CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21130/S-003, 21131/S-003, 21132/S-003
Name of drug:	Zyvox (Linezolid)
Applicant:	Pharmacia and Upjohn Company
Indication:	Resistant Gram Positive infections
Documents reviewed:	\\CDSESUB1\N21130\S_003\2002-06-21\clinstat\resistantgram-positiveinfections\0082.pdf and corresponding SAS data sets
Project manager:	Elizabeth Duvall-Miller
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Dates:	Received 6/24/02; user fee (6 months) 12/24/02
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Keywords: NDA review, clinical studies, resistance

1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS AND RECOMMENDATIONS

This study compared Linezolid to Vancomycin in pediatric patients with suspected resistant gram positive infections. The most common baseline diagnoses were complicated skin and skin-structure infection, bacteremia (catheter-related or of-unknown-source), or hospital-acquired pneumonia. A slight majority of the patients had documented gram-positive pathogens, and about one-quarter of

the patients had documented drug-resistant gram-positive infections at the time of randomization. While the sponsor's analyses found very similar clinical success rates across the two treatment arms, the reviewer's analyses, using a slightly different approach, suggested that there might possibly be a modest advantage of Vancomycin to Linezolid among patients with documented gram-positive infections, although the difference was not statistically significant. In the FDA Microbiological Intent to Treat (MITT) analysis, the reviewer's clinical success rate in the Linezolid arm was about .80 versus about .90 for the Vancomycin arm, with a corresponding 95% confidence interval for the treatment difference of (-.230, .027). The protocol did not appear to pre-specify a non-inferiority margin, and thus it is not straightforward to assess this result. Nonetheless, the confidence interval indicates that the difference may be as great as -.23, but the difference between the treatment groups did not reach statistical significance at the .05 level. Similarly, a slightly higher observed success rate in Vancomycin than Linezolid was found in a number of key MITT subgroups, but these differences were not statistically significant. In contrast, corresponding analyses among patients that met pre-specified "per-protocol" criteria and the intent to treat (ITT) analyses, showed little difference between the arms. Demonstration of efficacy against placebo is not tested directly in this study; however, if one can assume that the clinical success rates in this population with no antibiotic treatment would have been below .50, Linezolid can easily be shown to be superior to placebo. No safety concerns about Linezolid emerged from comparison of adverse events and examination of key lab values in this study. However, one concern was noted: the death rate in the Linezolid arm was numerically higher than the Vancomycin arm (.058 vs. .029), although this result could easily be due to chance. One can summarize this trial's results with three main conclusions. First, trial results indicated that the two treatments were fairly comparable with respect to efficacy, however, FDA MITT analyses, while not statistically significant, suggested the possibility of a slight Vancomycin advantage. Second, the observed clinical success rates for Linezolid from most analyses was roughly .80, which may be much better than placebo. Third, no clear safety concerns emerged from this trial.

1.2 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

Linezolid (Zyvox) was approved for adults in 2000 for the following indications: vancomycin-resistant enterococcus faecium (VRE) infections, nosocomial pneumonia, complicated skin and skin structure infections, uncomplicated skin and skin structure infections, and community acquired pneumonia. The current submission under review is an efficacy supplement intended to provide information relevant to pediatrics patients for the same indications. The sponsor's stated development strategy was to support the use of linezolid in children for uncomplicated skin and skin structure infections with an adequate and well-control trial, and the remaining indications with pharmacokinetic, efficacy and safety data in pediatrics patients plus efficacy data from adult trials. The submission includes uncontrolled studies in community-acquired pneumonia, otitis media, and compassionate use in patients with significant infections. Controlled studies were conducted for skin and skin structure infections and for resistant gram-positive infections. This review considers Study 0082, the trial of resistant gram-positive infections, only; Dr. Nancy Silliman has conducted a statistical review of the skin infection trial, Study 0065A. Study 0082 enrolled 321 patients, who were randomized to linezolid and vancomycin using a 2:1 allocation scheme. There were 59 investigators from the United States and seven Latin American countries.

