

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-130

21-131

21-132

STATISTICAL REVIEW(S)

APR 10 2000

STATISTICAL REVIEW AND EVALUATION

NDA: 21-130, 21-131, 21-132
DRUG: Zyvox® (linezolid): tablets, injections, oral suspension
SPONSOR: Pharmacia and Upjohn Company
INDICATIONS: Of 5 indications totally, 2 by this reviewer
1. Community acquired pneumonia
2. Hospital acquired pneumonia
3. MRSS
For the other 3 indications of this NDA, see statistical review reports
by Erica Brittan, Ph.D.

STATISTICAL REVIEWER: Joel Jiang, Ph.D., HFD-725
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*Review's Note: Throughout the review, the following terms are abbreviated and referred to as:
EOT = End of Treatment Visit, F-U = Follow-up, ITT = Intent-to-Treat, MITT = Modified Intent-to-Treat,
MRSA = methicillin-resistant Staphylococcus aureus, MRSE = methicillin-resistant Staphylococcus
species, MRSS = methicillin-resistant Staphylococcus species, TOC = test-of-cure. Reviewer comments
are given in italics throughout the review.*

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I. COMMUNITY ACQUIRED PNEUMONIAE

I.A. INTRODUCTION

The Sponsor submitted two phase III controlled studies as evidence to support that linezolid was safe and efficacious for the treatment of community acquired pneumonia when compared with current established therapies. Statistical review focuses on these comparative clinical trials which formed the basis of this application. The general design of the studies is as follows:

Study 33 was a randomized, open-label, comparative, multicenter (110 centers), and multinational trial which compared the efficacy and safety of a 7 to 14 consecutive days course of therapy with linezolid IV (600 mg BID) followed by linezolid oral (600 mg BID) with those of a 7 to 14 consecutive days course of therapy with ceftriaxone IV (1 g BID) followed by cefpodoxime oral (200 mg BID) in the treatment of *S. pneumoniae* pneumonia. It was initiated January 4, 1998 and completed on May 25, 1999.

Study 51 was a randomized, investigator-blind, comparative, multicenter (103 centers), and multinational trial which compared the efficacy and safety of a 10 to 14 consecutive days course of therapy with linezolid oral (600 mg BID) with those of a 10 to 14 consecutive days course of therapy with cefpodoxime proxetil oral (200 mg BID) in the treatment of community acquired pneumonia. It was initiated September 30, 1998 and completed on April 14, 1999.

I.B. STUDY 33

I.B.1. METHODS

In Study 33, approximately 760 inpatients at least 13 years of age with suspected gram-positive pneumonia were eligible for enrollment in this study provided that they met the inclusion/exclusion criteria. Eligible patients were randomly assigned in a 1:1 ratio to the two treatment groups and the trial was conducted as an open-label study. Efficacy assessments were based on patient disposition with regard to 1) clinical signs and symptoms after treatment compared with those at baseline, 2) radiographic assessments after treatment compared with those conducted at baseline, and 3) microbiological assessments after treatment compared with those conducted at baseline. The study consisted of the following: a baseline/screening visit; inpatient treatment; outpatient treatment, including a study visit at day 7, an EOT visit; and an F-U visit. Patients who returned between 12 and 28 days after the last dose of study medication were included in the TOC assessments. The safety of the study drugs was evaluated throughout the study by clinical observations, vital sign assessments, laboratory evaluations, and assessment of adverse events.

Primary efficacy was assessed by evaluating microbiological outcome at the TOC (F-U) visits. Since clinical and microbiologically outcomes appeared very similar, the evaluation was still mainly on clinical outcome. Analyses of efficacy variables were done separately for ITT, MITT, clinically evaluable, and microbiologically evaluable patients.

Reviewer's Note: *The Medical Officer generally agreed with the Sponsor's evaluability criteria for constructing ITT, MITT, clinically evaluable, and microbiologically evaluable populations. However, for certain groups of patients, such as who were discontinued from therapy for lack of efficacy and received*

at least four doses of study drug, who died of their initial infection before follow-up, and who were with missing clinical outcomes, the definition of analytic population was slightly different from the Sponsor's. The Medical Officer also applied different decision rules from the Sponsor in classifying outcomes, mainly in how outcomes of failure and missing were defined. The algorithm used for determining outcomes by this reviewer was adjusted accordingly to the changes by the Medical Officer.

The Medical Officer focused primarily on clinical outcome in evaluating efficacy.

Please refer to the Medical Officer's review for detailed descriptions of differences between the FDA's and the Sponsor's analytic populations and outcomes.

All patients who received at least one dose of study medication were evaluable for safety. All adverse events that occurred between receipt of the first dose of study medication and the final visit were recorded.

Reviewer's Note: FDA reviewers used the same definitions for adverse events, drug-related adverse events, and serious adverse events as the Sponsor. Death was attributed to infection using the criteria defined by the Medical Officer.

The comparisons of interest in these studies were conducted between linezolid and ceftriaxone/cefepodoxime.

Reviewer's Note: The following statistical analyses were performed by the reviewer to evaluate the efficacy and safety of linezolid versus ceftriaxone/cefepodoxime.

Evaluation of treatment difference with respect to the primary efficacy variables was assessed by computing the two-tailed 95% confidence interval of the difference in response rates. The confidence intervals were computed using a normal approximation to the binomial, and included a continuity correction.

In certain evaluation groups with missing and indeterminate outcomes, sensitivity analyses were performed, whereas missing and indeterminate outcomes were counted as failure.

Subset analyses by gender, age, race, and center site were performed for the primary efficacy variables. Homogeneity of treatment effect across subgroups was assessed via Breslow-Day's test.

This reviewer conducted safety analyses with the following variables: the rate of at least one adverse event, the rate of at least one drug-related adverse event, the rate of serious adverse events, the rate of discontinuation due to adverse events, the rate of mortality, and the rate of mortality related to infection. Statistical comparisons between the two treatment groups were performed using Fisher's exact test.

Prior to performing efficacy analyses, this reviewer assessed the comparability of the treatment groups with respect to pretreatment characteristics including demographics, baseline disease characteristics, and evaluability status. Quantitative variables were assessed using the t-test. Qualitative variables were assessed using Fisher's exact test.

All tests were two-sided and used a 5% level of significance. The test for homogeneity of treatment effect was deemed significant at the 0.15 level.

I.B.2. RESULTS

Of the 759 patients who enrolled in the study, 389 were randomized to the linezolid treatment group, and 370 were randomized to the ceftriaxone/cefepodoxime treatment group. A total of 747 patients received study medication and were included in the ITT analysis group, of whom 381 received linezolid and 366 received ceftriaxone/cefepodoxime.

Reviewer's Note: The number and percentage of patients included in each analysis group, evaluated by either the Sponsor or the Medical Officer, are presented in Table 1. There were no notable treatment differences with respect to the percentage of patients included in each analysis group. Demographic data are described for the FDA clinically evaluable patients in Table 2, and no statistically significant differences were detected in this pretreatment characteristics of the two treatment groups.

Evaluation Group	Patients Included	
	Linezolid	Ceftriaxone/ Cefepodoxime
All Randomized Patients	389	370
ITT Patients	381 (100%)	366 (100%)
MITT Patients	128 (33.6%)	126 (34.4%)
Sponsor Clinically Evaluable Patients	276 (72.4%)	258 (70.5%)
Sponsor Micro. Evaluable Patients	90 (23.6%)	95 (26.0%)
FDA Clinically Evaluable Patients	285 (74.8%)	274 (74.9%)
FDA Micro. Evaluable Patients	92 (24.1%)	99 (27.0%)

Parameters	Linezolid (N=285)	Ceftriaxone/ Cefepodoxime (N=274)	P-value
Gender			
Male	169 (59.3%)	149 (54.4%)	0.240
Female	116 (40.7%)	125 (45.6%)	
Age (yrs.)			
Total Reporting	285	274	*0.763
Range (Max, Min)	(96, 13)	(94, 14)	
Mean ± SD	54.8 ± 19.7	55.3 ± 19.3	
Distribution			
13 - 50	114 (40.0%)	114 (41.6%)	0.699
≥ 51	171 (60.0%)	160 (58.4%)	
Race			
White	184 (64.6%)	183 (66.8%)	0.855
Black	35 (12.3%)	32 (11.7%)	
Other	66 (23.2%)	59 (21.5%)	
Weight (kg)			
Total Reporting	278	267	*0.393
Mean ± SD	69.4 ± 16.0	68.1 ± 19.5	
Site			
USA	87 (30.5%)	96 (35.0%)	0.256
Non-USA	198 (69.5%)	178 (65.0%)	

* By t test. All others in the table, by Chi-squared test.

Reviewer's Note: The clinical responses are shown for ITT, MITT, FDA clinically evaluable, Sponsor clinically evaluable, FDA microbiologically evaluable, and Sponsor microbiologically evaluable populations in Tables 3, 4, 5, 6, 7, and 8, respectively, which include sensitivity analyses by counting missing and indeterminate as failure. The results from these analyses showed that the cure rates of linezolid were comparable to those of ceftriaxone/cefepodoxime. The results from sensitivity analyses were generally in line with those from protocol-specified analyses.

TABLE 3: STUDY 33: CLINICAL RESPONSES OF ITT PATIENTS AT TOC VISIT		
FDA'S ASSESSMENT		
Clinical Response	Linezolid (N=330)	Ceftriaxone/ Cefpodoxime (N=313)
Cured	267 (80.9%)	241 (77.0%)
Failed	63 (19.1%)	72 (23.0%)
Line. Versus Ceft./Cefp.: Difference in Cure Rate	3.9%, 95% C.I.: -2.7%, 10.5%	
SPONSOR'S ASSESSMENT		
Clinical Response	Linezolid (N=323)	Ceftriaxone/ Cefpodoxime (N=314)
Cured	268 (83.0%)	240 (76.4%)
Failed	55 (17.0%)	74 (23.6%)
Line. Versus Ceft./Cefp.: Difference in Cure Rate	6.5%, 95% C.I.: 0%, 13.1%	

TABLE 4: STUDY 33: CLINICAL RESPONSES OF ITT PATIENTS AT TOC VISIT (COUNTING INDETERMINATE AND MISSING AS FAILURE)		
FDA'S ASSESSMENT		
Clinical Response	Linezolid (N=381)	Ceftriaxone/ Cefpodoxime (N=366)
Cured	267 (70.1%)	241 (65.9%)
Failed	63 (16.5%)	72 (19.7%)
Indeterminate	6 (1.6%)	6 (1.6%)
Missing	45 (11.8%)	47 (12.8%)
Line. Versus Ceft./Cefp.: Difference in Cure Rate	4.2%, 95% C.I.: -2.7%, 11.2%	
SPONSOR'S ASSESSMENT		
Clinical Response	Linezolid (N=381)	Ceftriaxone/ Cefpodoxime (N=366)
Cured	268 (70.3%)	240 (65.6%)
Failed	55 (14.4%)	74 (20.2%)
Indeterminate	37 (9.7%)	35 (9.6%)
Missing	21 (5.5%)	17 (4.6%)
Line. Versus Ceft./Cefp.: Difference in Cure Rate	4.8%, 95% C.I.: -2.2%, 11.7%	

TABLE 5: STUDY 33: CLINICAL RESPONSES OF MITT PATIENTS AT TOC VISIT

FDA'S ASSESSMENT		
Clinical Response	Linezolid (N=109)	Ceftriaxone/ Cefpodoxime (N=117)
Cured	91 (83.5%)	90 (76.9%)
Failed	18 (16.5%)	27 (23.1%)
Line. Versus Ceft./Cefp.: Difference in Cure Rate	6.6%, 95% C.I.: -4.7%, 17.8%	
SPONSOR'S ASSESSMENT		
Clinical Response	Linezolid (N=107)	Ceftriaxone/ Cefpodoxime (N=115)
Cured	91 (85.0%)	89 (77.4%)
Failed	16 (15.0%)	26 (22.6%)
Line. Versus Ceft./Cefp.: Difference in Cure Rate	7.7%, 95% C.I.: -3.4%, 18.8%	

TABLE 6: STUDY 33: CLINICAL RESPONSES OF MITT PATIENTS AT TOC VISIT (COUNTING INDETERMINATE AND MISSING AS FAILURE)

FDA'S ASSESSMENT		
Clinical Response	Linezolid (N=128)	Ceftriaxone/ Cefpodoxime (N=126)
Cured	91 (71.1%)	90 (71.4%)
Failed	18 (14.1%)	27 (21.4%)
Indeterminate	3 (2.3%)	2 (1.6%)
Missing	16 (12.5%)	7 (5.6%)
Line. Versus Ceft./Cefp.: Difference in Cure Rate	-0.3%, 95% C.I.: -12.3%, 11.6%	
SPONSOR'S ASSESSMENT		
Clinical Response	Linezolid (N=128)	Ceftriaxone/ Cefpodoxime (N=126)
Cured	91 (71.1%)	89 (70.6%)
Failed	16 (12.5%)	26 (20.6%)
Indeterminate	14 (10.9%)	7 (5.6%)
Missing	7 (5.5%)	4 (3.2%)
Line. Versus Ceft./Cefp.: Difference in Cure Rate	0.5%, 95% C.I.: -11.5%, 12.4%	

TABLE 7: STUDY 33: CLINICAL RESPONSES OF CLINICAL EVALUABLE PATIENTS AT TOC VISIT		
FDA'S ASSESSMENT FOR FDA EVALUABLE PATIENTS		
Clinical Response	Linezolid (N=285)	Ceftriaxone/ Cefpodoxime (N=274)
Cured	246 (86.3%)	225 (82.1%)
Failed	39 (13.7%)	49 (17.9%)
Line. Versus Ceft./Cefp.: Difference in Cure Rate	4.2%, 95% C.I.: -2.2%, 10.6%	
SPONSOR'S ASSESSMENT FOR SPONSOR EVALUABLE PATIENTS		
Clinical Response	Linezolid (N=272)	Ceftriaxone/ Cefpodoxime (N=254)
Cured	247 (90.8%)	225 (88.6%)
Failed	25 (9.3%)	29 (11.4%)
Line. Versus Ceft./Cefp.: Difference in Cure Rate	2.2%, 95% C.I.: -3.4%, 7.8%	
SPONSOR'S ASSESSMENT FOR SPONSOR EVALUABLE PATIENTS (COUNTING INDETERMINATE AS FAILURE)		
Clinical Response	Linezolid (N=276)	Ceftriaxone/ Cefpodoxime (N=258)
Cured	247 (89.5%)	225 (87.2%)
Failed	25 (9.1%)	29 (11.2%)
Indeterminate	4 (1.4%)	4 (1.6%)
Line. Versus Ceft./Cefp.: Difference in Cure Rate	2.3%, 95% C.I.: -3.5%, 8.1%	

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TABLE 8: STUDY 33: CLINICAL RESPONSES OF MICROBIOLOGICAL EVALUABLE PATIENTS AT TOC VISIT		
FDA'S ASSESSMENT FOR FDA EVALUABLE PATIENTS		
Clinical Response	Linezolid (N=92)	Ceftriaxone/ Cefpodoxime (N=99)
Cured	80 (87.0%)	81 (81.8%)
Failed	12 (13.0%)	18 (18.2%)
Line. Versus Ceft./Cefp.: Difference in Cure Rate	5.1%, 95% C.I.: -6.2%, 16.4%	
SPONSOR'S ASSESSMENT FOR SPONSOR EVALUABLE PATIENTS		
Clinical Response	Linezolid (N=89)	Ceftriaxone/ Cefpodoxime (N=93)
Cured	80 (89.9%)	81 (87.1%)
Failed	9 (10.1%)	12 (12.9%)
Line. Versus Ceft./Cefp.: Difference in Cure Rate	2.8%, 95% C.I.: -7.6%, 13.1%	
SPONSOR'S ASSESSMENT FOR SPONSOR EVALUABLE PATIENTS (COUNTING INDETERMINATE AS FAILURE)		
Clinical Response	Linezolid (N=90)	Ceftriaxone/ Cefpodoxime (N=95)
Cured	80 (89.9%)	81 (87.3%)
Failed	9 (10.0%)	12 (12.6%)
Indeterminate	1 (1.1%)	2 (2.1%)
Line. Versus Ceft./Cefp.: Difference in Cure Rate	2.3%, 95% C.I.: -3.5%, 8.1%	

Reviewer's Note: The subset analyses of clinical response for microbiologically evaluable population with bacteremia is shown in Table 9. In this subgroup of patients, the linezolid group had numerically higher cure rates than the ceftriaxone/cefpodoxime group.

