia (5 sites). It was initiated on March 17, 2000 and completed on December 28, 2000.

Five hundred subjects were enrolled into this study to ensure 400 subjects (200 in each treatment group) were clinically evaluable. Subjects were stratified by presence or absence of a diagnosis of infected diabetic ulcer. A total of 571 subjects were randomized into the study and 562 received at least one dose of study medication.

2.2 DATA SOURCES

This submission contains data from two pivotal studies performed by the sponsor, 9801 and 9901, to support the cSSSI indication. All data files are maintained at specific network path location.

The submitted datasets for Studies 9801 and 9901 can be found respectively under:
\\Cdsesub1\N21572\N_000\2002-12-19\crt\datasets\dapsst9801,
\\Cdsesub1\N21572\N_000\2002-12-19\crt\datasets\dapsst9901

All the resubmitted datasets due to correction, revision, and modification are listed under:
\\Cdsesub1\N21572\

The two pivotal studies are described in Table 1.

TABLE 1. LISTING OF CLINICAL TRIALS			
Study	Population	Test Drugs	Enrollment
9801	Men and women 18 to 85 years of age, inclusive, who required hospitalization for clinical signs and symptoms of cSSSI were specific candidates for the study.	Daptomycin: 4 mg/kg I.V. QD x 7 to 14 days Vancomycin: 1 g I.V. BID x 7 to 14 days Or selected semi-synthetic penicillins: Nafcillin 4 to 12 g I.V. QD in equally divided doses x 7 to 14 days Cloxacillin 4 to 12 g I.V. QD in equally divided doses x 7 to 14 days Oxacillin 4 to 12 g I.V. QD in equally divided doses x 7 to 14 days.	272 Daptomycin 275 Comparator
9901	Men and women 18 to 85 years of age, inclusive, with clinical signs and symptoms of cSSSI were specific candidates for the study.	Daptomycin: 4 mg/kg I.V. QD x 7 to 14 days Vancomycin: 1 g I.V. BID x 7 to 14 days Or selected semi-synthetic penicillins: Nafcillin 4 to 12 g I.V. QD in equally divided doses x 7 to 14 days Cloxacillin 4 to 12 g I.V. QD in equally divided doses x 7 to 14 days Oxacillin 4 to 12 g I.V. QD in equally divided doses x 7 to 14 days.	277 Daptomycin 294 Comparator

A review by random sample method of at least 10% of the CRF stratified by treatment group was conducted to validate the sponsor's efficacy data and to check for agreement with investigators' evaluability and outcome assessments. The MO did not concur with some efficacy outcomes assessed by the sponsor, and also disagreed with some aspects of evaluability evaluated by the sponsor. Please refer to MO's review for detailed descriptions.

3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

Study 9801

The statistical objective of this study was to demonstrate the non-inferiority of Daptomycin to its comparator in clinical response at TOC.

Efficacy analyses were performed on four subject populations as ITT, MITT , CE, and ME. Subjects were analyzed for efficacy according to randomization, regardless of treatment administered. Subjects who were randomized but never received any study drug were excluded from all efficacy analyses.

The clinical outcome was defined as the basis for the primary efficacy variable. The outcomes success (cure, clinical improvement), failure, and non-evaluable were based primarily on the investigator's assessment of clinical response at the TOC evaluation. . The MO redefined these populations and reclassified efficacy outcomes after checking for agreement with investigators' evaluability and outcome assessments according to the protocol. The primary outcome measures under analysis were the clinical success rates at TOC for the CE and ITT populations.

The number and the proportion of subjects included in each evaluation group are presented in Table 2. A total of 547 subjects were randomized to study treatment; 272 received Daptomycin and 275 received comparator as designated by the investigator prior to randomization. Seventeen of the 547 randomized subjects discontinued from the study prior to receiving any study treatment due to "Other Infection Stratum" or "Diabetic Ulcer Stratum". Among the 530 subjects who received at least one dose of study drug, 264 to the Daptomycin arm and 266 to the comparator arm. One subject was randomized to receive comparator; but was administered one dose of Daptomycin in error. This subject was referred to as misrandomized. In all efficacy analyses, data for this subject were tabulated as randomized; in all safety analyses, data for this subject were tabulated as treated. Thirteen treated subjects, who were found not to have cSSSI and were designated as "rejected" and excluded from the efficacy analyses by the sponsor, were included by the MO in the ITT analysis. MO's CE population included approximately 78% of subjects in both treatment groups. The most common reason for exclusion was "CPK > 50% above ULN; require i.m. injections; rhabdomyolysis; receiving statins".

TABLE 2: STUDY 9801: NUMBER OF SUBJECTS INCLUDED IN EACH EVALUATION GROUP		
Evaluation Group	Number of Subjects	
	Daptomycin	Comparator
All Randomized Subjects	272	275
Safety (as treated)	265	265
MO's ITT Subjects	264 (100%)	266 (100%)
Sponsor's ITT Subjects	256 (97.0%)	261 (98.1%)
MO's MITT Subjects	215 (81.4%)	216 (81.2%)
Sponsor's MITT Subjects	209 (79.2%)	212 (79.7%)
MO'sCE Subjects	208 (78.8%)	206 (77.4%)
Sponsor's CE Subjects	223 (84.5%)	222 (83.5%)
MO's ME Subjects	174 (65.9%)	176 (66.2%)
Sponsor's ME Subjects	187 (70.8%)	189 (71.1%)

Data for baseline demographics and disease characteristics are described for MO's ITT subjects in Tables 3 and 4. The two treatment groups were comparable and no statistically significant differences were detected with regard to these characteristics.

TABLE 3: STUDY 9801: BASELINE DEMOGRAPHICS IN ITT SUBJECTS BY MO			
Variables	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
* By t test. All others in the table, by chi-square test.			

TABLE 4: STUDY 9801: BASELINE DISEASE CHARACTERISTICS IN ITT SUBJECTS BY MO			
Parameters	Daptomycin (N=264)	Comparator (N=266)	*P-value
Wound Infection	99 (37.5%)	116 (43.6%)	0.4591
Major Abscess	55 (20.8%)	43 (16.2%)	
Infected Diabetic Ulcer	38 (14.4%)	41 (15.4%)	
Infected Ulcer (non-diabetic)	33 (12.5%)	34 (12.8%)	
Other Infection	39 (14.8%)	32 (12.0%)	
* By chi-square test.			

The primary analyses are presented in Tables 5, 6, 7, and 8 for the clinical responses of CE and ITT subjects as per MO's and sponsor's at the TOC visit, respectively. The confidence interval results demonstrated Daptomycin was non-inferior to its comparator with respect to clinical success rates at TOC.

TABLE 5: STUDY 9801: CLINICAL RESPONSES OF CE SUBJECTS AT TOC VISIT BY MO		
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%	

TABLE 6: STUDY 9801: CLINICAL RESPONSES OF CE SUBJECTS AT TOC VISIT BY SPONSOR		
Clinical Response	Daptomycin (N=223)	Comparator (N=222)
Clinical Success	167 (74.9%)	166 (74.8%)
Clinical Failure	56 (25.1%)	56 (25.2%)
Difference in Success Rate Daptomycin vs. Comparator:	0.1%, 95% C.I.: -8.4%, 8.6%	

TABLE 7: STUDY 9801: CLINICAL RESPONSES OF ITT SUBJECTS AT TOC VISIT BY MO		
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 8: STUDY 9801: CLINICAL RESPONSES OF ITT SUBJECTS AT TOC VISIT BY SPONSOR		
Clinical Response	Daptomycin (N=256)	Comparator (N=261)
Clinical Success	167 (65.2%)	166 (63.6%)
Clinical Failure	89 (34.8%)	95 (36.4%)
Difference in Success Rate Daptomycin vs. Comparator:	1.6%, 95% C.I.: -7.0%, 10.3%	

The secondary analyses are presented in Tables 9, 10, 11, and 12 for the clinical responses of ME and MITT subjects as per MO's and sponsor's at the TOC visit, respectively. The confidence interval results showed Daptomycin was therapeutically non-inferior or marginally non-inferior to its comparator with respect to clinical success rates at TOC.