1.3 PRINCIPAL FINDINGS

This section describes the sponsor's results and conclusions, the results from the reviewer's analysis, and overall comments and conclusions.

1.3.1 SUMMARY OF SPONSOR'S RESULTS

When results from all sites of infections are collapsed, the sponsor found very similar results for both arms regardless of the population analyzed. In the intent to treat (ITT) population, the observed cure rate for Linezolid was .79 versus .74 in Vancomycin. In the MITT population, the observed rates were about .81 for both arms. The same pattern persisted in the corresponding per-protocol populations, but with higher observed success rates. The sponsor's clinical success rates were fairly similar for the two arms using the following subgroups: baseline diagnosis, diagnosis by pathogen, and pathogen; however, these subcategories generally had very small number of patients. In one exception, the sponsor notes that for patients diagnosed with hospital acquired pneumonia (HAP) in the ITT and clinically evaluable (CE) population, that Linezolid rates are somewhat lower than Vancomycin; however they also provide evidence suggesting that the Linezolid patients may have been sicker. The sponsor did not present corresponding MITT results by baseline diagnosis. The sponsor's safety analysis focused on reported adverse events and lab values; the conclusion was that the overall safety profiles of the two study arms were comparable. The sponsor provided the following overall conclusion at the end of its Study Report. "This study demonstrated that linezolid is well tolerated and equally as effective as vancomycin in treating infections in children due to suspected or proven gram-positive pathogens, including hospital acquired pneumonia, complicated skin and skin structure infections, catheter-related bacteremia, bacteremia of unknown source, and other infections.

1.3.2 SUMMARY OF FDA STATISTICAL REVIEWER'S RESULTS

The FDA statistical reviewer's analysis used a different algorithm for clinical assessment, and slightly different definitions for population inclusion (see Section 2.3.2). The goal of this alternate clinical assessment was to distinguish patients with good outcomes, poor outcomes, and unknown outcomes without regard to duration of therapy in the ITT and MITT analyses. When all diagnoses are collapsed, the reviewer's analysis also found very similar rates between the two arms for the ITT, CE, and microbiologically evaluable (ME) populations; however, for the FDA MITT population, there was an indication of a potential advantage of Vancomycin, although this difference did not reach statistical significance (i.e., $p>.05$). In the FDA MITT population when missing values were excluded, the observed cure rate for Linezolid was .796 (n=108) versus .898 (n=49) in the Vancomycin arm, with the corresponding 95% confidence interval for the difference of (-.230, .027). The lower bounds for the confidence intervals of the other three analysis populations ranged from -.109 for it FDA CE to -.148 for the FDA ME. (For details see Table 12.)

In the FDA statistical reviewer's analysis, the possible suggestion of a Vancomycin advantage in the FDA MITT population was consistently seen in most key subgroups, although the sample size, in these subgroup analyses, was small to very small, and should be interpreted very cautiously. For example, the observed Vancomycin clinical success rate was larger than the Linezolid clinical success rate for four of the five baseline diagnosis categories in the FDA MITT population; the exception was catheter-related bacteremia, in which case the estimates were nearly identical (Table 16.) Similarly, the observed rates by pathogen were generally higher in the Vancomycin group by pathogen. One of these differences was nominally statistically significant at the .05 level (with no adjustment for multiple comparisons): in MRSE patients the observed reviewer's MITT cure rate for Linezolid was .741 (n=27) versus 1.00 (n=9) in Vancomycin. A noticeable difference was also observed in the S. Aureus patients with Linezolid's cure rate of .851 (n=47) versus .966 (n=29) in Vancomycin patients (see Table 18). Analysis of diagnosis by pathogen subgroups were generally based on extremely small numbers; however several of these subgroups with sizeable results. For example, there was a clear suggestion of a Vancomycin advantage among patients with complicated skin and skin structure infections with a documented S. Aureus pathogen. On the other hand, the

patients with catheter-related bacteremia with *coagulase-negative staphylococcus* infections in Linezolid had numerically better results than the Vancomycin arm (see Table 19). Finally, the FDA statistical review found higher observed success rates in the Vancomycin arm than the Linezolid arm in virtually every demographic category considered (see Table 26).