TABLE 9: STUDY 33: CLINICAL RESPONSES OF MICROBIOLOGICAL EVALUABLE PATIENTS WITH BACTEREMIA AT TOC VISIT		
FDA'S ASSESSMENT FOR FDA EVALUABLE PATIENTS		
Clinical Response	Linezolid (N=31)	Ceftriaxone/ Cefpodoxime (N=26)
Cured	28 (90.3%)	16 (61.5%)
Failed	3 (9.7%)	10 (38.5%)
SPONSOR'S ASSESSMENT FOR SPONSOR EVALUABLE PATIENTS		
Clinical Response	Linezolid (N=30)	Ceftriaxone/ Cefpodoxime (N=23)
Cured	28 (93.3%)	16 (69.6%)
Failed	2 (6.7%)	7 (30.4%)

Reviewer's Note: Subset analyses by gender, age, race, and center site for clinical cure rates in the FDA clinically evaluable population are shown in Table 10. Results were consistent across all demographic aspects.

TABLE 10: STUDY 33: SUBSET ANALYSES BY DEMOGRAPHIC ASPECTS OF CLINICAL CURE RATE OF FDA CLINICAL EVALUABLE PATIENTS AT TOC VISIT

Subset	Linezolid (N=285)	Ceftriaxone/ Cefpodoxime (N=274)	95% C.I.	Breslow-Day's P-value
Male	142/169 (84.0%)	118/149 (79.2%)	(-4.3%, 14.0%)	0.913
Female	104/116 (89.7%)	107/125 (85.6%)	(-5.1%, 13.2%)	
13-44 yrs	84/93 (90.3%)	73/85 (85.9%)	(-6.2%, 15.1%)	0.764
45-64 yrs	76/85 (89.4%)	70/84 (83.3%)	(-5.4%, 17.6%)	
≥ 65 yrs	86/107 (80.4%)	82/105 (78.1%)	(-9.6%, 14.1%)	
13-50 yrs	100/114 (87.7%)	97/114 (85.1%)	(-7.1%, 12.4%)	0.752
≥ 51 yrs	146/171 (85.4%)	128/160 (80.0%)	(-3.4%, 14.1%)	
White	155/184 (84.2%)	149/183 (81.4%)	(-5.4%, 11.1%)	0.454
Other	91/101 (90.1%)	76/91 (83.5%)	(-4.1%, 17.2%)	
USA	75/87 (86.2%)	77/96 (80.2%)	(-5.9%, 17.9%)	0.711
Non-USA	171/198 (86.4%)	148/178 (83.2%)	(-4.6%, 11.0%)	

Reviewer's Note: Subset analyses by different baseline disease characteristics of the clinical outcome in FDA clinically evaluable population are summarized in Table 11. The clinical cure rates of the linezolid group were consistently numerically better than those of the ceftriaxone/cefpodoxime group across these subgroups.

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TABLE 11: STUDY 33: SUBSET ANALYSES OF CLINICAL CURE RATE OF FDA CLINICAL EVALUABLE PATIENTS AT TOC VISIT		
Subset	Linezolid (N=285)	Ceftriaxone/ Cefpodoxime (N=274)
With Multilobar Pneumonia at Baseline		
Yes	14/15 (93.3%)	5/7 (71.4%)
No	232/270 (85.9%)	220/267 (82.4%)
With Bilateral Pneumonia at Baseline		
Yes	9/10 (90.0%)	5/7 (71.4%)
No	237/275 (86.2%)	220/267 (82.4%)
With Hypotension at Baseline		
Yes	17/22 (77.3%)	25/35 (71.4%)
No	229/263 (87.1%)	200/239 (83.7%)
With Tachypnea at Baseline		
Yes	23/29 (79.3%)	23/31 (74.2%)
No	223/256 (87.1%)	202/243 (83.1%)
With History of Neoplastic Disease at Baseline		
Yes	75/87 (86.2%)	55/70 (78.6%)
No	171/198 (86.4%)	170/204 (83.3%)
With BUN > 7mmol/L at Baseline		
Yes	60/75 (80.0%)	44/63 (69.8%)
No	186/210 (88.6%)	181/211 (85.8%)
With Use of Aztreonam		
Yes	136/160 (85.0%)	2/3 (66.7%)
No	110/125 (88.0%)	223/271 (82.3%)
With HIV Infected		
Yes	7/7 (100%)	5/6 (83.3%)
No	239/278 (86.0%)	220/268 (82.1%)

Reviewer's Note: The FDA's assessment of patient clinical outcome by baseline pathogen for the FDA microbiologically evaluable population is presented in Table 12. The clinical cure rates of the linezolid group were consistently numerically better than those of the ceftriaxone/cefpodoxime group in most of subgroups.

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TABLE 12: STUDY 33: SUBSET ANALYSES OF CLINICAL CURE RATE OF FDA MICROBIOLOGICAL EVALUABLE PATIENTS AT TOC VISIT		
Subset	Linezolid (N=92)	Ceftriaxone/ Cefpodoxime (N=99)
<i>With S. pneumoniae</i>		
Yes	63/73 (86.3%)	62/73 (84.9%)
No	17/19 (89.5%)	19/26 (73.1%)
<i>With S. pneumoniae and Bacteremia</i>		
Yes	27/30 (90.0%)	15/24 (62.5%)
No	53/62 (85.5%)	66/75 (88.0%)
<i>With S. aureus</i>		
Yes	18/21 (85.7%)	13/19 (68.4%)
No	62/71 (87.3%)	68/80 (85.0%)
<i>With S. aureus and Bacteremia</i>		
Yes	1/1 (100%)	1/2 (50.0%)
No	79/91 (86.8%)	80/97 (82.5%)
<i>With S. aureus and MRSA</i>		
Yes	1/1 (100%)	0/0 (NA%)
No	79/91 (86.8%)	81/99 (81.8%)
<i>With H. influenzae</i>		
Yes	5/8 (62.5%)	10/12 (83.3%)
No	75/84 (89.3%)	71/87 (81.6%)
<i>With H. influenzae without Use of Aztreonam</i>		
Yes	4/7 (57.1%)	9/10 (90.0%)
No	76/85 (89.4%)	72/89 (80.9%)

Reviewer's Note: The microbiological responses are shown for MITT, FDA microbiologically evaluable, and Sponsor microbiologically evaluable populations in Tables 13, 14, and 15, which include sensitivity analyses by counting missing and indeterminate as failure and the two analyses reached the similar results. The results from these analyses showed that the cure rates of linezolid were comparable to those of ceftriaxone/cefpodoxime. The results from sensitivity analyses were generally in line with those from protocol-specified analyses.

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TABLE 13: STUDY 33: MICROBIOLOGICAL RESPONSES OF MITT PATIENTS AT TOC VISIT		
FDA'S ASSESSMENT		
Microbiological Response	Linezolid (N=110)	Ceftriaxone/ Cefpodoxime (N=118)
Success	91 (82.7%)	89 (75.4%)
Failed	19 (17.3%)	29 (24.6%)
Line. Versus Ceft./Cefp.: Difference in Success Rate	7.3%, 95% C.I.: -4.1%, 18.7%	
SPONSOR'S ASSESSMENT		
Microbiological Response	Linezolid (N=107)	Ceftriaxone/ Cefpodoxime (N=115)
Success	91 (85.0%)	89 (77.4%)
Failed	16 (15.0%)	26 (22.6%)
Line. Versus Ceft./Cefp.: Difference in Success Rate	7.7%, 95% C.I.: -3.4%, 18.8%	

TABLE 14: STUDY 33: MICROBIOLOGICAL RESPONSES OF MITT PATIENTS AT TOC VISIT (COUNTING INDETERMINATE AND MISSING AS FAILURE)		
FDA'S ASSESSMENT		
Microbiological Response	Linezolid (N=128)	Ceftriaxone/ Cefpodoxime (N=126)
Success	91 (71.1%)	89 (70.6%)
Failed	19 (14.9%)	29 (23.0%)
Indeterminate	13 (10.2%)	5 (4.0%)
Missing	5 (3.9%)	3 (2.4%)
Line. Versus Ceft./Cefp.: Difference in Success Rate	0.5%, 95% C.I.: -11.5%, 12.4%	
SPONSOR'S ASSESSMENT		
Microbiological Response	Linezolid (N=128)	Ceftriaxone/ Cefpodoxime (N=126)
Success	91 (71.1%)	89 (70.6%)
Failed	16 (12.5%)	26 (20.6%)
Indeterminate	14 (10.9%)	7 (5.6%)
Missing	7 (5.5%)	4 (3.2%)
Line. Versus Ceft./Cefp.: Difference in Success Rate	0.5%, 95% C.I.: -11.5%, 12.4%	

TABLE 15: STUDY 33: MICROBIOLOGICAL RESPONSES OF MICROBIOLOGICAL EVALUABLE PATIENTS AT TOC VISIT		
FDA'S ASSESSMENT FOR FDA EVALUABLE PATIENTS		
Microbiological Response	Linezolid (N=92)	Ceftriaxone/ Cefpodoxime (N=99)
Success	80 (87.0%)	81 (81.8%)
Failed	12 (13.0%)	18 (18.2%)
Line. Versus Ceft./Cefp.: Difference in Success Rate	5.1%, 95% C.I.: -6.2%, 16.4%	
SPONSOR'S ASSESSMENT FOR SPONSOR EVALUABLE PATIENTS		
Microbiological Response	Linezolid (N=89)	Ceftriaxone/ Cefpodoxime (N=93)
Success	80 (89.9%)	81 (87.1%)
Failed	9 (10.1%)	12 (12.9%)
Line. Versus Ceft./Cefp.: Difference in Success Rate	2.8%, 95% C.I.: -7.6%, 13.1%	
SPONSOR'S ASSESSMENT FOR SPONSOR EVALUABLE PATIENTS (COUNTING INDETERMINATE AS FAILURE)		
Microbiological Response	Linezolid (N=90)	Ceftriaxone/ Cefpodoxime (N=95)
Success	80 (88.9%)	81 (85.3%)
Failed	9 (10.0%)	12 (12.6%)
Indeterminate	1 (1.1%)	2 (2.1%)
Line. Versus Ceft./Cefp.: Difference in Success Rate	3.6%, 95% C.I.: -7.1%, 14.3%	

Reviewer's Note: Patient microbiological outcomes by baseline pathogen for MITT and microbiologically evaluable populations are presented in Tables 16 and 17, respectively. Numerically, two treatments appeared similar outcomes.

TABLE 16: STUDY 33: MICROBIOLOGICAL SUCCESS RATES BY PATHOGEN OF MITT PATIENTS AT TOC VISIT			
FDA'S ASSESSMENT			
Pathogen	Linezolid	Ceftriaxone/ Cefpodoxime	Fisher's P-value
<i>H. influenzae</i>	8/12 (66.7%)	10/13 (76.9%)	0.673
<i>S. aureus</i>	20/25 (80.0%)	15/22 (68.2%)	0.335
<i>S. pneumoniae</i>	71/85 (83.5%)	69/86 (80.2%)	0.692
SPONSOR'S ASSESSMENT			
Pathogen	Linezolid	Ceftriaxone/ Cefpodoxime	Fisher's P-value
<i>H. influenzae</i>	8/12 (66.7%)	10/13 (76.9%)	0.673
<i>S. aureus</i>	20/25 (80.0%)	15/21 (71.4%)	0.730
<i>S. pneumoniae</i>	71/82 (86.6%)	69/84 (82.1%)	0.523

TABLE 17: STUDY 33: MICROBIOLOGICAL SUCCESS RATES BY PATHOGEN OF MICROBIOLOGICAL EVALUABLE PATIENTS AT TOC VISIT			
FDA'S ASSESSMENT FOR SPONSOR EVALUABLE PATIENTS			
Pathogen	Linezolid	Ceftriaxone/ Cefpodoxime	Fisher's P-value
<i>H. influenzae</i>	5/8 (62.5%)	10/12 (83.3%)	0.347
<i>S. aureus</i>	18/21 (85.7%)	13/19 (68.4%)	0.265
<i>S. pneumoniae</i>	63/73 (86.3%)	62/73 (84.9%)	1.000
SPONSOR'S ASSESSMENT FOR SPONSOR EVALUABLE PATIENTS			
Pathogen	Linezolid	Ceftriaxone/ Cefpodoxime	Fisher's P-value
<i>H. influenzae</i>	5/8 (62.5%)	10/11 (90.9%)	0.262
<i>S. aureus</i>	18/20 (90.0%)	13/17 (76.5%)	0.383
<i>S. pneumoniae</i>	63/71 (88.7%)	62/69 (89.9%)	1.000

Reviewer's Note: The summaries of safety outcomes are presented in Table 18. The percentages of patients with one or more drug related adverse events or drug related adverse events resulting in discontinuation of study medication were significantly greater in the linezolid treatment group than in ceftriaxone/cefpodoxime group.

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TABLE 18: STUDY 33: ADVERSE EVENT RATES			
Safety Outcomes	Linezolid (N=381)	Ceftriaxone/ Cefpodoxime (N=366)	Fisher's P-value
Died	15 (3.9%)	19 (5.2%)	0.484
Died with Infection Related by TOC	4 (1.1%)	6 (1.6%)	0.539
Serious AEs	51 (13.4%)	54 (14.8%)	0.600
Discontinuation Due To AEs	23 (6.0%)	24 (6.6%)	0.880
Discontinuation Due To Drug related AEs	9 (2.4%)	1 (0.3%)	0.021
With Any AE	218 (57.2%)	200 (54.6%)	0.507
Digestive	106 (27.8%)	82 (22.4%)	0.092
Body	87 (22.8%)	76 (20.8%)	0.535
Respiratory	51 (13.4%)	74 (20.2%)	0.014
Skin	44 (11.5%)	27 (7.4%)	0.061
Nervous	41 (10.8%)	38 (10.4%)	0.906
Cardiovascular	31 (8.1%)	31 (8.5%)	0.895
Metabolic and Nutritional	26 (6.8%)	22 (6.0%)	0.658
Urogenital	26 (6.8%)	12 (3.3%)	0.030
Special Senses	12 (3.1%)	4 (1.1%)	0.075
Hemic and Lymphatic	9 (2.4%)	8 (2.2%)	1.000
Musculo-Skeletal	5 (1.3%)	4 (1.1%)	1.000
With Drug Related AE	81 (21.3%)	41 (11.2%)	< 0.001
Digestive	53 (13.9%)	19 (5.2%)	< 0.001
Body	18 (4.7%)	5 (1.4%)	0.010
Skin	13 (3.4%)	5 (1.4%)	0.093
Urogenital	11 (2.9%)	3 (0.8%)	0.056
Hemic and Lymphatic	4 (1.0%)	3 (0.8%)	1.000
Cardiovascular	4 (1.0%)	2 (0.5%)	0.687
Special Senses	4 (1.0)	0 (0%)	0.124
Metabolic and Nutritional	2 (0.5%)	4 (1.1%)	0.443
Nervous	2 (0.5%)	0 (0%)	0.500
Respiratory	0 (0%)	2 (0.5%)	0.240

Note: P-value should be interpreted with caution and adjusted with multiplicity

I.C. STUDY 51

I.C.1. METHODS

In Study 51, approximately 550 outpatients at least 18 years of age with a clinical picture compatible with community acquired pneumonia were eligible for enrollment in this study provided that they met the inclusion/exclusion criteria. Eligible patients were randomly assigned in a 1:1 ratio to the two treatment groups and the trial was conducted in an investigator-blind fashion. Efficacy assessments were based on patient disposition with regard to 1) clinical signs and symptoms assessed after treatment as compared with those observed at Baseline and 2) radiographic assessments after treatment compared with those conducted at Baseline. The study consisted of five visits: a baseline/screening visit, two patient treatment evaluation visits (Day 3 and Day 9, both ± 1 day), an EOT visit, and F-U visit. The TOC evaluation was

conducted at the F-U visit, scheduled for 15 to 21 days after the final dose of study medication. The safety of the study medication was monitored throughout the study by physical examination findings, vital sign assessments, laboratory evaluations, and assessment of adverse events.