TABLE 9: STUDY 9801: CLINICAL RESPONSES OF ME SUBJECTS AT TOC VISIT BY MO		
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%	

TABLE 10: STUDY 9801: CLINICAL RESPONSES OF ME SUBJECTS AT TOC VISIT BY SPONSOR		
Clinical Response	Daptomycin (N=187)	Comparator (N=189)
Clinical Success	140 (74.9%)	142 (75.1%)
Clinical Failure	47 (25.1%)	47 (24.9%)
Difference in Success Rate Daptomycin vs. Comparator:	-0.3%, 95% C.I.: -9.6%, 9.0%	

TABLE 11: STUDY 9801: CLINICAL RESPONSES OF MITT SUBJECTS AT TOC VISIT BY MO		
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 12: STUDY 9801: CLINICAL RESPONSES OF MITT SUBJECTS AT TOC VISIT BY SPONSOR		
Clinical Response	Daptomycin (N=209)	Comparator (N=212)
Clinical Success	140 (67.0%)	142 (67.0%)
Clinical Failure	69 (33.0%)	70 (33.0%)
Difference in Success Rate Daptomycin vs. Comparator:	0.0%, 95% C.I.: -9.5%, 9.5%	

The secondary analyses in Tables 13, 14, 15, and 16 present microbiologic success rates from ME subsets and MITT subsets as per MO's and sponsor's, respectively. Some of these results did not display non-inferiority of Daptomycin to its comparator.

TABLE 13: STUDY 9801: MICROBIOLOGIC RESPONSES OF ME SUBJECTS AT TOC VISIT BY MO		
Clinical 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%	

TABLE 14: STUDY 9801: MICROBIOLOGIC RESPONSES OF ME SUBJECTS AT TOC VISIT BY SPONSOR		
Clinical Response	Daptomycin (N=187)	Comparator (N=189)
Microbiologic Success	123 (65.8%)	125 (66.1%)
Microbiologic Failure	64 (34.2%)	64 (33.9%)
Difference in Success Rate Daptomycin vs. Comparator:	-0.4%, 95% C.I.: -10.5%, 9.7%	

TABLE 15: STUDY 9801: MICROBIOLOGIC RESPONSES OF MITT SUBJECTS AT TOC VISIT BY MO		
Clinical Response	Daptomycin (N=215)	Comparator (N=216)
Microbiologic Success	124 (57.7%)	124 (57.4%)
Microbiologic Failure	91 (42.3%)	92 (42.6%)
Difference in Success Rate Daptomycin vs. Comparator:	0.3%, 95% C.I.: -9.5%, 10.1%	

TABLE 16: STUDY 9801: MICROBIOLOGIC RESPONSES OF MITT SUBJECTS AT TOC VISIT BY SPONSOR		
Clinical Response	Daptomycin (N=209)	Comparator (N=212)
Microbiologic Success	123 (58.9%)	125 (59.0%)
Microbiologic Failure	86 (41.1%)	87 (41.0%)
Difference in Success Rate Daptomycin vs. Comparator:	-0.1%, 95% C.I.: -10.0%, 9.8%	

Tables 17, 18, 19, and 20 show pathogen clinical success rates for those infecting pathogens isolated most frequently at baseline of ME and MITT subjects as per MO's and sponsor's at the TOC visit, respectively.

TABLE 17: STUDY 9801: PATHOGEN CLINICAL SUCCESS RATES OF ME SUBJECTS AT TOC VISIT BY MO		
Baseline Isolate Pathogen	Daptomycin	Comparator
Group A *Streptococcus*	26/29 (89.7%)	25/29 (86.2%)
Group B *Streptococcus*	12/15 (80.0%)	14/16 (87.5%)
Enterococcus Faecalis	13/21 (61.9%)	19/29 (65.5%)
Enterococcus Faecium	1/4 (25.0%)	0/1 (0%)
Streptococcus Dysgalactiae	6/6 (100%)	3/5 (60.0%)
MSSA	69/87 (79.3%)	65/84 (77.4%)
MRSA	17/24 (70.8%)	16/27 (59.3%)

TABLE 18: STUDY 9801: PATHOGEN CLINICAL SUCCESS RATES OF ME SUBJECTS AT TOC VISIT BY SPONSOR		
Baseline Isolate Pathogen	Daptomycin	Comparator
Group A *Streptococcus*	27/32 (84.4%)	25/31 (80.6%)
Group B *Streptococcus*	13/16 (81.3%)	14/18 (77.8%)
Enterococcus Faecalis	13/21 (61.9%)	19/29 (65.5%)
Enterococcus Faecium	1/4 (25.0%)	0/1 (0%)
Streptococcus Dysgalactiae	7/7 (100%)	3/5 (60.0%)
MSSA	73/94 (77.7%)	66/88 (75.0%)
MRSA	17/26 (65.4%)	18/30 (60.0%)

TABLE 19: STUDY 9801: PATHOGEN CLINICAL SUCCESS RATES OF MITT SUBJECTS AT TOC VISIT BY MO		
Baseline Isolate Pathogen	Daptomycin	Comparator
Group A *Streptococcus*	27/33 (81.8%)	25/35 (71.4%)
Group B *Streptococcus*	13/17 (76.5%)	14/23 (60.9%)
Enterococcus Faecalis	13/25 (52.0%)	19/33 (57.6%)
Enterococcus Faecium	1/4 (25.0%)	0/1 (0%)
Streptococcus Dysgalactiae	7/8 (87.5%)	3/6 (50.0%)
MSSA	73/107 (68.2%)	65/99 (65.7%)
MRSA	17/35 (48.6%)	17/36 (47.2%)

TABLE 20: STUDY 9801: PATHOGEN CLINICAL SUCCESS RATES OF MITT SUBJECTS AT TOC VISIT BY SPONSOR		
Baseline Isolate Pathogen	Daptomycin	Comparator
Group A *Streptococcus*	27/33 (81.8%)	25/35 (71.4%)
Group B *Streptococcus*	13/17 (76.5%)	14/21 (66.7%)
Enterococcus Faecalis	13/25 (52.0%)	19/33 (57.6%)
Enterococcus Faecium	1/4 (25.0%)	0/1 (0%)
Streptococcus Dysgalactiae	7/8 (87.5%)	3/5 (60.0%)
MSSA	73/103 (70.9%)	66/97 (68.0%)
MRSA	17/34 (50.0%)	18/35 (51.4%)

Tables 21, 22, 23, and 24 show pathogen microbiologic success rates for those infecting pathogens isolated most frequently at baseline of ME and MITT subjects as per MO's and sponsor's at the TOC visit, respectively.

TABLE 21: STUDY 9801: PATHOGEN MICROBIOLOGIC SUCCESS RATES OF ME SUBJECTS AT TOC VISIT BY MO		
Baseline Isolate Pathogen	Daptomycin	Comparator
Group A *Streptococcus*	25/29 (86.2%)	22/29 (75.9%)
Group B *Streptococcus*	11/15 (73.3%)	12/16 (75.0%)
Enterococcus Faecalis	12/21 (57.1%)	17/29 (58.6%)
Enterococcus Faecium	1/4 (25.0%)	0/1 (100%)
Streptococcus Dysgalactiae	6/6 (100%)	3/5 (60.0%)
MSSA	59/87 (67.8%)	56/84 (66.7%)
MRSA	12/24 (50.0%)	13/27 (48.1%)

TABLE 22: STUDY 9801: PATHOGEN MICROBIOLOGIC SUCCESS RATES OF ME SUBJECTS AT TOC VISIT BY SPONSOR		
Baseline Isolate Pathogen	Daptomycin	Comparator
Group A *Streptococcus*	26/32 (81.2%)	22/31 (71.0%)
Group B *Streptococcus*	13/16 (81.3%)	14/18 (77.8%)
Enterococcus Faecalis	12/21 (57.1%)	17/29 (58.6%)
Enterococcus Faecium	3/4 (75.0%)	1/1 (100%)
Streptococcus Dysgalactiae	7/7 (100%)	3/5 (60.0%)
MSSA	64/94 (68.1%)	58/88 (65.9%)
MRSA	12/26 (46.2%)	15/30 (50.0%)

TABLE 23: STUDY 9801: PATHOGEN MICROBIOLOGIC SUCCESS RATES OF MITT SUBJECTS AT TOC VISIT BY MO		
Baseline Isolate Pathogen	Daptomycin	Comparator
Group A *Streptococcus*	26/33 (78.8%)	22/35 (62.9%)
Group B *Streptococcus*	12/17 (70.6%)	12/23 (52.2%)
Enterococcus Faecalis	12/25 (48.0%)	17/33 (51.5%)
Enterococcus Faecium	3/4 (75.0%)	1/1 (100%)
Streptococcus Dysgalactiae	7/8 (87.5%)	3/6 (50.0%)
MSSA	61/107 (57.0%)	56/99 (56.6%)
MRSA	12/35 (34.3%)	14/36 (38.9%)

TABLE 24: STUDY 9801: PATHOGEN MICROBIOLOGIC SUCCESS RATES OF MITT SUBJECTS AT TOC VISIT BY SPONSOR		
Baseline Isolate Pathogen	Daptomycin	Comparator
Group A *Streptococcus*	26/33 (78.8%)	22/35 (62.9%)
Group B *Streptococcus*	13/17 (76.5%)	14/21 (66.7%)
Enterococcus Faecalis	12/25 (48.0%)	17/33 (51.5%)
Enterococcus Faecium	3/4 (75.0%)	1/1 (100%)
Streptococcus Dysgalactiae	7/8 (87.5%)	3/5 (60.0%)
MSSA	64/103 (62.1%)	58/97 (59.8%)
MRSA	12/34 (35.3%)	15/35 (42.9%)

Study 9901

The statistical objective of this study was to demonstrate the non-inferiority of Daptomycin to its comparator in clinical response at TOC.

Efficacy analyses were performed on four subject populations as ITT, MITT , CE, and ME. Subjects were analyzed for efficacy according to randomization, regardless of treatment administered. Subjects who were randomized but never received any study drug were excluded from all efficacy analyses.

The clinical outcome was defined as the basis for the primary efficacy variable. The outcomes success (cure, clinical improvement), failure, and non-evaluable were based primarily on the investigator's assessment of clinical response at the TOC evaluation. The MO redefined CE and ME populations and reclassified efficacy outcomes after checking for agreement with investigators' evaluability and outcome assessments according to the protocol. The primary outcome measures under analysis were the clinical success rates at TOC for the CE and ITT populations.

The number and the proportion of subjects included in each evaluation group are presented in Table 25. A total of 571 subjects were randomized to study treatment; 277 received

Daptomycin and 294 received comparator as designated by the investigator prior to randomization. Nine of the 571 randomized subjects discontinued prior to receiving any study treatment due to "Other Infection Stratum" or "Diabetic Ulcer Stratum". Among the 562 subjects who received at least one dose of study drug, 270 to the Daptomycin arm and 292 to the comparator arm. One subject was randomized to receive Daptomycin but was administered only comparator as study medication. This subject was referred to as misrandomized. In all efficacy analyses, data for this subject are tabulated as randomized; in all safety analyses data for this subject were tabulated as treated. MO's CE population includes 88.1% and 85.6% of subjects in two treatment groups respectively. The most common reason for exclusion was "CPK > 50% above ULN; require i.m. injections; rhabdomyolysis; receiving statins".

TABLE 25: STUDY 9901: NUMBER OF SUBJECTS INCLUDED IN EACH EVALUATION GROUP

Evaluation Group	Number of Subjects	
	Daptomycin	Comparator
All Randomized Subjects	277	294
Safety (as treated)	269	293
ITT Subjects	270 (100%)	292 (100%)
MITT Subjects	213 (78.9%)	255 (87.3%)
MO's CE Subjects	238 (88.1%)	250 (85.6%)
Sponsor's CE Subjects	245 (90.7%)	262 (89.7%)
MO's ME Subjects	191 (70.7%)	220 (75.3%)
Sponsor's ME Subjects	196 (72.6%)	231 (79.1%)

Data for baseline demographics and disease characteristics are described for ITT subjects in Tables 26 and 27. The two treatment groups were comparable and no statistically significant differences were detected with regard to these characteristics.

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TABLE 26: STUDY 9901: BASELINE DEMOGRAPHICS IN ITT SUBJECTS

Variables	Daptomycin (N=270)	Comparator (N=292)	P-value
Age (yrs.)			
Range (Min, Max)	(18, 87)	(17, 85)	
Mean ± SD	47.9 ± 17.2	48.6 ± 16.7	*0.6284
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

* By t test. All others in the table, by chi-square test.

TABLE 27: STUDY 9901: BASELINE DISEASE CHARACTERISTICS IN ITT SUBJECTS

Parameters	Daptomycin (N=270)	Comparator (N=292)	*P-value
Wound Infection	102 (37.8%)	108 (37.0%)	0.7810
Major Abscess	59 (21.9%)	65 (22.3%)	
Infected Diabetic Ulcer	23 (8.5%)	31 (10.6%)	
Infected Ulcer (non-diabetic)	30 (11.1%)	37 (12.7%)	
Other Infection	56 (20.7%)	51 (17.5%)	

* By chi-square test.

The primary analyses are presented in Tables 28, 29, 30, and 31 for the clinical responses of CE and ITT subjects as per MO's and sponsor's at the TOC visit, respectively. The confidence interval results demonstrated Daptomycin was non-inferior to its comparator with respect to clinical success rates at TOC.

TABLE 28: STUDY 9901: CLINICAL RESPONSES OF CE SUBJECTS AT TOC VISIT BY MO		
Clinical Response	Daptomycin (N=238)	Comparator (N=250)
Clinical Success Clinical Failure	214 (89.9%) 24 (10.1%)	226 (90.4%) 24 (9.6%)
Difference in Success Rate Daptomycin vs. Comparator:	-0.5%, 95% C.I.: -6.2%, 5.2%	

TABLE 29: STUDY 9901: CLINICAL RESPONSES OF CE SUBJECTS AT TOC VISIT BY SPONSOR		
Clinical Response	Daptomycin (N=245)	Comparator (N=262)
Clinical Success Clinical Failure	217 (88.6%) 28 (11.4%)	235 (89.7%) 27 (10.3%)
Difference in Success Rate Daptomycin vs. Comparator:	-1.1%, 95% C.I.: -6.9%, 4.7%	

TABLE 30: STUDY 9901: CLINICAL RESPONSES OF ITT SUBJECTS AT TOC VISIT BY MO		
Clinical Response	Daptomycin (N=270)	Comparator (N=292)
Clinical Success Clinical Failure	217 (80.4%) 53 (19.6%)	235 (80.5%) 57 (19.5%)
Difference in Success Rate Daptomycin vs. Comparator:	-0.1%, 95% C.I.: -7.0%, 6.8%	

TABLE 31: STUDY 9901: CLINICAL RESPONSES OF ITT SUBJECTS AT TOC VISIT BY SPONSOR		
Clinical Response	Daptomycin (N=270)	Comparator (N=292)
Clinical Success Clinical Failure	218 (80.7%) 52 (19.3%)	237 (81.2%) 55 (18.8%)
Difference in Success Rate Daptomycin vs. Comparator:	-0.4%, 95% C.I.: -7.3%, 6.4%	

The secondary analyses are presented in Tables 32, 33, 34, and 35 for the clinical responses of ME and MITT subjects as per MO's and sponsor's at the TOC visit, respectively. The confidence interval results showed Daptomycin was therapeutically non-inferior to its

comparator with respect to clinical success rates at TOC.

TABLE 32: STUDY 9901: CLINICAL RESPONSES OF ME SUBJECTS AT TOC VISIT BY MO		
Clinical Response	Daptomycin (N=191)	Comparator (N=220)
Clinical Success Clinical Failure	176 (92.1%) 15 (7.9%)	203 (92.3%) 17 (7.7%)
Difference in Success Rate Daptomycin vs. Comparator:	-0.1%, 95% C.I.: -5.8%, 5.6%	

TABLE 33: STUDY 9901: CLINICAL RESPONSES OF ME SUBJECTS AT TOC VISIT BY SPONSOR		
Clinical Response	Daptomycin (N=196)	Comparator (N=231)
Clinical Success Clinical Failure	179 (91.3%) 17 (8.7%)	212 (91.8%) 19 (9.2%)
Difference in Success Rate Daptomycin vs. Comparator:	-0.4%, 95% C.I.: -6.2%, 5.3%	

TABLE 34: STUDY 9901: CLINICAL RESPONSES OF MITT SUBJECTS AT TOC VISIT BY MO		
Clinical Response	Daptomycin (N=213)	Comparator (N=255)
Clinical Success Clinical Failure	179 (84.0%) 34 (16.0%)	212 (83.1%) 43 (16.9%)
Difference in Success Rate Daptomycin vs. Comparator:	0.9%, 95% C.I.: -6.3%, 8.1%	

TABLE 35: STUDY 9901: CLINICAL RESPONSES OF MITT SUBJECTS AT TOC VISIT BY SPONSOR		
Clinical Response	Daptomycin (N=213)	Comparator (N=255)
Clinical Success Clinical Failure	180 (84.5%) 33 (15.5%)	214 (83.9%) 41 (16.1%)
Difference in Success Rate Daptomycin vs. Comparator:	0.6%, 95% C.I.: -6.5%, 7.6%	

The secondary analyses in Tables 36, 37, 38, and 39 present microbiologic success rates from ME subsets and MITT subsets as per MO's and sponsor's, respectively. The results all supported marginal non-inferiority of Daptomycin to its comparator.