Primary efficacy was assessed by evaluating clinical outcome at the TOC (F-U) visits. Analyses of efficacy variables were done separately for ITT, MITT, clinically evaluable, and microbiologically evaluable patients.

Reviewer's Note: *The Medical Officer generally agreed with the Sponsor's evaluability criteria for constructing ITT, MITT, clinically evaluable, and microbiologically evaluable populations. However, for certain groups of patients, such as who were discontinued from therapy for lack of efficacy and received at least four doses of study drug, who died of their initial infection before follow-up, and who were with missing clinical outcomes, the definition of analytic population was different from the Sponsor's. The Medical Officer also applied different decision rules from the Sponsor in classifying outcomes, mainly in how outcomes of failure and missing were defined. The algorithm used for determining outcomes by this reviewer was adjusted accordingly to the changes by the Medical Officer.*

Please refer to the Medical Officer's review for detailed descriptions of differences between the FDA's and the Sponsor's analytic populations and outcomes.

All patients who received at least one dose of study medication were evaluable for safety. All adverse events that occurred between receipt of the first dose of study medication and the final visit were recorded.

Reviewer's Note: *FDA reviewers used the same definitions for adverse events, drug-related adverse events, and serious adverse events as the Sponsor. Death was attributed to infection using the criteria defined by the Medical Officer.*

The comparisons of interest in these studies were conducted between linezolid and cefpodoxime.

Reviewer's Note: *The following statistical analyses were performed by the reviewer to evaluate the efficacy and safety of linezolid versus cefpodoxime.*

Evaluation of treatment difference with respect to the primary efficacy variables was assessed by computing the two-tailed 95% confidence interval of the difference in response rates. The confidence intervals were computed using a normal approximation to the binomial, and included a continuity correction.

In certain evaluation groups with missing and indeterminate outcomes, sensitivity analyses were performed, whereas missing and indeterminate outcomes were counted as failure.

Subset analyses by gender, age, race, and center site were performed for the primary efficacy variables. Homogeneity of treatment effect across subgroups was assessed via Breslow-Day's test.

This reviewer conducted safety analyses with the following variables: the rate of at least one adverse event, the rate of at least one drug-related adverse event, the rate of serious adverse events, the rate of discontinuation due to adverse events, the rate of mortality, and the rate of mortality related to infection. Statistical comparisons between the two treatment groups were performed using Fisher's exact test.

Prior to performing efficacy analyses, this reviewer assessed the comparability of the treatment groups with respect to pretreatment characteristics including demographics, baseline disease characteristics, and evaluability status. Quantitative variables were assessed using the t-test. Qualitative variables were assessed using Fisher's exact test.

All tests were two-sided and used a 5% level of significance. The test for homogeneity of treatment effect

was deemed significant at the 0.15 level.

I.C.2. RESULTS

Of the 548 patients who enrolled in the study, 278 were randomized to the linezolid treatment group, and 270 were randomized to the cefpodoxime treatment group. A total of 540 patients received study medication and were included in the ITT analysis group, of whom 272 received linezolid and 268 received cefpodoxime.

Reviewer's Note: The number and percentage of patients included in each analysis group, evaluated by either the Sponsor or the Medical Officer, are presented in Table 19. There were no notable treatment differences with respect to the percentage of patients included in each analysis group. Demographic data are described for the FDA clinically evaluable patients in Table 20, and no statistically significant differences were detected in this pretreatment characteristics of the two treatment groups.

TABLE 19: STUDY 51: NUMBER OF PATIENTS INCLUDED IN EACH EVALUATION GROUP		
Evaluation Group	Patients Included	
	Linezolid	Cefpodoxime
All Randomized Patients	278	270
ITT Patients	272 (100%)	268 (100%)
MITT Patients	60 (22.1%)	60 (22.4%)
Sponsor Clinically Evaluable Patients	205 (75.4%)	212 (79.1%)
Sponsor Micro. Evaluable Patients	50 (18.4%)	47 (17.5%)
FDA Clinically Evaluable Patients	213 (78.3%)	208 (77.6%)
FDA Micro. Evaluable Patients	50 (18.4%)	48 (17.9%)

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TABLE 20: STUDY 51: BASELINE DEMOGRAPHICS IN FDA CLINICAL EVALUABLE PATIENTS			
Parameters	Linezolid (N=213)	Cefpodoxime (N=208)	P-value
Gender			
Male	104 (48.8%)	114 (54.8%)	0.219
Female	109 (51.2%)	94 (45.2%)	
Age (yrs.)			
Total Reporting	213	208	*0.571
Range (Max, Min)	(95, 19)	(93, 18)	
Mean ± SD	47.9 ± 17.4	48.9 ± 18.2	
Distribution			
18 ~ 50	122 (57.3%)	110 (52.9%)	0.365
≥ 51	91 (42.7%)	98 (47.1%)	
Race			
White	158 (74.2%)	171 (82.2%)	0.135
Black	21 (9.9%)	15 (7.2%)	
Other	34 (16.0%)	22 (10.6%)	
Weight (kg)			
Total Reporting	213	208	*0.446
Mean ± SD	73.4 ± 18.0	74.8 ± 19.3	
Site			
USA	57 (26.8%)	63 (30.3%)	0.423
Non-USA	156 (73.2%)	145 (69.7%)	

* By t test. All others in the table, by Chi-squared test.

Reviewer's Note: The clinical responses are shown for ITT, MITT, FDA clinically evaluable, Sponsor clinically evaluable, FDA microbiologically evaluable, and Sponsor microbiologically evaluable populations in Tables 21, 22, 23, 24, 25, and 26, respectively, which include sensitivity analyses by counting missing and indeterminate as failure. The results from these analyses showed that the cure rates of linezolid were comparable to those of cefpodoxime. The results from sensitivity analyses were generally in line with those from protocol-specified analyses.

TABLE 21: STUDY 51: CLINICAL RESPONSES OF ITT PATIENTS AT TOC VISIT		
FDA'S ASSESSMENT		
Clinical Response	Linezolid (N=227)	Cefpodoxime (N=222)
Cured	188 (82.8%)	192 (86.5%)
Failed	39 (17.2%)	30 (13.5%)
Line. Versus Cefp.: Difference in Cure Rate	-3.7%, 95% C.I.: -10.8%, 3.4%	
SPONSOR'S ASSESSMENT		
Clinical Response	Linezolid (N=227)	Cefpodoxime (N=225)
Cured	186 (81.9%)	193 (85.8%)
Failed	41 (18.1%)	32 (14.2%)
Line. Versus Cefp.: Difference in Cure Rate	-3.8%, 95% C.I.: -11.1%, 3.4%	

TABLE 22: STUDY 51: CLINICAL RESPONSES OF ITT PATIENTS AT TOC VISIT (COUNTING INDETERMINATE AND MISSING AS FAILURE)		
FDA'S ASSESSMENT		
Clinical Response	Linezolid (N=272)	Cefpodoxime (N=268)
Cured	188 (69.1%)	192 (71.6%)
Failed	39 (14.3%)	30 (11.2%)
Indeterminate	5 (1.8%)	8 (3.0%)
Missing	40 (14.7%)	38 (14.2%)
Line. Versus Cefp.: Difference in Cure Rate	-2.5%, 95% C.I.: -10.6%, 5.5%	
SPONSOR'S ASSESSMENT		
Clinical Response	Linezolid (N=272)	Cefpodoxime (N=268)
Cured	186 (68.4%)	193 (72.0%)
Failed	41 (15.1%)	32 (11.9%)
Indeterminate	26 (9.6%)	33 (12.3%)
Missing	19 (7.0%)	10 (3.7%)
Line. Versus Cefp.: Difference in Cure Rate	-3.6%, 95% C.I.: -11.7%, 4.4%	

TABLE 23: STUDY 51: CLINICAL RESPONSES OF MITT PATIENTS AT TOC VISIT		
FDA'S ASSESSMENT		
Clinical Response	Linezolid (N=54)	Cefpodoxime (N=52)
Cured	46 (85.2%)	42 (80.8%)
Failed	8 (14.8%)	10 (19.2%)
Line. Versus Cefp.: Difference in Cure Rate	4.4%, 95% C.I.: -11.8%, 20.6%	
SPONSOR'S ASSESSMENT		
Clinical Response	Linezolid (N=55)	Cefpodoxime (N=52)
Cured	46 (83.6%)	42 (80.8%)
Failed	9 (16.4%)	10 (19.2%)
Line. Versus Cefp.: Difference in Cure Rate	2.9%, 95% C.I.: -13.5%, 19.2%	

TABLE 24: STUDY 51: CLINICAL RESPONSES OF MITT PATIENTS AT TOC VISIT (COUNTING INDETERMINATE AND MISSING AS FAILURE)		
FDA'S ASSESSMENT		
Clinical Response	Linezolid (N=60)	Cefpodoxime (N=60)
Cured	46 (76.7%)	42 (70.0%)
Failed	8 (13.3%)	10 (16.7%)
Indeterminate	2 (3.3%)	1 (1.7%)
Missing	4 (6.7%)	7 (11.7%)
Line. Versus Cefp.: Difference in Cure Rate	6.7%, 95% C.I.: -10.8%, 24.1%	
SPONSOR'S ASSESSMENT		
Clinical Response	Linezolid (N=60)	Cefpodoxime (N=60)
Cured	46 (76.7%)	42 (70.0%)
Failed	9 (15.0%)	10 (16.7%)
Indeterminate	4 (6.7%)	7 (11.7%)
Missing	1 (1.7%)	1 (1.7%)
Line. Versus Cefp.: Difference in Cure Rate	6.7%, 95% C.I.: -10.8%, 24.1%	

TABLE 25: STUDY 51: CLINICAL RESPONSES OF CLINICAL EVALUABLE PATIENTS AT TOC VISIT		
FDA'S ASSESSMENT FOR FDA EVALUABLE PATIENTS		
Clinical Response	Linezolid (N=213)	Cefpodoxime (N=208)
Cured	180 (84.5%)	187 (89.9%)
Failed	33 (15.5%)	21 (10.1%)
Line. Versus Cefp.: Difference in Cure Rate	-4.5%, 95% C.I.: -12.2%, 1.4%	
SPONSOR'S ASSESSMENT FOR SPONSOR EVALUABLE PATIENTS		
Clinical Response	Linezolid (N=201)	Cefpodoxime (N=206)
Cured	180 (89.6%)	187 (90.8%)
Failed	21 (10.4%)	19 (9.2%)
Line. Versus Cefp.: Difference in Cure Rate	-1.2%, 95% C.I.: -7.5%, 5.1%	
SPONSOR'S ASSESSMENT FOR SPONSOR EVALUABLE PATIENTS (COUNTING INDETERMINATE AS FAILURE)		
Clinical Response	Linezolid (N=205)	Cefpodoxime (N=212)
Cured	180 (87.8%)	187 (88.2%)
Failed	21 (10.2%)	19 (9.0%)
Indeterminate	4 (2.0%)	6 (2.8%)
Line. Versus Cefp.: Difference in Cure Rate	-0.4%, 95% C.I.: -7.1%, 6.3%	

TABLE 26: STUDY 51: CLINICAL RESPONSES OF MICROBIOLOGICAL EVALUABLE PATIENTS AT TOC VISIT		
FDA'S ASSESSMENT FOR FDA EVALUABLE PATIENTS		
Clinical Response	Linezolid (N=50)	Cefpodoxime (N=48)
Cured	44 (88.0%)	39 (81.3%)
Failed	6 (12.0%)	9 (18.7%)
Line. Versus Cefp.: Difference in Cure Rate	6.8%, 95% C.I.: -9.5%, 23.0%	
SPONSOR'S ASSESSMENT FOR SPONSOR EVALUABLE PATIENTS		
Clinical Response	Linezolid (N=49)	Cefpodoxime (N=47)
Cured	44 (89.8%)	39 (83.0%)
Failed	5 (10.2%)	8 (17.0%)
Line. Versus Cefp.: Difference in Cure Rate	6.8%, 95% C.I.: -9.0%, 22.6%	
SPONSOR'S ASSESSMENT FOR SPONSOR EVALUABLE PATIENTS (COUNTING INDETERMINATE AS FAILURE)		
Clinical Response	Linezolid (N=50)	Cefpodoxime (N=47)
Cured	44 (88.0%)	39 (83.0%)
Failed	5 (10.0%)	8 (17.0%)
Indeterminate	1 (2.0%)	0 (0%)
Line. Versus Cefp.: Difference in Cure Rate	5.0%, 95% C.I.: -11.1%, 21.1%	

Reviewer's Note: Subset analyses of clinical response for microbiologically evaluable population with bacteremia is shown in Table 27. The numbers of patients in this subgroup were extremely small.

TABLE 27: STUDY 51: CLINICAL RESPONSES OF MICROBIOLOGICAL EVALUABLE PATIENTS WITH BACTEREMIA AT TOC VISIT		
FDA'S ASSESSMENT FOR FDA EVALUABLE PATIENTS		
Clinical Response	Linezolid (N=3)	Cefpodoxime (N=5)
Cured	3 (100%)	3 (60.0%)
Failed	0 (0%)	2 (40.0%)
SPONSOR'S ASSESSMENT FOR SPONSOR EVALUABLE PATIENTS		
Clinical Response	Linezolid (N=3)	Cefpodoxime (N=5)
Cured	3 (100%)	3 (60.0%)
Failed	0 (0%)	2 (40.0%)

Reviewer's Note: Subset analyses for different baseline disease characteristics by gender, age, race, and center site for clinical cure rates in the FDA clinically evaluable population are shown in Table 28. The cure rate of white patients was numerically lower in linezolid arm.

TABLE 28: STUDY 51: SUBSET ANALYSES BY DEMOGRAPHIC ASPECTS OF CLINICAL CURE RATE OF FDA CLINICAL EVALUABLE PATIENTS AT TOC VISIT

Subset	Linezolid (N=213)	Cefpodoxime (N=208)	95% C.I.	Breslow-Day's P-value
Male	88/104 (84.6%)	102/114 (89.5%)	(-14.7%, 5.0%)	0.839
Female	92/109 (84.4%)	85/94 (90.4%)	(-16.1%, 4.0%)	
18~44 yrs	80/97 (82.5%)	78/92 (84.8%)	(-13.9%, 9.3%)	0.378
45~64 yrs	61/73 (83.6%)	65/69 (94.2%)	(-22.2%, 0.9%)	
≥ 65 yrs	39/43 (90.7%)	44/47 (93.6%)	(-16.3%, 10.5%)	
18~50 yrs	102/122 (83.6%)	95/110 (86.4%)	(-12.8%, 7.3%)	0.254
≥ 51 yrs	78/91 (85.7%)	92/98 (93.9%)	(-17.8%, 1.5%)	
White	132/158 (83.5%)	157/171 (91.8%)	(-16.0%, -0.6%)	0.059
Other	48/55 (87.3%)	30/37 (81.1%)	(-11.5%, 23.8%)	
USA	45/57 (78.9%)	58/63 (92.1%)	(-27.3%, 1.1%)	0.174
Non-USA	135/156 (86.5%)	129/145 (89.0%)	(-10.5%, 5.6%)	

Reviewer's Note: Subset analyses for the different baseline disease characteristics of the clinical outcome in FDA clinically evaluable population are summarized in Table 29. The clinical cure rates of the linezolid group were numerically worse than those of the cefpodoxime group in most of these subgroups.

TABLE 29: STUDY 51: SUBSET ANALYSES OF CLINICAL CURE RATE OF FDA CLINICAL EVALUABLE PATIENTS AT TOC VISIT

Subset	Linezolid (N=213)	Cefpodoxime (N=208)
With Multilobar Pneumonia at Baseline		
Yes	37/46 (80.4%)	34/39 (87.2%)
No	143/167 (85.6%)	153/169 (90.5%)
With Bilateral Pneumonia at Baseline		
Yes	25/30 (83.3%)	24/27 (88.9%)
No	155/183 (84.7%)	163/181 (90.1%)
With Hypotension at Baseline		
Yes	6/8 (75.0%)	10/12 (83.3%)
No	174/205 (84.9%)	177/196 (90.3%)
With Tachypnea at Baseline		
Yes	8/9 (88.9%)	6/7 (85.7%)
No	172/204 (84.3%)	181/201 (90.1%)
With BUN>7mmol/L at Baseline		
Yes	20/26 (76.9%)	22/23 (95.7%)
No	160/187 (85.6%)	165/185 (89.2%)
With HIV Infected		
Yes	3/4 (75.0%)	2/2 (100%)
No	177/209 (84.7%)	185/206 (89.8%)

Reviewer's Note: The FDA's assessment of patient clinical outcome by baseline pathogen for the FDA microbiologically evaluable population is presented in Table 30. The clinical cure rates of the linezolid group were numerically better than those of the cefpodoxime group in most of these subgroups.

TABLE 30: STUDY 51: SUBSET ANALYSES OF CLINICAL CURE RATE OF FDA MICROBIOLOGICAL EVALUABLE PATIENTS AT TOC VISIT		
Subset	Linezolid (N=50)	Cefpodoxime (N=48)
<i>With S. pneumoniae</i>		
Yes	25/27 (92.6%)	19/21 (90.5%)
No	19/23 (82.6%)	20/27 (74.1%)
<i>With S. pneumoniae and Bacteremia</i>		
Yes	3/3 (100%)	3/5 (60.0%)
No	41/47 (87.2%)	36/43 (83.7%)
<i>With S. aureus</i>		
Yes	11/12 (91.7%)	9/12 (75.0%)
No	33/38 (86.8%)	30/36 (83.3%)
<i>With S. aureus and Bacteremia</i>		
Yes	0/0 (NA)	0/0 (NA)
No	44/50 (88.0%)	39/48 (81.3%)
<i>With S. aureus and MRSA</i>		
Yes	1/1 (100%)	0/1 (0%)
No	43/49 (87.8%)	39/47 (83.0%)
<i>With H. influenzae</i>		
Yes	11/13 (84.6%)	13/15 (86.7%)
No	33/37 (89.2%)	26/33 (78.8%)

Reviewer's Note: The microbiological responses are shown for MITT, FDA microbiologically evaluable, and Sponsor microbiologically evaluable populations in Tables 31, 32, and 33, which include sensitivity analyses by counting missing and indeterminate as failure and the two analyses reached the similar results. The 95% confidence interval results from these analyses showed that the lower bounds of confidence intervals were smaller than -15%. The results from sensitivity analyses were generally in line with those from protocol-specified analyses.

TABLE 31: STUDY 51: MICROBIOLOGICAL RESPONSES OF MITT PATIENTS AT TOC VISIT		
FDA'S ASSESSMENT		
Microbiological Response	Linezolid (N=55)	Cefpodoxime (N=53)
Success	45 (81.8%)	45 (84.9%)
Failed	10 (18.2%)	8 (15.1%)
Line. Versus Cefp.: Difference in Success Rate	-3.1%, 95% C.I.: -19.0%, 12.8%	
SPONSOR'S ASSESSMENT		
Microbiological Response	Linezolid (N=55)	Cefpodoxime (N=52)
Cured	45 (81.8%)	45 (86.5%)
Failed	10 (18.2%)	7 (13.5%)
Line. Versus Cefp.: Difference in Success Rate	-4.7%, 95% C.I.: -20.4%, 10.9%	

TABLE 32: STUDY 51: MICROBIOLOGICAL RESPONSES OF MITT PATIENTS AT TOC VISIT (COUNTING INDETERMINATE AND MISSING AS FAILURE)		
FDA'S ASSESSMENT		
Microbiological Response	Linezolid (N=60)	Cefpodoxime (N=60)
Success	45 (75.0%)	45 (75.0%)
Failed	10 (16.7%)	8 (13.3%)
Indeterminate	4 (6.7%)	7 (11.7%)
Missing	1 (1.7%)	0 (0%)
Line. Versus Cefp.: Difference in Success Rate	0%, 95% C.I.: -17.2%, 17.2%	
SPONSOR'S ASSESSMENT		
Microbiological Response	Linezolid (N=60)	Cefpodoxime (N=60)
Success	45 (75.0%)	45 (75.0%)
Failed	10 (16.7%)	7 (11.7%)
Indeterminate	4 (6.7%)	7 (11.7%)
Missing	1 (1.7%)	1 (1.7%)
Line. Versus Cefp.: Difference in Success Rate	0%, 95% C.I.: -17.2%, 17.2%	

TABLE 33: STUDY 51: MICROBIOLOGICAL RESPONSES OF MICROBIOLOGICAL EVALUABLE PATIENTS AT TOC VISIT		
FDA'S ASSESSMENT FOR FDA EVLUABLE PATIENTS		
Microbiological Response	Linezolid (N=50)	Cefpodoxime (N=48)
Success	43 (86.0%)	42 (87.5%)
Failed	7 (14.0%)	6 (12.5%)
Line. Versus Cefp.: Difference in Success Rate	-1.5%, 95% C.I.: -17.0%, 14.0%	
SPONSOR'S ASSESSMENT FOR SPONSOR EVLUABLE PATIENTS		
Microbiological Response	Linezolid (N=49)	Cefpodoxime (N=47)
Success	43 (87.8%)	42 (89.4%)
Failed	6 (12.2%)	5 (10.6%)
Line. Versus Cefp.: Difference in Success Rate	-1.6%, 95% C.I.: -16.4%, 13.2%	
SPONSOR'S ASSESSMENT FOR SPONSOR EVLUABLE PATIENTS (COUNTING INDETERMINATE AS FAILURE)		
Microbiological Response	Linezolid (N=50)	Cefpodoxime (N=47)
Success	43 (86.0%)	42 (89.4%)
Failed	6 (12.0%)	5 (10.6%)
Indeterminate	1 (2.0%)	0 (0%)
Line. Versus Cefp.: Difference in Success Rate	-3.4%, 95% C.I.: -18.5%, 11.7%	

Reviewer's Note: Patient microbiological outcomes by baseline pathogen for MITT and microbiologically evaluable populations are presented in Tables 34 and 35, respectively. Numerically, two treatments appeared similar outcomes.

TABLE 34: STUDY 51: MICROBIOLOGICAL SUCCESS RATES BY PATHOGEN OF MITT PATIENTS AT TOC VISIT			
FDA'S ASSESSMENT			
Pathogen	Linezolid	Cefpodoxime	Fisher's P-value
<i>H. influenzae</i>	10/14 (71.4%)	14/16 (87.5%)	0.378
<i>S. aureus</i>	12/14 (85.7%)	11/13 (84.6%)	1.000
<i>S. pneumoniae</i>	24/27 (88.9%)	19/22 (86.4%)	1.000
SPONSOR'S ASSESSMENT			
Pathogen	Linezolid	Cefpodoxime	Fisher's P-value
<i>H. influenzae</i>	10/14 (71.4%)	14/16 (87.5%)	0.378
<i>S. aureus</i>	12/14 (85.7%)	11/13 (84.6%)	1.000
<i>S. pneumoniae</i>	24/27 (88.9%)	19/21 (90.5%)	1.000

TABLE 35: STUDY 51: MICROBIOLOGICAL SUCCESS RATES BY PATHOGEN OF MICROBIOLOGICAL EVALUABLE PATIENTS AT TOC VISIT			
FDA'S ASSESSMENT FOR SPONSOR EVALUABLE PATIENTS			
Pathogen	Linezolid	Cefpodoxime	Fisher's P-value
<i>H. influenzae</i>	10/13 (76.9%)	13/15 (86.7%)	0.639
<i>S. aureus</i>	11/12 (91.7%)	11/12 (91.7%)	0.383
<i>S. pneumoniae</i>	24/27 (88.9%)	19/21 (90.5%)	1.000
SPONSOR'S ASSESSMENT FOR SPONSOR EVALUABLE PATIENTS			
Pathogen	Linezolid	Cefpodoxime	Fisher's P-value
<i>H. influenzae</i>	10/12 (83.3%)	13/15 (86.7%)	1.000
<i>S. aureus</i>	11/12 (91.7%)	11/12 (91.7%)	1.000
<i>S. pneumoniae</i>	24/27 (88.9%)	19/21 (90.5%)	1.000

Reviewer's Note: The summaries of safety outcomes are presented in Table 36. The percentages of patients who experienced any study emergent adverse events, drug related adverse events, adverse events causing study medication discontinuation, or serious adverse events in the linezolid group were notably greater than in the cefpodoxime group.

TABLE 36: STUDY 51: ADVERSE EVENT RATES			
Safety Outcomes	Linezolid (N=272)	Cefpodoxime (N=268)	Fisher's P-value
Died	2 (0.7%)	0 (0%)	0.499
Died with Infection Related by TOC	1 (0.4%)	0 (0%)	1.000
Serious AEs	21 (7.7%)	9 (3.4%)	0.037
Discontinuation Due To AEs	27 (9.9%)	7 (2.6%)	0.001
Discontinuation Due To Drug related AEs	10 (3.7%)	2 (0.7%)	0.037
With Any AE	164 (60.3%)	115 (42.9%)	< 0.001
Digestive	77 (28.4%)	54 (20.1%)	0.028
Body	69 (25.4%)	44 (16.4%)	0.011
Respiratory	48 (17.6%)	40 (14.9%)	0.416
Nervous	24 (8.8%)	17 (6.3%)	0.330
Special Senses	19 (7.0%)	6 (2.2%)	0.013
Skin	17 (6.3%)	6 (2.2%)	0.031
Urogenital	16 (5.9%)	9 (3.4%)	0.219
Cardiovascular	11 (4.0%)	9 (3.4%)	0.821
Hemic and Lymphatic	6 (2.2%)	1 (0.4%)	0.123
Metabolic and Nutritional	6 (2.2%)	5 (1.9%)	1.000
Musculo-Skeletal	3 (1.1%)	4 (1.5%)	0.723
Endocrine	0 (0%)	1 (0.4%)	0.496
With Drug Related AE	86 (31.6%)	48 (17.9%)	< 0.001
Digestive	53 (19.5%)	32 (11.9%)	0.018
Body	24 (8.8%)	11 (4.1%)	0.035
Skin	11 (4.0%)	3 (1.1%)	0.054
Nervous	10 (3.7%)	11 (4.1%)	0.827
Metabolic and Nutritional	5 (1.8%)	3 (1.1%)	0.725
Special Senses	5 (1.8%)	4 (1.5%)	1.000
Urogenital	5 (1.8%)	6 (2.2%)	0.771
Cardiovascular	1 (0.4%)	2 (0.7%)	0.622
Hemic and Lymphatic	1 (0.4%)	0 (0%)	1.000
Respiratory	1 (0.4%)	2 (0.7%)	0.622

Note: P-value should be interpreted with caution and adjusted with multiplicity.

Reviewer's Summaries and Conclusions: See Section IV.

**APPEARS THIS WAY
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II. HOSPITAL ACQUIRED PNEUMONIAE

II.A. INTRODUCTION

The Sponsor submitted one phase III controlled study as evidence to support that linezolid plus aztreonam therapy was safe and efficacious for the treatment of nosocomial pneumonia when compared with vancomycin plus aztreonam therapy. Statistical review focuses on this comparative clinical trial which formed the basis of this application. The general design of the studies is as follows:

Study 48A was a randomized, double-blind, comparative, multicenter (90 centers), and multinational trial which compared the efficacy and safety of a 10 to 14 consecutive days course of therapy with linezolid oral (600 mg BID) plus aztreonam IV (1-2 g Q3D) with those of a 10 to 14 consecutive days course of therapy with vancomycin IV (1 g BID) plus aztreonam IV (1-2 g Q3D) in the treatment of nosocomial pneumonia. It was initiated October 13, 1998 and completed on July 16, 1999.

II.B. STUDY 48A

II.B.1. METHODS

In Study 48a, approximately 400 patients at least 18 years of age with hospital acquired pneumonia were eligible for enrollment in this study provided that they met the inclusion/exclusion criteria. Eligible patients were randomly assigned in a 1:1 ratio to the two treatment groups and the trial was conducted in a double-blind fashion. Efficacy assessments were based on patient disposition with regard to 1) clinical signs and symptoms including body temperature and respiratory rate assessed after treatment as compared with those observed at baseline and 2) radiographic assessments after treatment compared with those conducted at baseline. The study consisted of a baseline/screening visit, a patient treatment evaluation phase, an EOT visit, and a F-U visit. The TOC evaluation was conducted at the F-U visit, 15 to 21 days after the final dose of study medication. The safety of the study medication was monitored throughout the study by physical examination findings, vital sign assessments, laboratory evaluations, and assessment of adverse events.

Primary efficacy was assessed by evaluating clinical and microbiological outcomes at the TOC (F-U) visits. Analyses of efficacy variables were done separately for ITT, MITT, clinically evaluable, and microbiologically evaluable patients.

Reviewer's Note: *The Medical Officer generally agreed with the Sponsor's evaluability criteria for constructing ITT, MITT, clinically evaluable, and microbiologically evaluable populations. However, for certain groups of patients, such as who were discontinued from therapy for lack of efficacy and received at least four doses of study drug, who died of their initial infection before follow-up, and who were with missing clinical outcomes, the definition of analytic population was different from the Sponsor's. The Medical Officer also applied different decision rules from the Sponsor in classifying outcomes, mainly in how outcomes of failure and missing were defined. The algorithm used for determining outcomes by this reviewer was adjusted accordingly to the changes by the Medical Officer. The Medical Officer focused primarily on clinical outcome in evaluating efficacy.*

Please refer to the Medical Officer's review for detailed descriptions of differences between the FDA's and the Sponsor's analytic populations and outcomes.

All patients who received at least one dose of study medication were evaluable for safety. All adverse events that occurred between receipt of the first dose of study medication and the final visit were recorded.

Reviewer's Note: *FDA reviewers used the same definitions for adverse events, drug-related adverse events, and serious adverse events as the Sponsor. Death was attributed to infection using the criteria defined by the Medical Officer.*

The comparisons of interest in these studies were conducted between linezolid and vancomycin.

Reviewer's Note: *The following statistical analyses were performed by the reviewer to evaluate the efficacy and safety of linezolid versus vancomycin.*

Evaluation of treatments difference with respect to the primary efficacy variables was assessed by computing the two-tailed 95% confidence interval of the difference in response rates. The confidence intervals were computed using a normal approximation to the binomial, and included a continuity correction.

In certain evaluation groups with missing and indeterminate outcomes, sensitivity analyses were performed, whereas missing and indeterminate outcomes were counted as failure.

Subset analyses by gender, age, race, and center site were performed for the primary efficacy variables. Homogeneity of treatment effect across subgroups was assessed via Breslow-Day's test.

This reviewer conducted safety analyses with the following variables: the rate of at least one adverse event, the rate of at least one drug-related adverse event, the rate of serious adverse events, the rate of discontinuation due to adverse events, the rate of mortality, and the rate of mortality related to infection. Statistical comparisons between the two treatment groups were performed using Fisher's exact test.

Prior to performing efficacy analyses, this reviewer assessed the comparability of the treatment groups with respect to pretreatment characteristics including demographics, baseline disease characteristics, and evaluability status. Quantitative variables were assessed using the t-test. Qualitative variables were assessed using Fisher's exact test.