TABLE 36: STUDY 9901: MICROBIOLOGIC RESPONSES OF ME SUBJECTS AT TOC VISIT BY MO		
Clinical Response	Daptomycin (N=191)	Comparator (N=220)
Microbiologic Success	153 (80.1%)	182 (82.7%)
Microbiologic Failure	38 (19.9%)	38 (17.3%)
Difference in Success Rate Daptomycin vs. Comparator:	-2.6%, 95% C.I.: -10.7%, 5.4%	

TABLE 37: STUDY 9901: MICROBIOLOGIC RESPONSES OF ME SUBJECTS AT TOC VISIT BY SPONSOR		
Clinical Response	Daptomycin (N=196)	Comparator (N=231)
Microbiologic Success	156 (79.6%)	190 (82.3%)
Microbiologic Failure	40 (20.4%)	41 (17.7%)
Difference in Success Rate Daptomycin vs. Comparator:	-2.7%, 95% C.I.: -10.6%, 5.3%	

TABLE 38: STUDY 9901: MICROBIOLOGIC RESPONSES OF MITT SUBJECTS AT TOC VISIT BY MO		
Clinical Response	Daptomycin (N=213)	Comparator (N=255)
Microbiologic Success	155 (72.8%)	192 (75.3%)
Microbiologic Failure	58 (27.2%)	63 (24.7%)
Difference in Success Rate Daptomycin vs. Comparator:	-2.5%, 95% C.I.: -10.9%, 5.9%	

TABLE 39: STUDY 9901: MICROBIOLOGIC RESPONSES OF MITT SUBJECTS AT TOC VISIT BY SPONSOR		
Clinical Response	Daptomycin (N=213)	Comparator (N=255)
Microbiologic Success	156 (73.2%)	192 (75.3%)
Microbiologic Failure	57 (26.8%)	63 (24.7%)
Difference in Success Rate Daptomycin vs. Comparator:	-2.1%, 95% C.I.: -10.4%, 6.3%	

Tables 40, 41, 42, and 43 show pathogen clinical success rates for those infecting pathogens isolated most frequently at baseline of ME and MITT subjects as per MO's and sponsor's at the TOC visit, respectively.

TABLE 40: STUDY 9901: PATHOGEN CLINICAL SUCCESS RATES OF ME SUBJECTS AT TOC VISIT BY MO		
Baseline Isolate Pathogen	Daptomycin	Comparator
Group A *Streptococcus*	53/55 (96.4%)	55/59 (93.2%)
Group B *Streptococcus*	11/12 (91.7%)	8/13 (61.5%)
Enterococcus Faecalis	14/16 (87.5%)	21/24 (87.5%)
Enterococcus Faecium	2/2 (100%)	2/2 (100%)
Streptococcus Dysgalactiae	2/2 (100%)	6/6 (100%)
MSSA	101/111 (91.0%)	115/123 (93.5%)
MRSA	4/4 (100%)	9/9 (100%)

TABLE 41: STUDY 9901: PATHOGEN CLINICAL SUCCESS RATES OF ME SUBJECTS AT TOC VISIT BY SPONSOR		
Baseline Isolate Pathogen	Daptomycin	Comparator
Group A *Streptococcus*	53/55 (96.4%)	57/63 (90.5%)
Group B *Streptococcus*	11/12 (91.7%)	8/13 (61.5%)
Enterococcus Faecalis	14/18 (77.8%)	22/25 (88.0%)
Enterococcus Faecium	2/2 (100%)	2/2 (100%)
Streptococcus Dysgalactiae	2/2 (100%)	7/7 (100%)
MSSA	103/114 (90.4%)	119/128 (93.0%)
MRSA	4/4 (100%)	9/9 (100%)

TABLE 42: STUDY 9901: PATHOGEN CLINICAL SUCCESS RATES OF MITT SUBJECTS AT TOC VISIT BY MO		
Baseline Isolate Pathogen	Daptomycin	Comparator
Group A *Streptococcus*	53/59 (89.8%)	57/68 (83.8%)
Group B *Streptococcus*	11/13 (84.6%)	8/18 (44.4%)
Enterococcus Faecalis	14/20 (70.0%)	22/28 (78.6%)
Enterococcus Faecium	2/2 (100%)	2/2 (100%)
Streptococcus Dysgalactiae	2/4 (100%)	7/9 (77.8%)
MSSA	103/124 (83.1%)	119/140 (85.0%)
MRSA	4/5 (80.0%)	9/11 (81.8%)

TABLE 43: STUDY 9901: PATHOGEN CLINICAL SUCCESS RATES OF MITT SUBJECTS AT TOC VISIT BY SPONSOR		
Baseline Isolate Pathogen	Daptomycin	Comparator
Group A *Streptococcus*	54/59 (91.5%)	57/68 (83.8%)
Group B *Streptococcus*	11/13 (84.6%)	9/18 (50.0%)
Enterococcus Faecalis	14/20 (70.0%)	23/28 (82.1%)
Enterococcus Faecium	2/2 (100%)	2/2 (100%)
Streptococcus Dysgalactiae	2/2 (100%)	7/9 (77.8%)
MSSA	104/124 (83.9%)	119/140 (85.0%)
MRSA	4/5 (80.0%)	9/11 (81.8%)

Tables 44, 45, 46, and 47 show pathogen microbiologic success rates for those infecting pathogens isolated most frequently at baseline of ME and MITT subjects as per MO's and sponsor's at the TOC visit, respectively.

TABLE 44: STUDY 9901: PATHOGEN MICROBIOLOGIC SUCCESS RATES OF ME SUBJECTS AT TOC VISIT BY MO		
Baseline Isolate Pathogen	Daptomycin	Comparator
Group A *Streptococcus*	52/55 (94.5%)	50/59 (84.7%)
Group B *Streptococcus*	10/12 (83.3%)	7/13 (53.8%)
Enterococcus Faecalis	13/16 (81.3%)	17/24 (70.8%)
Enterococcus Faecium	2/2 (100%)	2/2 (100%)
Streptococcus Dysgalactiae	2/2 (100%)	6/6 (100%)
MSSA	83/111 (74.8%)	99/123 (80.5%)
MRSA	3/4 (75.0%)	8/9 (88.9%)

TABLE 45: STUDY 9901: PATHOGEN MICROBIOLOGIC SUCCESS RATES OF ME SUBJECTS AT TOC VISIT BY SPONSOR		
Baseline Isolate Pathogen	Daptomycin	Comparator
Group A *Streptococcus*	52/55 (94.5%)	52/63 (82.5%)
Group B *Streptococcus*	10/12 (83.3%)	7/13 (53.8%)
Enterococcus Faecalis	13/18 (72.2%)	18/25 (72.0%)
Enterococcus Faecium	2/2 (100%)	2/2 (100%)
Streptococcus Dysgalactiae	2/2 (100%)	7/7 (100%)
MSSA	84/114 (73.7%)	103/128 (80.5%)
MRSA	3/4 (75.0%)	8/9 (88.9%)

TABLE 46: STUDY 9901: PATHOGEN MICROBIOLOGIC SUCCESS RATES OF MITT SUBJECTS AT TOC VISIT BY MO		
Baseline Isolate Pathogen	Daptomycin	Comparator
Group A *Streptococcus*	52/59 (88.1%)	52/68 (76.5%)
Group B *Streptococcus*	10/13 (76.9%)	8/18 (44.4%)
Enterococcus Faecalis	13/20 (65.0%)	19/28 (67.9%)
Enterococcus Faecium	2/2 (100%)	2/2 (100%)
Streptococcus Dysgalactiae	2/4 (50.0%)	7/9 (77.8%)
MSSA	84/124 (67.7%)	103/140 (73.6%)
MRSA	3/5 (60.0%)	8/11 (72.7%)