All tests were two-sided and used a 5% level of significance. The test for homogeneity of treatment effect was deemed significant at the 0.15 level.

II.B.2. RESULTS

Of the 402 patients who enrolled in the study, 205 were randomized to the linezolid treatment group, and 197 were randomized to the vancomycin treatment group. A total of 396 patients received study medication and were included in the ITT analysis group, of whom 203 received linezolid and 193 received vancomycin.

Reviewer's Note: *The number and percentage of patients included in each analysis group, evaluated by either the Sponsor or the Medical Officer, are presented in Table 37. There were no notable treatment differences with respect to the percentage of patients included in each analysis group. Demographic data are described for the FDA clinically evaluable patients in Table 38, and no statistically significant differences were detected in this pretreatment characteristics of the two treatment groups.*

TABLE 37: STUDY 48a: NUMBER OF PATIENTS INCLUDED IN EACH EVALUATION GROUP		
Evaluation Group	Patients Included.	
	Linezolid	Vancomycin
All Randomized Patients	205	197
ITT Patients	203 (100%)	193 (100%)
MITT Patients	94 (46.3%)	83 (43.0%)
Sponsor Clinically Evaluable Patients	108 (53.2%)	97 (49.2%)
Sponsor Micro. Evaluable Patients	54 (26.6%)	40 (20.7%)
FDA Clinically Evaluable Patients	122 (60.1%)	103 (53.4%)
FDA Micro. Evaluable Patients	54 (26.6%)	41 (21.2%)

TABLE 38: STUDY 48a: BASELINE DEMOGRAPHICS IN FDA CLINICAL EVALUABLE PATIENTS			
Parameters	Linezolid (N=122)	Vancomycin (N=103)	P-value
Gender			
Male	86 (70.5%)	69 (67.0%)	0.572
Female	36 (29.5%)	34 (33.0%)	
Age (yrs.)			
Total Reporting	122	103	*0.189
Range (Max, Min)	(91, 18)	(90, 18)	
Mean ± SD	62.9 ± 18.5	59.7 ± 17.3	
Distribution			
18 ~ 50	30 (24.6%)	32 (31.1%)	0.297
≥ 51	92 (75.4%)	71 (68.9%)	
Race			
White	112 (91.8%)	95 (92.2%)	0.051
Black	7 (5.7%)	1 (1.0%)	
Other	3 (2.5%)	7 (6.8%)	
Weight (kg)			
Total Reporting	119	102	*0.776
Mean ± SD	73.1 ± 18.1	72.4 ± 18.3	
Site			
USA	43 (35.3%)	27 (26.2%)	0.145
Non-USA	79 (64.7%)	76 (73.8%)	

* By t test. All others in the table, by Chi-squared test.

Reviewer's Note: The clinical responses are shown for ITT, MITT, FDA clinically evaluable, Sponsor clinically evaluable, FDA microbiologically evaluable, and Sponsor microbiologically evaluable populations in Tables 39, 40, 41, 42, 43, and 44, respectively, which include sensitivity analyses by counting missing and indeterminate as failure. The results from these analyses showed that the cure rates of linezolid were comparable to those of vancomycin. The results from sensitivity analyses were generally in line with those from protocol-specified analyses.

TABLE 39: STUDY 48a: CLINICAL RESPONSES OF ITT PATIENTS AT TOC VISIT		
FDA'S ASSESSMENT		
Clinical Response	Linezolid (N=174)	Vancomycin (N=164)
Cured	85 (48.9%)	73 (44.5%)
Failed	89 (51.1%)	91 (55.5%)
Line. Versus Vanc.: Difference in Cure Rate	4.3%, 95% C.I.: -6.9%, 15.6%	
SPONSOR'S ASSESSMENT		
Clinical Response	Linezolid (N=161)	Vancomycin (N=142)
Cured	86 (53.4%)	74 (52.1%)
Failed	75 (46.6%)	68 (47.9%)
Line. Versus Vanc.: Difference in Cure Rate	1.3%, 95% C.I.: -10.6%, 13.2%	

TABLE 40: STUDY 48a: CLINICAL RESPONSES OF ITT PATIENTS AT TOC VISIT (COUNTING INDETERMINATE AND MISSING AS FAILURE)		
FDA'S ASSESSMENT		
Clinical Response	Linezolid (N=203)	Vancomycin (N=193)
Cured	85 (41.9%)	73 (37.8%)
Failed	89 (43.8%)	91 (47.2%)
Indeterminate	5 (2.5%)	7 (3.6%)
Missing	24 (11.8%)	22 (11.4%)
Line. Versus Vanc.: Difference in Cure Rate	4.0%, 95% C.I.: -6.1%, 14.2%	
SPONSOR'S ASSESSMENT		
Clinical Response	Linezolid (N=203)	Vancomycin (N=193)
Cured	86 (42.4%)	74 (38.3%)
Failed	75 (37.0%)	68 (35.2%)
Indeterminate	26 (12.8%)	31 (16.1%)
Missing	16 (7.9%)	20 (10.4%)
Line. Versus Vanc.: Difference in Cure Rate	4.0%, 95% C.I.: -6.1%, 14.2%	

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TABLE 41: STUDY 48a: CLINICAL RESPONSES OF MITT PATIENTS AT TOC VISIT		
FDA'S ASSESSMENT		
Clinical Response	Linezolid (N=82)	Vancomycin (N=72)
Cured	47 (57.3%)	33 (45.8%)
Failed	35 (42.7%)	39 (54.2%)
Line. Versus Vanc.: Difference in Cure Rate	11.5%, 95% C.I.: -5.5%, 28.5%	
SPONSOR'S ASSESSMENT		
Clinical Response	Linezolid (N=78)	Vancomycin (N=63)
Cured	49 (62.8%)	33 (52.4%)
Failed	29 (37.2%)	30 (47.6%)
Line. Versus Vanc.: Difference in Cure Rate	10.4%, 95% C.I.: -7.3%, 28.2%	

TABLE 42: STUDY 48a: CLINICAL RESPONSES OF MITT PATIENTS AT TOC VISIT (COUNTING INDETERMINATE AND MISSING AS FAILURE)		
FDA'S ASSESSMENT		
Clinical Response	Linezolid (N=94)	Vancomycin (N=83)
Cured	47 (50.0%)	33 (39.8%)
Failed	35 (37.2%)	39 (40.0%)
Indeterminate	2 (2.1%)	3 (3.6%)
Missing	10 (10.6%)	8 (9.6%)
Line. Versus Vanc.: Difference in Cure Rate	10.2%, 95% C.I.: -5.5%, 26.0%	
SPONSOR'S ASSESSMENT		
Clinical Response	Linezolid (N=94)	Vancomycin (N=83)
Cured	49 (52.1%)	33 (39.8%)
Failed	29 (30.9%)	30 (36.1%)
Indeterminate	12 (12.8%)	16 (19.3%)
Missing	4 (4.3%)	4 (4.8%)
Line. Versus Vanc.: Difference in Cure Rate	12.4%, 95% C.I.: -3.4%, 28.1%	

TABLE 43: STUDY 48a: CLINICAL RESPONSES OF CLINICAL EVALUABLE PATIENTS AT TOC VISIT		
FDA'S ASSESSMENT FOR FDA EVALUABLE PATIENTS		
Clinical Response	Linezolid (N=122)	Vancomycin (N=103)
Cured	70 (57.4%)	62 (60.2%)
Failed	52 (42.6%)	41 (39.8%)
Line. Versus Vanc.: Difference in Cure Rate	-2.8%, 95% C.I.: -16.6%, 11.0%	
SPONSOR'S ASSESSMENT FOR SPONSOR EVALUABLE PATIENTS		
Clinical Response	Linezolid (N=107)	Vancomycin (N=91)
Cured	71 (66.4%)	62 (68.1%)
Failed	36 (33.6%)	29 (31.9%)
Line. Versus Vanc.: Difference in Cure Rate	-1.8%, 95% C.I.: -15.9%, 12.3%	
SPONSOR'S ASSESSMENT FOR SPONSOR EVALUABLE PATIENTS (COUNTING INDETERMINATE AS FAILURE)		
Clinical Response	Linezolid (N=108)	Vancomycin (N=97)
Cured	71 (65.7%)	62 (63.9%)
Failed	36 (33.3%)	29 (29.9%)
Indeterminate	1 (0.9%)	6 (6.2%)
Line. Versus Vanc.: Difference in Cure Rate	1.8%, 95% C.I.: -12.2%, 15.9%	

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TABLE 44: STUDY 48a: CLINICAL RESPONSES OF MICROBIOLOGICAL EVALUABLE PATIENTS AT TOC VISIT		
FDA'S ASSESSMENT FOR FDA EVALUABLE PATIENTS		
Clinical Response	Linezolid (N=54)	Vancomycin (N=41)
Cured	36 (66.7%)	26 (63.4%)
Failed	18 (33.3%)	15 (36.6%)
Line. Versus Vanc.: Difference in Cure Rate	3.3%, 95% C.I.: -18.3%, 24.8%	
SPONSOR'S ASSESSMENT FOR SPONSOR EVALUABLE PATIENTS		
Clinical Response	Linezolid (N=53)	Vancomycin (N=38)
Cured	37 (69.8%)	26 (68.4%)
Failed	16 (30.2%)	12 (31.6%)
Line. Versus Vanc.: Difference in Cure Rate	1.4%, 95% C.I.: -20.1%, 22.9%	
SPONSOR'S ASSESSMENT FOR SPONSOR EVALUABLE PATIENTS (COUNTING INDETERMINATE AS FAILURE)		
Clinical Response	Linezolid (N=54)	Vancomycin (N=40)
Cured	37 (68.5%)	26 (65.0%)
Failed	16 (29.6%)	12 (30.0%)
Indeterminate	1 (1.9%)	2 (5.0%)
Line. Versus Vanc.: Difference in Cure Rate	3.5%, 95% C.I.: -17.9%, 25.0%	

Reviewer's Note: Subset analyses of clinical response for microbiologically evaluable population with bacteremia is shown in Table 45. The number of patients in this subgroup was extremely small.

TABLE 45: STUDY 48a: CLINICAL RESPONSES OF MICROBIOLOGICAL EVALUABLE PATIENTS WITH BACTEREMIA AT TOC VISIT		
FDA'S ASSESSMENT FOR FDA EVALUABLE PATIENTS		
Clinical Response	Linezolid (N=4)	Vancomycin (N=6)
Cured	2 (50.0%)	4 (66.7%)
Failed	2 (50.0%)	2 (33.3%)
SPONSOR'S ASSESSMENT FOR SPONSOR EVALUABLE PATIENTS		
Clinical Response	Linezolid (N=5)	Vancomycin (N=6)
Cured	2 (40.0%)	4 (66.7%)
Failed	3 (60.0%)	2 (33.3%)

Reviewer's Note: Subset analyses by gender, age, race, and center site for clinical cure rates in the FDA clinically evaluable population are shown in Table 46. The cure rate of the patients in "Other" ethical group was numerically lower in linezolid arm, however, its sample size was extremely small.

TABLE 46: STUDY 48a: SUBSET ANALYSES BY DEMOGRAPHIC ASPECTS OF CLINICAL CURE RATE OF FDA CLINICAL EVALUABLE PATIENTS AT TOC VISIT				
Subset	Linezolid (N=122)	Vancomycin (N=103)	95% C.I.	Breslow-Day's P-value
Male	49/86 (57.0%)	44/69 (63.8%)	(-23.5%, 9.9%)	0.390
Female	21/36 (58.3%)	18/34 (52.9%)	(-20.7%, 31.5%)	
18-44 yrs	12/21 (57.1%)	12/23 (52.2%)	(-29.0%, 38.9%)	0.852
45-64 yrs	19/29 (65.5%)	22/31 (71.0%)	(-32.3%, 21.4%)	
≥ 65 yrs	39/72 (54.2%)	28/49 (57.1%)	(-22.7%, 16.8%)	
18-50 yrs	19/30 (63.3%)	18/32 (56.3%)	(-20.5%, 34.7%)	0.355
≥ 51 yrs	51/92 (55.4%)	44/71 (62.0%)	(-23.0%, 9.9%)	
White	65/112 (58.0%)	55/95 (57.9%)	(-14.3%, 14.6%)	0.104
Other	5/10 (50.0%)	7/8 (87.5%)	(-87.3%, 12.3%)	
USA	19/43 (44.2%)	13/27 (48.2%)	(-31.0%, 23.0%)	0.784
Non-USA	51/79 (64.6%)	49/76 (64.5%)	(-16.3%, 16.4%)	

Reviewer's Note: Subset analyses by baseline disease characteristics and other concomitant medicines of the clinical outcome in FDA clinically evaluable population are summarized in Tables 47 and 48.

TABLE 47: STUDY 48a: SUBSET ANALYSES BY PRETREATMENT VENTILATOR STATUS OF CLINICAL CURE RATE OF CLINICAL EVALUABLE PATIENTS AT TOC VISIT		
Subset	Linezolid (N=122)	Vancomycin (N=103)
On Vent at Baseline		
Yes	32/68 (47.1%)	19/48 (39.6%)
No	38/54 (70.4%)	43/55 (78.2%)
On Vent at Baseline and With MSRA Infection		
Yes	11/18 (61.1%)	3/5 (50.0%)
No	59/104 (56.7%)	59/98 (60.2%)

TABLE 48: STUDY 48a: SUBSET ANALYSES OF CLINICAL CURE RATE OF CLINICAL EVALUABLE PATIENTS AT TOC VISIT		
Subset	Linezolid (N=122)	Vancomycin (N=103)
With Pseudomonas Infection		
Yes	7/14 (50.0%)	6/12 (50.0%)
No	63/108 (58.3%)	56/91 (61.5%)
With MRSA Infection		
Yes	14/24 (58.3%)	8/12 (66.7%)
No	56/98 (57.1%)	54/91 (59.3%)
Receiving Aminoglycosides		
Yes	5/25 (20.0%)	6/20 (30.0%)
No	65/97 (67.0%)	56/83 (67.5%)
With Resistant Pneumococcus		
Yes	2/2 (100%)	0/0 (NA%)
No	68/120 (56.7%)	62/103 (60.2%)

Reviewer's Note: The FDA's assessment of patient clinical outcome by baseline pathogen for the FDA microbiologically evaluable population is presented in Table 49.

TABLE 49: STUDY 48a: SUBSET ANALYSES OF CLINICAL CURE RATE OF FDA MICROBIOLOGICAL EVALUABLE SUBJECTS AT TOC VISIT		
Subset	Linezolid (N=54)	Vancomycin (N=41)
<i>With S. pneumoniae</i>		
Yes	9/9 (100%)	9/10 (90.0%)
No	27/45 (60.0%)	17/31 (54.8%)
<i>With S. aureus</i>		
Yes	23/38 (60.5%)	14/23 (60.9%)
No	13/16 (81.3%)	12/18 (66.7%)

Reviewer's Note: The microbiological responses are shown for MITT, FDA microbiologically evaluable, and Sponsor microbiologically evaluable populations in Tables 50, 51, and 52, which include sensitivity analyses by counting missing and indeterminate as failure and the two analyses reached the similar results. The 95% confidence interval results from these analyses showed that the lower bound of confidence intervals was smaller than -20% in the microbiologically evaluable population. The results from sensitivity analyses were generally in line with those from protocol-specified analyses.

TABLE 50: STUDY 48a: MICROBIOLOGICAL RESPONSES OF MITT PATIENTS AT TOC VISIT		
FDA'S ASSESSMENT		
Microbiological Response	Linezolid (N=82)	Vancomycin (N=74)
Success	45 (54.9%)	37 (50.0%)
Failed	37 (45.1%)	37 (50.0%)
Line. Versus Vanc.: Difference in Success Rate	4.9%, 95% C.I.: -12.1%, 21.8%	
SPONSOR'S ASSESSMENT		
Microbiological Response	Linezolid (N=78)	Vancomycin (N=66)
Success	47 (60.3%)	37 (43.0%)
Failed	31 (39.7%)	29 (57.0%)
Line. Versus Vanc.: Difference in Success Rate	4.2%, 95% C.I.: -13.4%, 21.8%	

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ON ORIGINAL**

TABLE 51: STUDY 48a: MICROBIOLOGICAL RESPONSES OF MITT PATIENTS AT TOC VISIT (COUNTING INDETERMINATE AND MISSING AS FAILURE)		
FDA'S ASSESSMENT		
Microbiological Response	Linezolid (N=94)	Vancomycin (N=83)
Success	45 (47.9%)	37 (44.6%)
Failed	37 (39.4%)	37 (44.6%)
Indeterminate	9 (9.6%)	8 (9.6%)
Missing	3 (3.2%)	1 (1.2%)
Line. Versus Vanc.: Difference in Success Rate	3.3%, 95% C.I.: -12.5%, 19.1%	
SPONSOR'S ASSESSMENT		
Microbiological Response	Linezolid (N=94)	Vancomycin (N=83)
Success	47 (50.0%)	37 (44.6%)
Failed	31 (33.0%)	29 (34.9%)
Indeterminate	12 (12.8%)	13 (15.7%)
Missing	4 (4.3%)	4 (4.8%)
Line. Versus Vanc.: Difference in Success Rate	5.4%, 95% C.I.: -10.4%, 21.3%	

TABLE 52: STUDY 48a: MICROBIOLOGICAL RESPONSES OF MICROBIOLOGICAL EVALUABLE PATIENTS AT TOC VISIT		
FDA'S ASSESSMENT FOR FDA EVALUABLE PATIENTS		
Microbiological Response	Linezolid (N=54)	Vancomycin (N=41)
Success	35 (64.8%)	27 (65.9%)
Failed	19 (35.2%)	14 (34.2%)
Line. Versus Vanc.: Difference in Success Rate	-1.0%, 95% C.I.: -22.5%, 20.4%	
SPONSOR'S ASSESSMENT FOR SPONSOR EVALUABLE PATIENTS		
Microbiological Response	Linezolid (N=53)	Vancomycin (N=39)
Success	36 (67.9%)	28 (73.7%)
Failed	17 (32.1%)	11 (26.3%)
Line. Versus Vanc.: Difference in Success Rate	-5.8%, 95% C.I.: -26.8%, 15.3%	
SPONSOR'S ASSESSMENT FOR SPONSOR EVALUABLE PATIENTS (COUNTING INDETERMINATE AS FAILURE)		
Microbiological Response	Linezolid (N=54)	Vancomycin (N=40)
Success	36 (66.7%)	28 (70.0%)
Failed	17 (31.5%)	11 (27.5%)
Indeterminate	1 (1.9%)	1 (2.5%)
Missing	0 (0%)	0 (0%)
Line. Versus Vanc.: Difference in Success Rate	-3.3%, 95% C.I.: -24.5%, 17.8%	

Reviewer's Note: Patient microbiological outcomes by baseline pathogen for MITT and microbiologically evaluable population are presented in Tables 53 and 54, respectively. Numerically, two treatments appeared similar outcomes.

TABLE 53: STUDY 48a: MICROBIOLOGICAL SUCCESS RATES BY PATHOGEN OF MITT PATIENTS AT TOC VISIT			
FDA'S ASSESSMENT			
Pathogen	Linezolid	Vancomycin	Fisher's P-value
<i>S. aureus</i>	26/53 (49.1%)	22/49 (44.9%)	0.696
<i>S. pneumoniae</i>	10/14 (71.4%)	10/13 (76.9%)	1.000
SPONSOR'S ASSESSMENT			
Pathogen	Linezolid	Vancomycin	Fisher's P-value
<i>S. aureus</i>	28/51 (54.9%)	22/42 (52.4%)	0.837
<i>S. pneumoniae</i>	10/13 (76.9%)	10/13 (76.9%)	1.000

TABLE 54: STUDY 48a: MICROBIOLOGICAL SUCCESS RATES BY PATHOGEN OF MICROBIOLOGICAL EVALUABLE PATIENTS AT TOC VISIT			
FDA'S ASSESSMENT FOR SPONSOR EVLUABLE PATIENTS			
Pathogen	Linezolid	Vancomycin	Fisher's P-value
<i>S. aureus</i>	23/38 (60.5%)	15/23 (65.2%)	0.790
<i>S. pneumoniae</i>	9/9 (100%)	9/10 (90.0%)	1.000
SPONSOR'S ASSESSMENT FOR SPONSOR EVLUABLE PATIENTS			
Pathogen	Linezolid	Vancomycin	Fisher's P-value
<i>S. aureus</i>	25/41 (61.0%)	14/23 (60.9%)	1.000
<i>S. pneumoniae</i>	9/9 (100%)	9/9 (100%)	1.000

Reviewer's Note: The clinical cure rates by total Apache score are summarized for ITT, MITT, FDA clinically evaluable, Sponsor clinically evaluable, FDA microbiologically evaluable, and Sponsor microbiologically evaluable populations in Table 55.

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TABLE 55: STUDY 48a: CLINICAL CURE RATES BY TOTAL APACHE SCORE		
Total Apache Score	Patients Included	
	Linezolid	Vancomycin
ITT	85/174 (48.9%)	73/164 (44.5%)
0 ~ 11	38/57 (66.7%)	26/39 (66.7%)
12 ~ 15	19/38 (50.0%)	27/50 (54.0%)
16 ~ 19	13/34 (38.2%)	11/32 (34.4%)
20 ~ 39	14/43 (32.6%)	8/41 (19.5%)
Missing Score	1/2 (50.0%)	1/2 (50.0%)
MITT	47/82 (57.3%)	33/72 (45.8%)
0 ~ 11	15/21 (71.4%)	14/19 (73.7%)
12 ~ 15	11/19 (57.9%)	13/23 (56.5%)
16 ~ 19	8/15 (53.3%)	3/12 (25.0%)
20 ~ 39	12/26 (46.2%)	3/18 (16.7%)
Missing Score	1/1 (100%)	0/0 (NA)
FDA Clinical Evaluable	70/122 (57.4%)	62/103 (60.2%)
0 ~ 11	35/49 (71.4%)	22/29 (75.9%)
12 ~ 15	14/25 (56.0%)	26/37 (70.3%)
16 ~ 19	10/22 (45.5%)	7/17 (41.2%)
20 ~ 39	10/24 (41.7%)	6/18 (33.3%)
Missing Score	1/2 (50.0%)	1/2 (50.0%)
FDA Microbiological Evaluable	36/54 (66.7%)	26/41 (63.4%)
0 ~ 11	13/18 (72.2%)	10/12 (83.3%)
12 ~ 15	8/12 (66.7%)	12/16 (75.0%)
16 ~ 19	6/10 (60.0%)	2/5 (40.0%)
20 ~ 39	8/13 (61.5%)	2/8 (25.0%)
Missing Score	1/1 (100%)	0/0 (NA)
FDA Bacteremia ME	2/4 (50.0%)	4/6 (66.7%)
0 ~ 11	1/1 (100%)	0/0 (NA)
12 ~ 15	0/0 (NA)	4/4 (100%)
16 ~ 19	0/1 (0%)	0/0 (NA)
20 ~ 39	1/2 (50.0%)	0/2 (0%)
Missing Score	0/0 (NA)	0/0 (NA%)

Reviewer's Note: The summaries of safety outcomes are presented in Table 56. In general, the frequencies of study emergent adverse events, adverse events resulting in discontinuation of study medication, deaths, and serious adverse events were comparable between the linezolid and vancomycin treatment groups. Although a slightly higher percentage of patients died in the vancomycin group than in the linezolid group, this difference was not statistically significant.

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TABLE 56: STUDY 48a: ADVERSE EVENT RATES			
Safety Outcomes	Linezolid (N=203)	Vancomycin (N=193)	Fisher's P-value
Died	36 (17.7%)	49 (25.4%)	0.067
Died with Infection Related by TOC	11 (5.4%)	17 (8.8%)	0.240
Serious AEs	63 (31.0%)	65 (33.7%)	0.592
Discontinuation Due To AEs	13 (6.4%)	20 (10.4%)	0.203
Discontinuation Due To Drug related AEs	3 (1.5%)	4 (2.1%)	0.718
With Any AE	143 (70.4%)	143 (74.1%)	0.434
Body	58 (28.6%)	56 (29.0%)	1.000
Cardiovascular	54 (26.6%)	45 (23.3%)	0.487
Digestive	58 (28.6%)	50 (25.9%)	0.574
Hemic and Lymphatic	20 (9.9%)	15 (7.8%)	0.485
Metabolic and Nutritional	20 (9.9%)	17 (8.8%)	0.734
Musculo-Skeletal	2 (1.0%)	0 (0%)	0.499
Nervous	31 (15.3%)	31 (16.1%)	0.890
Respiratory	50 (24.6%)	54 (28.0%)	0.494
Skin	27 (13.3%)	31 (16.1%)	0.479
Special Senses	4 (2.0%)	3 (1.6%)	1.000
Urogenital	31 (15.3%)	23 (11.9%)	0.380
With Drug Related AE	27 (13.3%)	30 (15.5%)	0.568
Body	3 (1.5%)	4 (2.1%)	0.718
Cardiovascular	0 (0%)	4 (2.1%)	0.056
Digestive	14 (6.9%)	15 (7.8%)	0.848
Hemic and Lymphatic	3 (1.5%)	3 (1.6%)	1.000
Metabolic and Nutritional	3 (1.5%)	5 (2.6%)	0.494
Respiratory	1 (0.5%)	0 (0%)	1.000
Skin	5 (2.5%)	7 (3.6%)	0.567
Urogenital	2 (1.0%)	1 (0.5%)	1.000

Note: P-value should be interpreted with caution and adjusted with multiplicity

Reviewer's Summaries and Conclusions: See Section IV.

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III. Methicillin-Resistant *Staphylococcus* Species (MRSS)

III.A. INTRODUCTION

The Sponsor submitted one phase III controlled study as evidence to support that IV and administered linezolid was safe and efficacious for the treatment of MRSS infection when compared with vancomycin IV. Statistical review focuses on this comparative clinical trial which formed the basis of assessing linezolid in the treatment of MRSS infection. The general design of the study is as follows (also see Table 1):

Study 31 was a randomized, open-label, comparative, multicenter (104 centers), and multinational trial which compared the efficacy and safety of a 7 to 28 days course of therapy with linezolid IV (600 mg BID) for the entire treatment period or switched to linezolid oral (600 mg BID) with those of a 7 to 28 days course of therapy with vancomycin IV (1 g BID) in the treatment of MRSS infection. It was initiated July 2, 1998 and completed on July 21, 1999.

III.B. STUDY 31

III.B.1. METHODS

In Study 31, approximately 470 patients at least 13 years of age with suspected MRSS infection were eligible for enrollment in this study provided that they met the inclusion/exclusion criteria. Eligible patients were randomly assigned in a 1:1 ratio to the two treatment groups and the trial was conducted as an open-label study. Efficacy assessments were based on 1) clinical signs and symptoms assessed after treatment as compared with those observed at baseline, 2) microbiological assessments after treatment compared with those observed at baseline, and 3) radiological assessments after treatment compared with those conducted at baseline. The TOC evaluation was conducted at F-U. The safety of the study medications was monitored throughout the study by physical examination findings, vital sign assessments, laboratory evaluations, and assessment of adverse events.

Primary efficacy was assessed by evaluating clinical outcome and microbiological outcome at the TOC (F-U) visits. Analyses of efficacy variables were done separately for ITT, MITT, clinically evaluable, and microbiologically evaluable patients.

Reviewer's Note: *The Medical Officer generally agreed with the Sponsor's evaluability criteria for constructing ITT, MITT, clinically evaluable, and microbiologically evaluable populations. However, for certain groups of patients, such as who were discontinued from therapy for lack of efficacy and received at least four doses of study drug, who died of their initial infection before follow-up, and who were with missing clinical outcomes, the definition of analytic population was different from the Sponsor's. The Medical Officer also applied different decision rules from the Sponsor in classifying outcomes, mainly in how outcomes of failure and missing were defined. The algorithm used for determining outcomes by this reviewer was adjusted accordingly to the changes by the Medical Officer. The Medical Officer focused primarily on clinical outcome in evaluating efficacy.*

Please refer to the Medical Officer's review for detailed descriptions of differences between the FDA's and the Sponsor's analytic populations and outcomes.

All patients who received at least one dose of study medication were evaluable for safety. All adverse events that occurred between receipt of the first dose of study medication and the final visit were recorded.

Reviewer's Note: FDA reviewers used the same definitions for adverse events, drug-related adverse events, and serious adverse events as the Sponsor. Death was attributed to infection using the criteria defined by the Medical Officer.

The comparisons of interest in these studies were conducted between linezolid and vancomycin.

Reviewer's Note: The following statistical analyses were performed by the reviewer to evaluate the efficacy and safety of linezolid versus vancomycin.

Evaluation of treatment difference with respect to the primary efficacy variables was assessed by computing the two-tailed 95% confidence interval of the difference in response rates. The confidence intervals were computed using a normal approximation to the binomial, and included a continuity correction.

In certain evaluation groups with missing and indeterminate outcomes, sensitivity analyses were performed, whereas missing and indeterminate outcomes were counted as failure.

Subset analyses by gender, age, race, and center site were performed for the primary efficacy variables. Homogeneity of treatment effect across subgroups was assessed via Breslow-Day's test.

This reviewer conducted safety analyses with the following variables: the rate of at least one adverse event, the rate of at least one drug-related adverse event, the rate of serious adverse events, the rate of discontinuation due to adverse events, the rate of mortality, and the rate of mortality related to infection. Statistical comparisons between the two treatment groups were performed using Fisher's exact test.

Prior to performing efficacy analyses, this reviewer assessed the comparability of the treatment groups with respect to pretreatment characteristics including demographics, baseline disease characteristics, and evaluability status. Quantitative variables were assessed using the t-test. Qualitative variables were assessed using Fisher's exact test.

All tests were two-sided and used a 5% level of significance. The test for homogeneity of treatment effect was deemed significant at the 0.15 level.

III.B.2. RESULTS

Of the 468 patients who enrolled in the study, 243 were randomized to the linezolid treatment group, and 225 were randomized to the vancomycin treatment group. A total of 460 patients received study medication and were included in the ITT analysis group, of whom 240 received linezolid and 220 received vancomycin.

Reviewer's Note: The number and percentage of patients included in each analysis group, evaluated by either the Sponsor or the Medical Officer, are presented in Table 57. There were no notable treatment differences with respect to the percentage of patients included in each analysis group. Demographic data are described for the FDA clinically evaluable patients in Table 58, and no statistically significant differences were detected in this pretreatment characteristics of the two treatment groups.

TABLE 57: STUDY 31: NUMBER OF PATIENTS INCLUDED IN EACH EVALUATION GROUP

Evaluation Group	Patients Included	
	Linezolid	Vancomycin
All Randomized Patients	243	225
ITT Patients	240 (100%)	220 (100%)
MITT Patients	157 (65.4%)	144 (65.5%)
Sponsor Clinically Evaluable Patients	124 (51.7%)	130 (59.1%)
Sponsor Micro. Evaluable Patients	64 (26.7%)	70 (31.8%)
FDA Clinically Evaluable Patients	116 (48.3%)	125 (56.8%)
FDA Micro. Evaluable Patients	59 (24.6%)	67 (30.5%)

TABLE 58: STUDY 31: BASELINE DEMOGRAPHICS IN FDA CLINICAL EVALUABLE PATIENTS

Parameters	Linezolid (N=116)	Vancomycin (N=125)	P-value
Gender			
Male	70 (60.3%)	77 (61.6%)	0.842
Female	46 (39.7%)	48 (38.4%)	
Age (yrs.)			
Total Reporting	122	103	*0.190
Range (Max, Min)	(91, 18)	(90, 18)	
Mean ± SD	62.9 ± 18.5	59.7 ± 17.3	
Distribution			
18 ~ 50	27 (23.3%)	43 (34.4%)	0.057
≥ 51	89 (76.7%)	82 (65.6%)	
Race			
White	92 (79.3%)	95 (76.0%)	0.754
Black	9 (7.8%)	13 (10.4%)	
Other	15 (12.9%)	17 (13.6%)	
Weight (kg)			
Total Reporting	119	102	*0.776
Mean ± SD	73.1 ± 18.1	72.4 ± 18.3	
Site			
USA	45 (38.8%)	47 (37.6%)	0.849
Non-USA	71 (61.2%)	78 (62.4%)	

* by t test. All others in the table, by Chi-squared test.