TABLE 47: STUDY 9901: PATHOGEN MICROBIOLOGIC SUCCESS RATES OF MITT SUBJECTS AT TOC VISIT BY SPONSOR		
Baseline Isolate Pathogen	Daptomycin	Comparator
Group A *Streptococcus*	52/59 (88.1%)	52/68 (76.5%)
Group B *Streptococcus*	10/13 (76.9%)	8/18 (44.4%)
Enterococcus Faecalis	13/20 (65.0%)	19/28 (67.9%)
Enterococcus Faecium	2/2 (100%)	2/2 (100%)
Streptococcus Dysgalactiae	2/4 (50.0%)	7/9 (77.8%)
MSSA	84/124 (67.7%)	103/140 (73.6%)
MRSA	3/5 (60.0%)	8/11 (72.7%)

3.2 EVALUATION OF SAFETY

Study 9801

For all subjects who received one or more doses of study medication, the rates as per at least one AE, treatment related AEs, severe AEs, Serious AEs, Died, discontinuation due to AE,

discontinuation due to treatment related AEs are present in Table 48. The safety of Daptomycin and the comparator was evaluated in 530 subjects (265 in each treatment group). The proportion of subjects with at least one AE and the proportion of subject with treatment related AEs were significantly lower in the Daptomycin drug exposure group than in the comparator group. No significantly differences were detected regarding all the rest of these safety variables between the two treatment groups.

TABLE 48: STUDY 9801: ADVERSE EVENT RATES

Safety Outcome	Daptomycin (N=265)	Comparator (N=265)	Fisher's P-value
	n (%)	n (%)	
At Least One AE	171 (64.5%)	193 (72.8%)	0.0490
Treatment Related AEs	64 (24.2%)	90 (34.0%)	0.0166
Severe AEs	34 (12.8%)	36 (13.6%)	0.8980
Serious AEs	32 (12.1%)	32 (12.1%)	1.0000
Died	2 (0.8%)	6 (2.3%)	0.2853
Discontinuation Due to AEs	9 (3.4%)	12 (4.5%)	0.6571
Discontinuation Due to Treatment Related AEs	3 (1.1%)	9 (3.4%)	0.1414

AEs were most commonly reported in the gastrointestinal disorders SOC, with 27.5% and 37.0% of subjects in the Daptomycin and comparator drug exposure groups, respectively. Other SOCs with incidence rates of reported events of > 20% in either treatment group included the nervous system disorders SOC, general disorders/administration site conditions SOC; and infections and infestations SOC. The most frequently reported AE was nausea. Nausea was reported more frequently among subjects receiving the comparator agents (15.5%) than among subjects receiving Daptomycin (8.7%). Other events reported in > 5% of subjects in either treatment group included constipation, diarrhea, vomiting, insomnia, headache, dermatitis and pruritus. The only treatment related AE reported with incidence > 5% in either treatment group was nausea reported in 3.4% of Daptomycin subjects and 5.7% of comparator subjects. The only severe events with incidence ≥ 1% were elevations in CPK and gangrene. The only serious AEs with reported incidence ≥ 1% were cellulitis, occurring in 1.5% of subjects in the Daptomycin group, and urosepsis, occurring in 1.1% of subjects in this group. Although a total of 8 subjects died during the study, none of the deaths were judged to be related to study treatment.

Study 9901

For all subjects who received one or more doses of study medication, the rates as per at least one AE, treatment related AEs, severe AEs, Serious AEs, Died, discontinuation due to AE, discontinuation due to treatment related AEs are present in Table 49. The safety of Daptomycin and the comparator was evaluated in 562 subjects (Daptomycin: 269; Comparator: 293). A significantly higher percentage of subjects in the Daptomycin group

subjects experienced severe adverse events. No significantly differences were detected regarding all the rest of these safety variables between the two treatment groups.

TABLE 49: STUDY 9901: ADVERSE EVENT RATES

Safety Outcome	Daptomycin (N=269)	Comparator (N=293)	Fisher's P-value
	n (%)	n (%)	
At Least One AE	103 (38.3%)	100 (34.1%)	0.3338
Treatment Related AEs	30 (11.2%)	29 (9.9%)	0.6803
Severe AEs	26 (9.7%)	13 (4.4%)	0.0192
Serious AEs	26 (9.7%)	17 (5.8%)	0.1114
Died	6 (2.2%)	2 (0.7%)	0.1610
Discontinuation Due to AEs	6 (2.2%)	5 (1.7%)	0.7647
Discontinuation Due to Treatment Related AEs	3 (1.1%)	2 (0.7%)	0.6741

AEs were most commonly reported in the gastrointestinal disorders SOC, with 11.2% and 8.5% of subjects in the Daptomycin and comparator drug exposure groups, respectively. The most frequently reported AE was headache, with 4.1% in the Daptomycin group and 2.7% in the comparator group. Other events reported in 2 to 4% of subjects in either treatment group included constipation, nausea, injection site thrombosis, injection site phlebitis, increased CPK, insomnia, diarrhea, and dermatitis. No treatment related AEs were reported with incidence > 2% in either treatment group. The only severe AE with incidence ≥ 1% was sepsis NOS, which was reported in 3 subjects (1.1%) in the Daptomycin group and none of the subjects in the comparator group. The only serious AE with reported incidence ≥ 1% was cellulitis occurring in 1.1% of subjects in the Daptomycin group and none of the subjects in the comparator group. Although a total of 8 subjects died during the study, none of the deaths were judged to be related to study treatment.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 GENDER, RACE AND AGE

Study 9801

The results of subgroup analyses by gender, race and age for the clinical responses are showed in Tables 50 and 51. The test results from both CE and ITT populations did only reveal a statistically significance difference across the age subgroup between the treatments, where Daptomycin was more favored in the subjects younger than 65 years of age and the comparator was more favored in the older subjects. No statistically heterogeneous treatment effect was detected among other subgroups.

TABLE 50: STUDY 9801: SUBGROUP ANALYSES BY DEMOGRAPHICS CHARACTERISTICS OF CLINICAL RESPONSES IN CE SUBJECTS BY MO

Subgroup	Daptomycin (N=208)	Comparator (N=206)	95% C.I.	P-value Breslow-Day's
Age				
< 65	113/137 (82.5%)	109/145 (75.2%)	(-2.9%, 17.5%)	0.0089
≥ 65	45/71 (63.4%)	49/61 (80.3%)	(-33.5%, -0.4%)	
Gender				
Male	81/108 (75.0%)	83/112 (74.1%)	(-11.5%, 13.3%)	0.6503
Female	77/100 (77.0%)	75/94 (79.8%)	(-15.4%, 9.8%)	
Race				
White	96/133 (72.2%)	90/121 (74.4%)	(-13.9%, 9.5%)	0.8498
Black	42/47 (89.4%)	46/52 (88.5%)	(-13.5%, 15.3%)	
Other	20/28 (71.4%)	22/33 (66.7%)	(-21.7%,31.3%)	

TABLE 51: STUDY 9801: SUBGROUP ANALYSES BY DEMOGRAPHICS CHARACTERISTICS OF CLINICAL RESPONSES IN ITT SUBJECTS BY MO				
Subgroup	Daptomycin (N=264)	Comparator (N=266)	95% C.I.	P-value Breslow-Day's
Age				
< 65	119/173 (68.8%)	112/183 (61.2%)	(-2.9%, 18.0%)	0.0548
≥ 65	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%)	0.9575
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%)	0.8420
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%)	

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The results of subgroup analyses by gender, race and age for the clinical responses in MO's CE and ITT populations are showed in Tables 52 and 53. Results were homogenous across all these demographic aspects.

TABLE 52: STUDY 9901: SUBGROUP ANALYSES BY DEMOGRAPHICS CHARACTERISTICS OF CLINICAL RESPONSES IN CE SUBJECTS BY MO				
Subgroup	Daptomycin (N=238)	Comparator (N=250)	95% C.I.	P-value Breslow-Day's
Age				
< 65	178/197 (90.4%)	187/205 (91.2%)	(-7.0%, 5.3%)	0.7793
≥ 65	36/41 (87.8%)	39/45 (86.7%)	(-15.3%, 17.6%)	
Gender				
Male	120/132 (90.9%)	121/133 (91.0%)	(-7.7%, 7.6%)	0.8664
Female	94/106 (88.7%)	105/117 (89.7%)	(-10.1%, 8.0%)	
Race				
White	107/119 (89.9%)	108/124 (87.1%)	(-6.0%, 11.6%)	0.2933
Black	75/84 (89.3%)	71/78 (91.0%)	(-12.1%, 8.7%)	
Other	32/35 (91.4%)	47/48 (97.9%)	(-19.1%, 6.1%)	

TABLE 53: STUDY 9901: SUBGROUP ANALYSES BY DEMOGRAPHICS CHARACTERISTICS OF CLINICAL RESPONSES IN ITT SUBJECTS BY MO				
Subgroup	Daptomycin (N=270)	Comparator (N=292)	95% C.I.	P-value Breslow-Day's
Age				
< 65	181/216 (83.8%)	194/236 (82.3%)	(-5.8%, 9.0%)	0.3822
≥ 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%)	0.2713
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%)	0.5396
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%)	

4.2 OTHER SPECIAL SUBGROUP POPULATIONS

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Subgroup analyses by other baseline and prognostic factors in CE and ITT populations are presented in Tables 54-69. Significant heterogeneity of treatment effects existed only among the following subgroups when Daptomycin was compared with its comparator: with versus without diabetic history (where Daptomycin was more favored in those with diabetic history); from South Africa versus from other countries (where Daptomycin was more favored in those from South Africa); with versus without concomitant procedures (where Daptomycin was more favored in those without concomitant procedures), and the findings were consistent between CE and ITT analyses. No significant heterogeneity of treatment effects was detected among the other subgroups.

TABLE 54: STUDY 9801: SUBGROUP ANALYSES BY BASELINE DISEASE CHARACTERISTICS OF CLINICAL RESPONSES IN CE SUBJECTS BY MO				
Subgroup	Daptomycin (N=208)	Comparator (N=206)	95% C.I.	P-value Breslow-Day's
Primary Diagnosis				
Wound Infection	64/82 (78.0%)	73/93 (78.5%)	(-13.8%, 12.9%)	0.3040
Major Abscess	42/44 (95.5%)	29/35 (82.9%)	(-3.9%, 29.1%)	
Infected Diabetic Ulcer	18/28 (64.3%)	19/28 (67.9%)	(-31.9%, 24.8%)	
Infected Ulcer (non-diabetic)	14/21 (66.7%)	20/27 (74.1%)	(-37.7%, 22.9%)	
Other Infection	20/33 (60.6%)	17/23 (73.9%)	(-41.5%, 14.9%)	

TABLE 55: STUDY 9801: SUBGROUP ANALYSES BY BASELINE DISEASE CHARACTERISTICS OF CLINICAL RESPONSES IN ITT SUBJECTS BY MO				
Subgroup	Daptomycin (N=264)	Comparator (N=266)	95% C.I.	P-value Breslow-Day's
Primary Diagnosis				
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%)	

TABLE 56: STUDY 9801: SUBGROUP ANALYSES BY INFECTION WITH OR WITHOUT DIABETIC ULCER OF CLINICAL RESPONSES IN CE SUBJECTS BY MO				
Subgroup	Daptomycin (N=208)	Comparator (N=206)	95% C.I.	P-value Breslow-Day's
Diabetic Ulcer				
With	18/31 (58.1%)	21/32 (65.6%)	(-34.7%, 19.5%)	0.5559
Without	140/177 (79.1%)	137/174 (78.7%)	(-8.7%, 9.5%)	

TABLE 57: STUDY 9801: SUBGROUP ANALYSES BY INFECTION WITH OR WITHOUT DIABETIC ULCER OF CLINICAL RESPONSES IN ITT SUBJECTS BY MO				
Subgroup	Daptomycin (N=264)	Comparator (N=266)	95% C.I.	P-value Breslow-Day's
Diabetic Ulcer				
With	20/42 (47.6%)	22/46 (47.8%)	(-23.4%, 23.0%)	0.8625
Without	145/222 (65.3%)	140/220 (63.6%)	(-7.7%, 11.1%)	

TABLE 58: STUDY 9801: SUBGROUP ANALYSES BY INFECTION WITH OR WITHOUT RELEVANT PATHOGENS OF CLINICAL RESPONSES IN CE SUBJECTS BY MO				
Subgroup	Daptomycin (N=208)	Comparator (N=206)	95% C.I.	P-value Breslow-Day's
Relevant Pathogens				
With	128/165 (77.6%)	127/163 (77.9%)	(-10.0%, 9.3%)	0.8639
Without	30/43 (69.8%)	31/43 (72.1%)	(-23.8%, 19.2%)	

TABLE 59: STUDY 9801: SUBGROUP ANALYSES BY INFECTION WITH OR WITHOUT RELEVANT PATHOGENS OF CLINICAL RESPONSES IN ITT SUBJECTS BY MO				
Subgroup	Daptomycin (N=264)	Comparator (N=266)	95% C.I.	P-value Breslow-Day's
Relevant Pathogens				
With	135/206 (65.5%)	128/202 (63.4%)	(-7.6%, 11.9%)	0.7182
Without	30/58 (51.7%)	34/64 (53.1%)	(-20.8%, 18.0%)	

TABLE 60: STUDY 9801: SUBGROUP ANALYSES BY INFECTION WITH OR WITHOUT *S.Aureus* OF CLINICAL RESPONSES IN CE SUBJECTS BY MO				
Subgroup	Daptomycin (N=208)	Comparator (N=206)	95% C.I.	P-value Breslow-Day's
S. Aureus				
With	95/121 (78.5%)	93/123 (75.6%)	(-8.5%, 14.3%)	0.3039
Without	63/87 (72.4%)	65/83 (78.3%)	(-20.0%, 8.2%)	

TABLE 61: STUDY 9801: SUBGROUP ANALYSES BY INFECTION WITH OR WITHOUT *S.Aureus* OF CLINICAL RESPONSES IN ITT SUBJECTS BY MO				
Subgroup	Daptomycin (N=264)	Comparator (N=266)	95% C.I.	P-value Breslow-Day's
S. Aureus				
With	100/156 (64.1%)	94/150 (62.7%)	(-10.0%, 12.9%)	0.9934
Without	65/108 (60.2%)	68/116 (58.6%)	(-12.2%, 15.3%)	

TABLE 62: STUDY 9801: SUBGROUP ANALYSES BY DIABETIC HISTORY OF CLINICAL RESPONSES IN CE SUBJECTS BY MO				
Subgroup	Daptomycin (N=208)	Comparator (N=206)	95% C.I.	P-value Breslow-Day's
Diabetic History				
Yes	65/88 (73.9%)	64/95 (67.4%)	(-7.8%, 20.7%)	0.0952
No	93/120 (77.5%)	94/111 (84.7%)	(-18.1%, 3.7%)	

TABLE 63: STUDY 9801: SUBGROUP ANALYSES BY DIABETIC HISTORY OF CLINICAL RESPONSES IN ITT SUBJECTS BY MO				
Subgroup	Daptomycin (N=264)	Comparator (N=266)	95% C.I.	P-value Breslow-Day's
Diabetic History				
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%)	

TABLE 64: STUDY 9801: SUBGROUP ANALYSES BY GEOGRAPHIC CHARACTERISTICS OF CLINICAL RESPONSES IN CE SUBJECTS BY MO				
Subgroup	Daptomycin (N=208)	Comparator (N=206)	95% C.I.	P-value Breslow-Day's
Country				
South Africa	45/45 (100%)	38/41 (92.7%)	(-3.0%, 17.6%)	0.0512
The USA	113/163 (69.3%)	120/165 (72.7%)	(-13.8%, 7.0%)	

TABLE 65: STUDY 9801: SUBGROUP ANALYSES BY GEOGRAPHIC CHARACTERISTICS OF CLINICAL RESPONSES IN ITT SUBJECTS BY MO				
Subgroup	Daptomycin (N=264)	Comparator (N=266)	95% C.I.	P-value Breslow-Day's
Country				
South Africa	46/49 (93.9%)	38/48 (79.2%)	(-0.7%, 30.1%)	0.0339
The USA	119/215 (55.4%)	124/218 (56.9%)	(-11.3%, 8.3%)	