Reviewer's Note: The clinical responses are shown for ITT, MITT, FDA clinically evaluable, Sponsor clinically evaluable, FDA microbiologically evaluable, and Sponsor microbiologically evaluable populations in Tables 59, 60, 61, 62, 63, and 64, respectively, which include sensitivity analyses by counting missing and indeterminate as failure. The lower bound of 95% confidence interval in MITT population was notably lower than those of other populations which implied the performance of linezolid versus vancomycin was not consistent among the evaluation groups. The results by the imputation of missing and indeterminate favored linezolid in most of the analysis groups.

TABLE 59: STUDY 31: CLINICAL RESPONSES OF ITT PATIENTS AT TOC VISIT		
FDA'S ASSESSMENT		
Clinical Response	Linezolid (N=181)	Vancomycin (N=160)
Cured	111 (61.3%)	101 (63.1%)
Failed	70 (38.7%)	59 (36.9%)
Line. Versus Vanc.: Difference in Cure Rate	-1.8%, 95% C.I.: -12.7%, 9.1%	
SPONSOR'S ASSESSMENT		
Clinical Response	Linezolid (N=192)	Vancomycin (N=169)
Cured	109 (56.8%)	93 (55.0%)
Failed	83 (43.2%)	76 (45.0%)
Line. Versus Vanc.: Difference in Cure Rate	1.7%, 95% C.I.: -9.1%, 12.6%	

TABLE 60: STUDY 31: CLINICAL RESPONSES OF ITT PATIENTS AT TOC VISIT (COUNTING INDETERMINATE AND MISSING AS FAILURE)		
FDA'S ASSESSMENT		
Clinical Response	Linezolid (N=240)	Vancomycin (N=220)
Cured	111 (46.3%)	101 (45.9%)
Failed	70 (29.2%)	59 (26.8%)
Indeterminate	10 (4.2%)	12 (5.5%)
Missing	49 (20.4%)	48 (21.8%)
Line. Versus Vanc.: Difference in Cure Rate	0.3%, 95% C.I.: -9.2%, 9.9%	
SPONSOR'S ASSESSMENT		
Clinical Response	Linezolid (N=240)	Vancomycin (N=220)
Cured	109 (45.4%)	93 (42.3%)
Failed	83 (34.6%)	76 (34.6%)
Indeterminate	27 (11.3%)	27 (12.3%)
Missing	21 (8.8%)	24 (10.9%)
Line. Versus Vanc.: Difference in Cure Rate	3.1%, 95% C.I.: -6.4%, 12.7%	

TABLE 61: STUDY 31: CLINICAL RESPONSES OF MITT PATIENTS AT TOC VISIT		
FDA'S ASSESSMENT		
Clinical Response	Linezolid (N=128)	Vancomycin (N=112)
Cured	75 (58.6%)	74 (66.1%)
Failed	53 (41.4%)	38 (33.9%)
Line. Versus Vanc.: Difference in Cure Rate	-7.5%, 95% C.I.: -20.5%, 5.6%	
SPONSOR'S ASSESSMENT		
Clinical Response	Linezolid (N=125)	Vancomycin (N=117)
Cured	75 (60.0%)	69 (59.0%)
Failed	50 (40.0%)	48 (41.0%)
Line. Versus Vanc.: Difference in Cure Rate	1.0%, 95% C.I.: -12.2%, 14.2%	

TABLE 62: STUDY 31: CLINICAL RESPONSES OF MITT PATIENTS AT TOC VISIT (COUNTING INDETERMINATE AND MISSING AS FAILURE)		
FDA'S ASSESSMENT		
Clinical Response	Linezolid (N=157)	Vancomycin (N=144)
Cured	75 (47.8%)	74 (51.4%)
Failed	53 (33.8%)	38 (26.4%)
Indeterminate	5 (3.2%)	10 (6.9%)
Missing	24 (15.3%)	22 (15.3%)
Line. Versus Vanc.: Difference in Cure Rate	-3.6%, 95% C.I.: -15.6%, 8.3%	
SPONSOR'S ASSESSMENT		
Clinical Response	Linezolid (N=157)	Vancomycin (N=144)
Cured	75 (47.8%)	69 (47.9%)
Failed	50 (31.9%)	48 (33.3%)
Indeterminate	22 (14.0%)	19 (13.2%)
Missing	10 (6.4%)	8 (5.6%)
Line. Versus Vanc.: Difference in Cure Rate	-0.1%, 95% C.I.: -12.1%, 11.8%	

TABLE 63: STUDY 31: CLINICAL RESPONSES OF CLINICAL EVALUABLE PATIENTS AT TOC VISIT		
FDA'S ASSESSMENT FOR FDA EVALUABLE PATIENTS		
Clinical Response	Linezolid (N=116)	Vancomycin (N=125)
Cured	93 (80.2%)	90 (72.0%)
Failed	23 (19.8%)	35 (28.0%)
Line. Versus Vanc.: Difference in Cure Rate	8.2%, 95% C.I.: -3.4%, 19.7%	
SPONSOR'S ASSESSMENT FOR SPONSOR EVALUABLE PATIENTS		
Clinical Response	Linezolid (N=122)	Vancomycin (N=117)
Cured	94 (77.0%)	87 (74.4%)
Failed	28 (23.0%)	30 (25.6%)
Line. Versus Vanc.: Difference in Cure Rate	2.7%, 95% C.I.: -9.0%, 14.4%	
SPONSOR'S ASSESSMENT FOR SPONSOR EVALUABLE PATIENTS (COUNTING INDETERMINATE AND MISSING AS FAILURE)		
Clinical Response	Linezolid (N=124)	Vancomycin (N=130)
Cured	94 (75.8%)	87 (66.9%)
Failed	28 (22.6%)	30 (23.1%)
Indeterminate	2 (1.6%)	9 (6.9%)
Missing	0 (0%)	4 (3.1%)
Line. Versus Vanc.: Difference in Cure Rate	8.9%, 95% C.I.: -3.0%, 20.7%	

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TABLE 64: STUDY 31: CLINICAL RESPONSES OF MICROBIOLOGICAL EVALUABLE PATIENTS AT TOC VISIT		
FDA'S ASSESSMENT FOR FDA EVALUABLE PATIENTS		
Clinical Response	Linezolid (N=59)	Vancomycin (N=67)
Cured	45 (76.3%)	48 (71.6%)
Failed	14 (23.7%)	19 (28.4%)
Line. Versus Vanc.: Difference in Cure Rate	4.6%, 95% C.I.: -12.3%, 21.5%	
SPONSOR'S ASSESSMENT FOR SPONSOR EVALUABLE PATIENTS		
Clinical Response	Linezolid (N=64)	Vancomycin (N=62)
Cured	46 (71.9%)	45 (72.6%)
Failed	18 (28.1%)	17 (27.4%)
Line. Versus Vanc.: Difference in Cure Rate	-0.7%, 95% C.I.: -17.9%, 16.5%	
SPONSOR'S ASSESSMENT FOR SPONSOR EVALUABLE PATIENTS (COUNTING INDETERMINATE AND MISSING AS FAILURE)		
Clinical Response	Linezolid (N=64)	Vancomycin (N=70)
Cured	46 (71.9%)	45 (64.3%)
Failed	18 (28.1%)	17 (24.3%)
Indeterminate	0 (0%)	5 (7.1%)
missing	0 (0%)	3 (4.3%)
Line. Versus Vanc.: Difference in Cure Rate	7.6%, 95% C.I.: -9.6%, 24.8%	

Reviewer's Note: Subset analyses of clinical response for microbiologically evaluable population with bacteremia is shown in Table 65. The linezolid group had numerically lower cure rates than the vancomycin group.

TABLE 65: STUDY 31: CLINICAL RESPONSES OF MICROBIOLOGICAL EVALUABLE PATIENTS WITH BACTEREMIA AT TOC VISIT		
FDA'S ASSESSMENT FOR FDA EVALUABLE PATIENTS		
Clinical Response	Linezolid (N=17)	Vancomycin (N=14)
Cured	10 (58.8%)	10 (71.4%)
Failed	7 (41.2%)	4 (28.6%)
FDA'S ASSESSMENT FOR SPONSOR EVALUABLE PATIENTS		
Clinical Response	Linezolid (N=20)	Vancomycin (N=14)
Cured	11 (55.0%)	10 (71.4%)
Failed	9 (45.0%)	4 (28.6%)

Reviewer's Note: Subset analyses by gender, age, race, and center site for clinical cure rates in the FDA clinically evaluable population are shown in Table 66. Results were consistent across all demographic aspects.

TABLE 66: STUDY 31: SUBSET ANALYSES BY DEMOGRAPHIC ASPECTS OF CLINICAL CURE RATE OF FDA CLINICAL EVALUABLE PATIENTS AT TOC VISIT

Subset	Linezolid (N=116)	Vancomycin (N=125)	95% C.I.	Breslow-Day's P-value
Male	56/70 (80.0%)	56/77 (72.7%)	(-7.8%, 22.3%)	0.847
Female	37/46 (80.4%)	34/48 (70.8%)	(-9.8%, 29.0%)	
13-44 yrs	16/20 (80.0%)	27/35 (77.1%)	(-23.5%, 29.2%)	0.878
45-64 yrs	33/41 (80.5%)	18/26 (69.2%)	(-13.4%, 35.9%)	
≥ 65 yrs	44/55 (80.0%)	45/64 (70.3%)	(-7.4%, 26.8%)	
13-50 yrs	23/27 (85.2%)	32/43 (74.4%)	(-10.9%, 32.5%)	0.724
≥ 51 yrs	70/89 (78.7%)	58/82 (70.7%)	(-6.3%, 22.1%)	
White	74/92 (80.4%)	69/95 (72.6%)	(-5.4%, 21.0%)	0.945
Other	19/24 (79.2%)	21/30 (70.0%)	(-17.7%, 36.0%)	
USA	33/45 (73.3%)	28/47 (59.6%)	(-7.5%, 35.0%)	0.651
Non-USA	60/71 (84.5%)	62/78 (79.5%)	(-8.6%, 18.7%)	

Reviewer's Note: Clinical cure rates by source of MRSA infection are summarized for MITT, FDA clinically evaluable, and FDA microbiologically evaluable populations in Tables 67, 68, and 69, respectively.

TABLE 67: STUDY 31: CLINICAL CURE RATES OF MITT PATIENTS BY SOURCE OF MRSA INFECTION

MRSA Infection Source	Patients Included	
	Linezolid	Vancomycin
All Sources	58/104 (55.8%)	58/88 (65.9%)
Pneumonia	12/28 (42.9%)	15/28 (53.6%)
- with Bacteremia	4/8 (50.0%)	2/5 (40.0%)
Skin and Soft Tissue Infection	36/52 (69.2%)	34/44 (77.3%)
- with Bacteremia	3/7 (42.9%)	3/3 (100%)
Urinary Tract Infection	2/6 (33.3%)	4/4 (100%)
- with Bacteremia	0/1 (0%)	0/0 (NA)
Other	6/13 (46.2%)	3/7 (42.9%)
- with Bacteremia	3/6 (50.0%)	3/6 (50.0%)
Bacteremia of Unknown Source	2/5 (40.0%)	2/5 (40.0%)

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TABLE 68: STUDY 31: CLINICAL CURE RATES OF FDA CLINICALLY EVALUABLE PATIENTS BY SOURCE OF MRSA INFECTION

MRSA Infection Source	Patients Included	
	Linezolid	Vancomycin
All Sources	49/62 (79.0%)	50/69 (72.5%)
Pneumonia	10/11 (90.9%)	12/17 (70.6%)
- with Bacteremia	3/3 (100%)	2/3 (66.7%)
Skin and Soft Tissue Infection	31/38 (81.6%)	31/41 (75.6%)
- with Bacteremia	3/5 (60.0%)	3/3 (100%)
Urinary Tract Infection	2/2 (100%)	2/2 (100%)
- with Bacteremia	0/0 (NA)	0/0 (NA)
Other	4/9 (44.4%)	3/6 (50.0%)
- with Bacteremia	1/3 (33.3%)	3/5 (60.0%)
Bacteremia of Unknown Source	2/2 (100%)	2/3 (66.7%)

TABLE 69: STUDY 31: CLINICAL CURE RATES OF FDA MICROBIOLOGICALLY EVALUABLE PATIENTS BY SOURCE OF MRSA INFECTION

MRSA Infection Source	Patients Included	
	Linezolid	Vancomycin
All Sources	40/51 (78.4%)	41/57 (71.9%)
Pneumonia	9/10 (90.0%)	12/17 (70.6%)
- with Bacteremia	3/3 (100%)	2/3 (66.7%)
Skin and Soft Tissue Infection	26/33 (78.8%)	24/33 (72.7%)
- with Bacteremia	2/4 (50.0%)	2/2 (100%)
Urinary Tract Infection	0/0 (NA%)	2/2 (100%)
- with Bacteremia	0/0 (NA)	0/0 (NA)
Other	3/6 (50.0%)	2/4 (50.0%)
- with Bacteremia	1/3 (33.3%)	2/4 (50.0%)
Bacteremia of Unknown Source	2/2 (100%)	1/1 (100%)

Reviewer's Note: Subset analyses of the clinical outcome in FDA clinically evaluable population are summarized in Table 70. The clinical cure rates of the linezolid were consistently numerically better than those of the vancomycin group across these subgroups.

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TABLE 70: STUDY 31: SUBSET ANALYSES OF CLINICAL CURE RATE OF CLINICAL EVALUABLE PATIENTS AT TOC VISIT		
Subset	Linezolid (N=116)	Vancomycin (N=125)
Receiving Aminoglycosides		
Yes	17/20 (85.0%)	17/28 (60.7%)
No	76/96 (79.2%)	73/97 (75.3%)
With MRSA Infection		
Yes	49/62 (79.0%)	50/69 (72.5%)
No	44/54 (81.5%)	40/56 (71.4%)
With MRSE Infection		
Yes	7/9 (77.8%)	9/12 (75.0%)
No	86/107 (80.4%)	81/113 (71.7%)
With MSSA Infection		
Yes	3/4 (75.0%)	2/3 (66.7%)
No	90/112 (80.4%)	88/122 (72.1%)
With S. aureus		
Yes	54/68 (79.4%)	53/74 (71.6%)
No	39/48 (81.3%)	37/51 (72.6%)

Reviewer's Note: The microbiological responses are shown for MITT, FDA microbiologically evaluable, and Sponsor microbiologically evaluable populations in Tables 71; 72, and 73, which include sensitivity analyses by counting missing and indeterminate as failure and the two analyses reached the similar results.