TABLE 66: STUDY 9801: SUBGROUP ANALYSES BY INFECTION WITH CONCOMITANT ANTIBIOTICS OF CLINICAL RESPONSES IN CE SUBJECTS BY MO				
Subgroup	Daptomycin (N=208)	Comparator (N=206)	95% C.I.	P-value Breslow-Day's
Concomitant Antibiotics				
Yes	22/30 (73.3%)	16/21 (76.2%)	(-31.0%, 25.3%)	0.8512
No	136/178 (76.4%)	142/185 (76.8%)	(-9.6%, 8.9%)	

TABLE 67: STUDY 9801: SUBGROUP ANALYSES BY INFECTION WITH CONCOMITANT ANTIBIOTICS OF CLINICAL RESPONSES IN ITT SUBJECTS BY MO				
Subgroup	Daptomycin (N=264)	Comparator (N=266)	95% C.I.	P-value Breslow-Day's
Concomitant Antibiotics				
Yes	22/35 (62.9%)	18/31 (58.1%)	(-21.9%, 31.5%)	0.7795
No	143/229 (62.4%)	144/235 (61.3%)	(-8.1%, 10.4%)	

TABLE 68: STUDY 9801: SUBGROUP ANALYSES BY CONCOMITANT PROCEDURES OF CLINICAL RESPONSES IN CE SUBJECTS BY MO				
Subgroup	Daptomycin (N=208)	Comparator (N=206)	95% C.I.	P-value Breslow-Day's
Concomitant procedures				
Yes	47/61 (77.1%)	55/61 (90.2%)	(-27.7 %, 1.5%)	0.0330
No	111/147 (75.5%)	103/145 (71.0%)	(-6.3%, 15.3%)	

TABLE 69: STUDY 9801: SUBGROUP ANALYSES BY CONCOMITANT PROCEDURES OF CLINICAL RESPONSES IN ITT SUBJECTS BY MO				
Subgroup	Daptomycin (N=264)	Comparator (N=266)	95% C.I.	P-value Breslow-Day's
Concomitant procedures				
Yes	49/75 (65.3%)	57/78 (73.1%)	(-23.6%, 8.2%)	0.1471
No	116/189 (61.4%)	105/188 (55.9%)	(-4.9%, 16.0%)	

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Subgroup analyses by other baseline and prognostic factors in CE and ITT populations are presented in Tables 70-87. Significant heterogeneity of treatment effects existed only among the following subgroups in ITT population when Daptomycin was compared with its comparator: with versus without concomitant antibiotics (where Daptomycin was more favored in those without taking concomitant antibiotics); with versus without concomitant procedures (where Daptomycin was more favored in those with concomitant procedures). No significant heterogeneity of treatment effects was detected among the other subgroups in ITT population. Results from CE population were all consistent which means the treatment effects were homogeneous across all these factors in CE subjects.

TABLE 70: STUDY 9901: SUBGROUP ANALYSES BY BASELINE DISEASE CHARACTERISTICS OF CLINICAL RESPONSES IN CE SUBJECTS BY MO				
Subgroup	Daptomycin (N=238)	Comparator (N=250)	95% C.I.	P-value Breslow-Day's
Primary Diagnosis				
Wound Infection	78/87 (89.7%)	83/87 (95.4%)	(-14.7%, 3.2%)	0.1758
Major Abscess	52/58 (89.7%)	52/57 (91.2%)	(-14.1%, 10.9%)	
Infected Diabetic Ulcer	13/19 (68.4%)	20/28 (71.4%)	(-34.2%, 28.2%)	
Infected Ulcer (non-diabetic)	23/26 (88.5%)	28/31 (90.1%)	(-21.5%, 17.8%)	
Other Infection	48/48 (100%)	43/47 (91.5%)	(-1.6%, 18.6%)	

TABLE 71: STUDY 9901: SUBGROUP ANALYSES BY BASELINE DISEASE CHARACTERISTICS OF CLINICAL RESPONSES IN ITT SUBJECTS BY MO				
Subgroup	Daptomycin (N=270)	Comparator (N=292)	95% C.I.	P-value Breslow-Day's
Primary Diagnosis				
Wound Infection	81/102 (79.4%)	88/108 (81.5%)	(-13.8%, 9.6%)	0.7191
Major Abscess	52/59 (88.1%)	53/65 (81.5%)	(-7.6%, 20.7%)	
Infected Diabetic Ulcer	13/23 (56.5%)	21/31 (67.7%)	(-41.1%, 18.7%)	
Infected Ulcer (non-diabetic)	23/30 (76.7%)	30/37 (81.1%)	(-27.1%, 18.3%)	
Other Infection	48/56 (85.7%)	43/51 (84.3%)	(-14.0%, 16.8%)	

TABLE 72: STUDY 9901: SUBGROUP ANALYSES BY INFECTION WITH OR WITHOUT DIABETIC ULCER OF CLINICAL RESPONSES IN CE SUBJECTS BY MO				
Subgroup	Daptomycin (N=238)	Comparator (N=250)	95% C.I.	P-value Breslow-Day's
Diabetic Ulcer				
With	16/24 (66.7%)	23/32 (71.9%)	(-33.3%, 22.9%)	0.8224
Without	198/214 (92.5%)	203/218 (93.1%)	(-5.9%, 4.7%)	

TABLE 73: STUDY 9901: SUBGROUP ANALYSES BY INFECTION WITH OR WITHOUT DIABETIC ULCER OF CLINICAL RESPONSES IN ITT SUBJECTS BY MO				
Subgroup	Daptomycin (N=270)	Comparator (N=292)	95% C.I.	P-value Breslow-Day's
Diabetic Ulcer				
With	16/28 (57.1%)	25/39 (64.1%)	(-33.7%, 19.8%)	0.5975
Without	201/242 (83.1%)	210/253 (83.0%)	(-7.0%, 7.1%)	

TABLE 74: STUDY 9901: SUBGROUP ANALYSES BY INFECTION WITH OR WITHOUT RELEVANT PATHOGENS OF CLINICAL RESPONSES IN CE SUBJECTS BY MO				
Subgroup	Daptomycin (N=238)	Comparator (N=250)	95% C.I.	P-value Breslow-Day's
Relevant Pathogens				
With	165/177 (93.2%)	187/203 (92.1%)	(-4.7%, 6.9%)	0.5961
Without	49/61 (80.3%)	39/47 (83.0%)	(-19.2%, 13.9%)	

TABLE 75: STUDY 9901: SUBGROUP ANALYSES BY INFECTION WITH OR WITHOUT RELEVANT PATHOGENS OF CLINICAL RESPONSES IN ITT SUBJECTS BY MO				
Subgroup	Daptomycin (N=270)	Comparator (N=292)	95% C.I.	P-value Breslow-Day's
Relevant Pathogens				
With	168/199 (84.4%)	194/235 (82.6%)	(-9.3%, 8.2%)	0.5567
Without	49/71 (69.0%)	41/57 (71.9%)	(-10.1%, 12.5%)	

TABLE 76: STUDY 9901: SUBGROUP ANALYSES BY INFECTION WITH *S.Aureus* OF CLINICAL RESPONSES IN CE SUBJECTS BY MO				
Subgroup	Daptomycin (N=238)	Comparator (N=250)	95% C.I.	P-value Breslow-Day's
S. Aureus				
With	119/129 (92.2%)	140/149 (94.0%)	(-8.4%, 5.0%)	0.4822
Without	95/109 (87.2%)	86/101 (85.1%)	(-8.3%, 12.3%)	

TABLE 77: STUDY 9901: SUBGROUP ANALYSES BY INFECTION WITH *S.Aureus* OF CLINICAL RESPONSES IN ITT SUBJECTS BY MO				
Subgroup	Daptomycin (N=270)	Comparator (N=292)	95% C.I.	P-value Breslow-Day's
S. Aureus				
With	122/149 (81.9%)	144/173 (83.2%)	(-10.3%, 7.6%)	0.6204
Without	95/121 (78.5%)	91/119 (76.5%)	(-9.4%, 13.4%)	

TABLE 78: STUDY 9901: SUBGROUP ANALYSES BY DIABETIC HISTORY OF CLINICAL RESPONSES IN CE SUBJECTS BY MO				
Subgroup	Daptomycin (N=238)	Comparator (N=250)	95% C.I.	P-value Breslow-Day's
Diabetic History				
Yes	33/43 (76.7%)	47/58 (81.0%)	(-22.5%, 13.9%)	0.7579
No	181/195 (92.8%)	179/192 (93.2%)	(-6.0%, 5.2%)	