TABLE 71: STUDY 31: MICROBIOLOGICAL RESPONSES OF MITT PATIENTS AT TOC VISIT		
FDA'S ASSESSMENT		
Microbiological Response	Linezolid (N=134)	Vancomycin (N=125)
Success	62 (46.3%)	62 (49.6%)
Failed	72 (53.7%)	63 (50.4%)
Line. Versus Vanc.: Difference in Success Rate	-3.3%, 95% C.I.: -16.3%, 9.6%	
SPONSOR'S ASSESSMENT		
Microbiological Response	Linezolid (N=122)	Vancomycin (N=120)
Success	62 (50.8%)	62 (51.7%)
Failed	60 (49.2%)	58 (48.3%)
Line. Versus Vanc.: Difference in Success Rate	-0.8%, 95% C.I.: -14.3%, 12.6%	

TABLE 72: STUDY 31: MICROBIOLOGICAL RESPONSES OF MITT PATIENTS AT TOC VISIT (COUNTING INDETERMINATE AND MISSING AS FAILURE)		
FDA'S ASSESSMENT		
Microbiological Response	Linezolid (N=157)	Vancomycin (N=144)
Success	62 (39.5%)	62 (43.1%)
Failed	72 (45.9%)	63 (43.8%)
Indeterminate	11 (7.0%)	10 (6.9%)
Missing	12 (7.6%)	9 (6.3%)
Line. Versus Vanc.: Difference in Success Rate	-3.6%, 95% C.I.: -15.4%, 8.2%	
SPONSOR'S ASSESSMENT		
Microbiological Response	Linezolid (N=157)	Vancomycin (N=144)
Success	62 (39.5%)	62 (43.1%)
Failed	60 (38.2%)	58 (40.3%)
Indeterminate	20 (12.7%)	14 (9.7%)
Missing	15 (9.6%)	10 (6.9%)
Line. Versus Vanc.: Difference in Success Rate	-3.6%, 95% C.I.: -15.4%, 8.2%	

TABLE 73: STUDY 31: MICROBIOLOGICAL RESPONSES OF MICROBIOLOGICAL EVALUABLE PATIENTS AT TOC VISIT		
FDA'S ASSESSMENT FOR FDA EVALUABLE PATIENTS		
Microbiological Response	Linezolid (N=59)	Vancomycin (N=67)
Success	38 (64.4%)	41 (61.2%)
Failed	21 (35.6%)	26 (38.8%)
Line. Versus Vanc.: Difference in Success Rate	3.2%, 95% C.I.: -15.3%, 21.7%	
SPONSOR'S ASSESSMENT FOR SPONSOR EVALUABLE PATIENTS		
Microbiological Response	Linezolid (N=64)	Vancomycin (N=67)
Success	38 (59.4%)	43 (64.2%)
Failed	26 (40.6%)	24 (35.8%)
Line. Versus Vanc.: Difference in Success Rate	-4.8%, 95% C.I.: -23.0%, 13.4%	
SPONSOR'S ASSESSMENT FOR SPONSOR EVALUABLE PATIENTS (COUNTING INDETERMINATE AS FAILURE)		
Microbiological Response	Linezolid (N=64)	Vancomycin (N=70)
Success	38 (59.4%)	43 (61.4%)
Failed	26 (40.6%)	24 (34.3%)
Indeterminate	0 (0%)	1 (1.4%)
Missing	0 (0%)	2 (2.9%)
Line. Versus Vanc.: Difference in Success Rate	-2.1%, 95% C.I.: -20.1%, 16.0%	

Reviewer's Note: The summaries of safety outcomes are presented in Table 74. The percentage of patients with one or more study emergent adverse events was comparable between the treatment groups. The percentage of patients with one or more drug related adverse events was greater in linezolid treated patients compared with vancomycin treated patients. The percentage of patients who experienced drug related adverse events resulting in the discontinuation of study medication was comparable between the treatment groups. The percentage of patients with one or more serious adverse events was also comparable between the treatment groups.

TABLE 74: STUDY 31: ADVERSE EVENT RATES			
Safety Outcomes	Linezolid (N=240)	Vancomycin (N=220)	Fisher's P-value
Died	40 (16.7%)	30 (13.6%)	0.436
Died with Infection Related by TOC	10 (4.2%)	11 (5.0%)	0.824
Serious AEs	64 (26.7%)	56 (25.5%)	0.832
Discontinuation Due To AEs	10 (4.2%)	10 (4.5%)	1.000
Discontinuation Due To Drug related AEs	5 (2.1%)	3 (1.4%)	0.726
With Any AE	164 (68.3%)	136 (61.8%)	0.170
Body	78 (32.5%)	62 (28.2%)	0.361
Cardiovascular	47 (19.6%)	33 (15.0%)	0.219
Digestive	77 (32.1%)	46 (20.9%)	0.008
Endocrine	0 (0%)	2 (0.9%)	0.228
Hemic and Lymphatic	22 (9.2%)	13 (5.9%)	0.220
Metabolic and Nutritional	24 (10.0%)	19 (8.6%)	0.635
Musculo-Skeletal	1 (0.4%)	4 (1.8%)	0.198
Nervous	33 (13.8%)	18 (8.2%)	0.074
Respiratory	46 (19.2%)	40 (18.2%)	0.812
Skin	32 (13.3%)	29 (13.2%)	1.000
Special Senses	13 (5.4%)	8 (3.6%)	0.382
Urogenital	29 (12.1%)	32 (14.5%)	0.492
With Drug Related AE	44 (18.3%)	18 (8.2%)	0.001
Body	8 (3.3%)	4 (1.8%)	0.387
Cardiovascular	5 (2.1%)	2 (0.9%)	0.453
Digestive	22 (9.2%)	3 (1.4%)	< 0.001
Hemic and Lymphatic	6 (2.5%)	1 (0.5%)	0.125
Metabolic and Nutritional	2 (0.8%)	1 (0.5%)	1.000
Nervous	3 (1.3%)	0 (0%)	0.250
Respiratory	1 (0.4%)	0 (0%)	1.000
Skin	7 (2.9%)	5 (2.3%)	0.774
Special Senses	6 (2.5%)	0 (0%)	0.031
Urogenital	5 (2.1%)	6 (2.7%)	0.764

Note: P-value should be interpreted with caution and adjusted with multiplicity

Reviewer's Summaries and Conclusions: See Section IV.

IV. SUMMARY AND CONCLUSIONS **(Which May be Conveyed to the Sponsor)**

Reviewer's Note: In this section, confidence intervals for differences in cure rates (linezolid minus control) are reported as $n_1, n_2(l, u)_{p_1, p_2}$, where n_1 is the number of linezolid patients, n_2 is the number of control patients, l and u are the lower and upper bounds of the 95% confidence interval, respectively, p_1 is the response rate in linezolid subjects, and p_2 is the response rate in control subjects.

COMMUNITY ACQUIRED PNEUMONIAE

This indication was primarily supported by two controlled studies to demonstrate the efficacy and safety of linezolid.

Statistical evaluation of efficacy was based upon the two-sided 95% confidence interval of the difference in clinical cure rates between linezolid and control for ITT, MITT, clinically evaluable, and microbiologically evaluable patients.

An overview of clinical cure rates for patients in Study 33 (open-label) is presented in Figure 1 and Table 75.

FIGURE 1: STUDY 33: 95% CONFIDENCE INTERVALS OF DIFFERENCES IN CLINICAL CURE RATES.

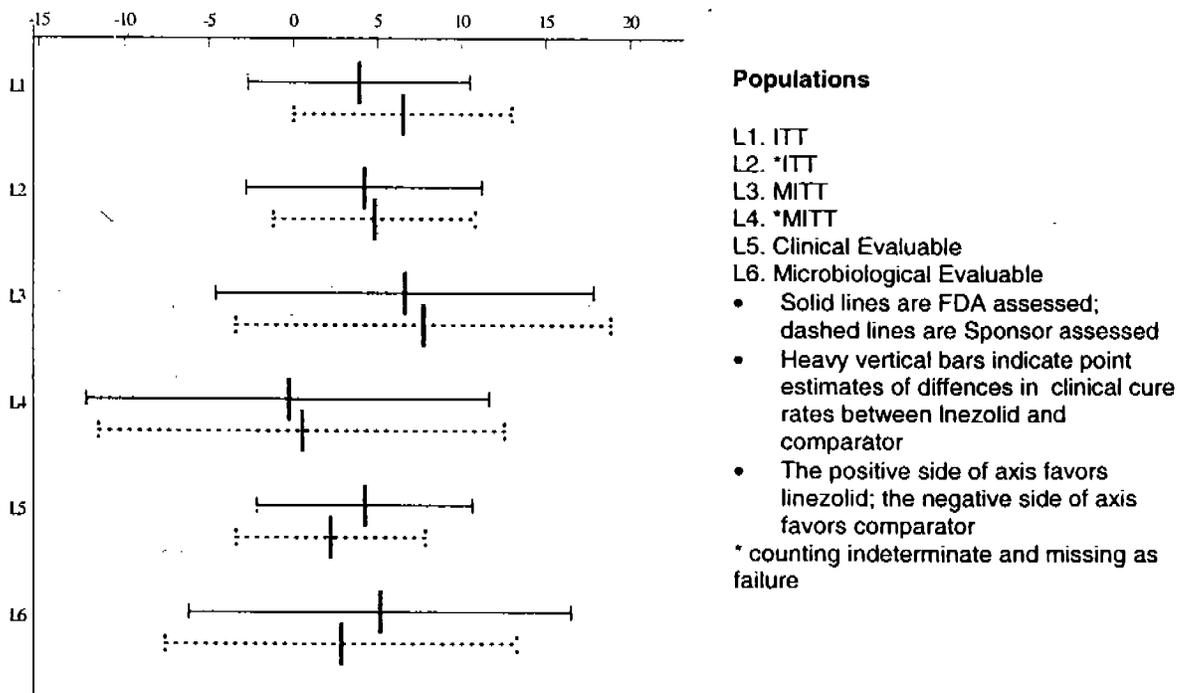


TABLE 75: STUDY 33: CLINICAL CURE RATES			
Population	Linezolid	Ceftriaxone/ Cefpodoxime	C.I.
	n/N (%)	n/N (%)	
ITT	267/330 (80.9%)	241/313 (77.0%)	-2.7%, 10.5%
*ITT	267/381 (70.1%)	241/366 (65.9%)	-2.7%, 11.2%
MITT	91/109 (83.5%)	90/117 (76.9%)	-4.7%, 17.8%
*MITT	91/128 (71.7%)	90/126 (71.4%)	-12.3%, 11.6%
FDA Clin. Evaluable	246/285 (86.3%)	225/274 (82.1%)	-2.2%, 10.6%
FDA Micro. Evaluable	80/92 (87.0%)	81/99 (81.8%)	-6.2%, 16.4%

* counting indeterminate and missing as failure

An overview of clinical cure rates for patients in Study 51 (investigator-blind) is presented in Figure 2 and Table 76.

FIGURE 2: STUDY 51: 95% CONFIDENCE INTERVALS OF DIFFERENCES IN CLINICAL CURE RATES.

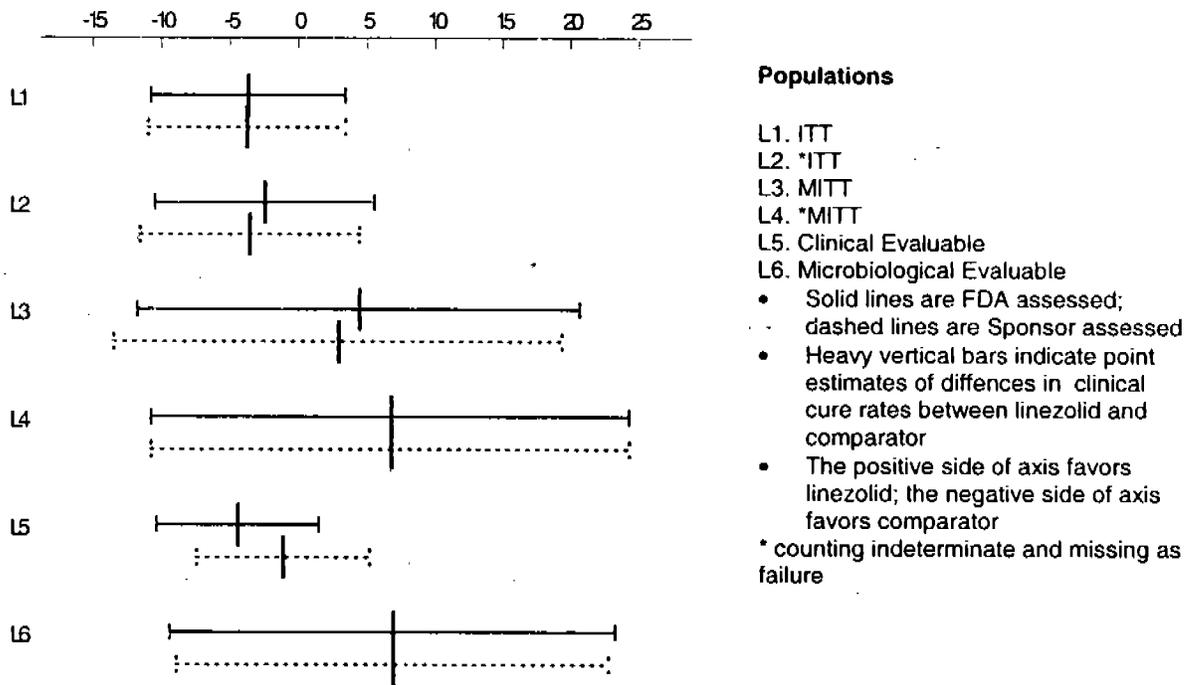


TABLE 76: STUDY 51: CLINICAL CURE RATES			
Population	Linezolid	Cefpodoxime	C.I.
	n/N (%)	n/N (%)	
ITT	188/227 (82.8%)	192/222 (86.5%)	-10.8%, 3.4%
*ITT	188/272 (69.1%)	192/268 (71.6%)	-10.6%, 5.5%
MITT	46/54 (85.2%)	42/52 (80.8%)	-11.8%, 20.6%
*MITT	46/60 (76.7%)	42/60 (70.0%)	-10.8%, 24.1%
FDA Clin. Evaluable	180/213 (84.5%)	187/208 (89.9%)	-12.2%, 1.4%
FDA Micro. Evaluable	44/50 (88.0%)	39/48 (81.3%)	-9.5%, 23.0%

* counting indeterminate and missing as failure

Reviewer's Summary For The Results Of Two Studies Regarding This Indication:

- In both studies, the pretreatment characteristics were comparable between treatments across all analysis groups.
- In Study 33, the confidence interval for the difference in clinical cure rates of linezolid minus ceftriaxone/cefepodoxime in clinically evaluable subjects was $_{285, 274}(-2.2\%, 10.6\%)_{86.3\%, 82.1\%}$. The efficacy analyses demonstrated the cure rate of linezolid was comparable to that of ceftriaxone/cefepodoxime. The results from ITT, MITT, and microbiologically evaluable populations were consistent to those from clinically evaluable population.
- In Study 51, the confidence interval for the difference in clinical cure rates of linezolid minus cefpodoxime in clinically evaluable subjects was $_{213, 208}(-12.2\%, 1.4\%)_{84.5\%, 89.5\%}$. The efficacy analyses demonstrated the cure rate of linezolid was comparable to that of cefpodoxime. The results from ITT, MITT, and microbiologically evaluable populations were consistent to those from clinically evaluable population.
- In Study 33, results from the clinical response were consistent across all demographic aspects. In Study 51, the treatment effects less favored linezolid in white population.
- In both studies, linezolid and its comparator had similar microbiologic success rates against the target pathogens, however, meaningful difference was difficult to detect due to small sample sizes.
- In Study 33, the percentage of patients was greater in the linezolid group than the ceftriaxone/cefepodoxime group in the following safety variables: drug related adverse event (21.3% vs. 11.2%) and discontinuation due to drug related adverse events (2.4% vs. 0.3%).
- In Study 51, the percentage of patients was greater in the linezolid group than the cefpodoxime group in the following safety variables: any adverse event (60.3% vs. 42.9%), drug related adverse event (31.6% vs. 17.9%), discontinuation due to adverse events (9.9% vs. 2.6%), discontinuation due to drug related adverse events (3.7% vs. 0.7%), and serious adverse events (7.7% vs. 3.4%).

HOSPITAL ACQUIRED PNEUMONIAE

This indication was primarily supported by one controlled study to demonstrate the efficacy and safety of linezolid.

Statistical evaluation of efficacy was based upon the two-sided 95% confidence interval of the difference in clinical cure rates between linezolid and control for ITT, MITT, clinically evaluable, and microbiologically evaluable patients.