TABLE 79: STUDY 9901: SUBGROUP ANALYSES BY DIABETIC HISTORY OF CLINICAL RESPONSES IN ITT SUBJECTS BY MO				
Subgroup	Daptomycin (N=270)	Comparator (N=292)	95% C.I.	P-value Breslow-Day's
Diabetic History				
Yes	33/50 (66.0%)	49/68 (72.1%)	(-24.7%, 12.6%)	0.4918
No	184/220 (83.6%)	186/224 (83.0%)	(-6.8%, 8.0%)	

TABLE 80: STUDY 9901: SUBGROUP ANALYSES BY GEOGRAPHIC CHARACTERISTICS OF CLINICAL RESPONSES IN CE SUBJECTS BY MO				
Subgroup	Daptomycin (N=238)	Comparator (N=250)	95% C.I.	P-value Breslow-Day's
Country				
South Africa	120/134 (89.6%)	126/136 (92.7%)	(-10.6%, 4.4%)	0.2827
Other	94/104 (90.4%)	100/114 (87.7%)	(-6.5%, 11.9%)	

TABLE 81: STUDY 9901: SUBGROUP ANALYSES BY GEOGRAPHIC CHARACTERISTICS OF CLINICAL RESPONSES IN ITT SUBJECTS BY MO				
Subgroup	Daptomycin (N=270)	Comparator (N=292)	95% C.I.	P-value Breslow-Day's
Country				
South Africa	123/149 (82.6%)	131/154 (85.1%)	(-11.5%, 6.4%)	0.4629
Other	94/121 (77.7%)	104/138 (75.4%)	(-8.8%, 13.4%)	

TABLE 82: STUDY 9901: SUBGROUP ANALYSES BY INVESTIGATIONAL CENTER OF CLINICAL RESPONSES IN CE SUBJECTS BY MO				
Subgroup	Daptomycin (N=238)	Comparator (N=250)	95% C.I.	P-value Breslow-Day's
Center				
501 & 502	26/26 (100%)	27/27 (100%)	(-3.8%, 3.8%)	NA
Other	188/212 (88.7%)	199/223 (89.2%)	(-6.9%, 5.8%)	

TABLE 83: STUDY 9901: SUBGROUP ANALYSES BY INVESTIGATIONAL CENTER OF CLINICAL RESPONSES IN ITT SUBJECTS BY MO				
Subgroup	Daptomycin (N=270)	Comparator (N=292)	95% C.I.	P-value Breslow-Day's
Center				
501 & 502	26/28 (92.9%)	27/28 (96.4%)	(-18.9%, 11.8%)	0.5548
Other	191/242 (78.9%)	208/264 (78.8%)	(-7.4%, 7.7%)	

TABLE 84: STUDY 9901: SUBGROUP ANALYSES BY INFECTION WITH CONCOMITANT ANTIBIOTICS OF CLINICAL RESPONSES IN CE SUBJECTS BY MO				
Subgroup	Daptomycin (N=238)	Comparator (N=250)	95% C.I.	P-value Breslow-Day's
Concomitant Antibiotics				
Yes	23/29 (79.3%)	34/38 (89.5%)	(-30.9%, 10.6%)	0.2442
No	191/209 (91.4%)	192/212 (90.6%)	(-5.1%, 6.8%)	

TABLE 85: STUDY 9901: SUBGROUP ANALYSES BY INFECTION WITH CONCOMITANT ANTIBIOTICS OF CLINICAL RESPONSES IN ITT SUBJECTS BY MO				
Subgroup	Daptomycin (N=270)	Comparator (N=292)	95% C.I.	P-value Breslow-Day's
Concomitant Antibiotics				
Yes	23/33 (69.7%)	39/46 (84.8%)	(-36.5%, 6.3%)	0.0857
No	194/237 (81.9%)	196/246 (79.7%)	(-5.3%, 9.6%)	

TABLE 86: STUDY 9901: SUBGROUP ANALYSES BY CONCOMITANT PROCEDURES OF CLINICAL RESPONSES IN CE SUBJECTS BY MO				
Subgroup	Daptomycin (N=238)	Comparator (N=250)	95% C.I.	P-value Breslow-Day's
Concomitant procedures				
Yes	92/104 (88.5%)	86/101 (85.2%)	(-6.9 %, 13.6%)	0.2450
No	122/134 (91.0%)	140/149 (94.0%)	(-9.8%, 4.0%)	

TABLE 87: STUDY 9901: SUBGROUP ANALYSES BY CONCOMITANT PROCEDURES OF CLINICAL RESPONSES IN ITT SUBJECTS BY MO				
Subgroup	Daptomycin (N=270)	Comparator (N=292)	95% C.I.	P-value Breslow-Day's
Concomitant procedures				
Yes	94/113 (83.2%)	91/120 (75.8%)	(-3.8%, 18.5%)	0.0623
No	123/157 (78.3%)	144/172 (83.7%)	(-14.5%, 3.7%)	

5 SUMMARY AND CONCLUSIONS

5.1 COLLECTIVE EVIDENCE

Based on all the available data from the two studies, the following summaries the evaluation by this reviewer. The conclusions presented in the review were drawn mainly focused on MO's redefined populations and reclassified outcomes, which was believed to provide a more accurate and validated interpretation and description for efficacy and safety of the studies. This submission was primarily supported by two controlled studies (9801 and 9901) to demonstrate the efficacy and safety of Daptomycin in the treatment of cSSSI.

For statistical evaluation of efficacy, statistical non-inferiority on clinical response was analyzed based upon the two-sided 95% confidence interval of the difference in clinical success rates at TOC between Daptomycin and its comparator for CE and ITT subjects.

STUDY 9801

- The 95% confidence interval of the difference in clinical success rates of Daptomycin minus its comparator for CE subjects were $_{208,\ 206}(-9.4\%,\ 7.9\%)_{76.0\%,\ 76.7\%}$. The results demonstrated Daptomycin was non-inferior to its comparator in clinical success rate at TOC.

- The 95% confidence interval of the difference in clinical success rates of Daptomycin minus its comparator for ITT subjects were $_{264,\ 266}(-7.1\%,\ 10.3\%)_{62.5\%,\ 60.9\%}$. The results demonstrated Daptomycin was non-inferior to its comparator in clinical success rate at TOC.

- The safety profile of Daptomycin and its comparator appeared comparable.

STUDY 9901

- The 95% confidence interval of the difference in clinical success rates of Daptomycin minus Cortisporin for CE subjects were $_{238,\ 250}(-6.2\%,\ 5.2\%)_{89.9\%,\ 90.4\%}$, which demonstrated Daptomycin was non-inferior to its comparator in clinical success rate at TOC.

- The 95% confidence interval of the difference in clinical success rates of Daptomycin minus Cortisporin for ITT subjects were $_{270,\ 292}(-7.0\%,\ 6.8\%)_{80.4\%,\ 80.5\%}$, which demonstrated Daptomycin was non-inferior to its comparator in clinical success rate at TOC.

- It is noteworthy that Study 9901 (international study without site in the United States) had better efficacy outcomes than Study 9801 (majority of subjects of this study were recruited from the Unites States sites, 79.2% in CE subjects and 81.7% in ITT subjects).

Divergence in the pretreatment status and baseline characteristics of enrolled subjects could cause the differences in efficacy outcome between the two studies.

- The safety profile of Daptomycin and its comparator appeared comparable.

5.2 CONCLUSIONS AND RECOMMENDATIONS

This NDA submission was to evaluate the efficacy and safety of Daptomycin in the treatment of cSSSI, which was supported by two pivotal studies.

Both Study 9801 and Study 9901 demonstrated that Daptomycin was non-inferior to its comparator for the treatment of cSSSI. These studies supported approval of Daptomycin (4 mg/kg I.V. QD x 7 to 14 days) for the treatment of cSSSI.

In addition, both pivotal studies displayed that Daptomycin and its comparator provided substantially comparable safety profiles.

Based on the above findings, it is the opinion of this reviewer to conclude that the accessible data from two pivotal studies of this submission supported the use of Daptomycin with proposed treatment regimen in the treatment of cSSSI, and the studies provided sufficient evidence to confirm that Daptomycin as an effective and safe medicine in this indication. From the statistical perspective, Daptomycin is recommended for approval in the treatment of cSSSI.

6 APPENDICES

There is no appendix to this review.

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/s/

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9/11/03 08:29:38 PM
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