The FDA statistical review considered some slightly different analyses of safety, but no new safety concerns emerged. However, the higher observed death rate in the Linezolid arm than in the Vancomycin arm, while not statistically significant, is noted.

1.3.3 COMMENTS AND CONCLUSIONS

This study was not designed to provide formal statistical evidence of equivalence between the two treatment arms; that is, no sample size calculations were performed in the protocol, and no non-inferiority margin was pre-specified.

The sponsors' conclusion that the study "demonstrated that linezolid is well tolerated and equally as effective as vancomycin in treating infections in children due to suspected or proven gram-positive pathogens, including hospital acquired pneumonia, ..." is not well supported by the data. While no clear safety concerns emerged in this study, the study did not demonstrate that the two drugs are "equally effective" in treating suspected gram-positive pediatric infections in each of the named infections. First, this conclusion appears to suggest that equal efficacy of the two drugs was demonstrated for each of the indications listed, whereas the sample size per indication is too small to provide more than a sense of very rough comparability. Second, the FDA statistical reviewer's MITT analyses, while not clearly conclusive or pre-specified, cast some doubt on whether the two drugs are "equally effective", when considered by indication, or overall. Third, since no non-inferiority margin was pre-specified, it is difficult to conclude that the arms are "equally effective".

The FDA statistical reviewer's analysis differed from the sponsor's in a number of ways and was designed to address perceived concerns about the sponsor's approach (see Section 2.3.2). The reviewer's analysis found similar results across the two arms in the ITT and per-protocol populations, but a modest, but not statistically significant, advantage of Vancomycin in efficacy, was found in the MITT analysis. The reviewer's MITT analysis is arguably an important analysis for several reasons. First, it is based on patients with strongest evidence of bacterial disease. Second, it is faithful to intent-to-treat principles by analyzing patient as randomized and without regard to duration of treatment. Third, when the treatment difference in the MITT population is *larger* than the ME population, then one should pay particular attention to the MITT results, as the primary reason for considering the ME results in the non-inferiority setting is out of concern that the MITT results will underestimate treatment differences. That said, since the observed differences of the primary analyses were not statistically significant (even ignoring multiple comparisons) they need to be considered very cautiously. Furthermore, since no non-inferiority margin appeared to be pre-specified, it is difficult to interpret the wide confidence intervals.

This study compares two active arms, and thus cannot provide a direct assessment of whether Linezolid is superior to placebo, which is the purest test of efficacy. However, given the seriousness of the indications considered in this protocol, it *might* be reasonable to assume that the placebo rate for such a population would be less than .50. Under this assumption, the overall cure rate is statistically significantly greater than .50 for all major analyses. The subgroups are mostly too small to meet this standard, but virtually every point-estimate presented in this review is at least .50. However, it must be understood that this .50 value is essentially arbitrary, and not the result of a literature review. Unfortunately, satisfactory data that can provide fully compelling evidence about the placebo rates in these indications probably do not exist. Pre-antibiotic era data may exist for

some included indications, but any attempt to consider this should factor in the fact that supportive care beyond antibiotic treatment was very limited then compared to what occurs today.

In summary, no safety concerns emerged in this study of pediatric Gram positive infections, and observed efficacy rates were roughly comparable between the treatment groups. There were possible hints of a modest Vancomycin advantage in efficacy in some key FDA MITT analyses, although this was not statistically significant, and was not seen in the sponsor's analyses. A slightly higher death rate observed in the Linezolid arm than the Vancomycin arm was noted, but it could easily be due to chance.

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 INTRODUCTION AND BACKGROUND

Linezolid was approved for adults in 2000 for the following indications: vancomycin-resistant enterococcus faecium (VRE) infections, nosocomial pneumonia, complicated skin and skin structure infections, uncomplicated skin and skin structure infections, and community acquired pneumonia. The current submission under review is an efficacy supplement intended to provide information relevant to pediatrics patients for the same indications.

In a letter dated 6/21/02, the sponsor outlined the rationale of the submission:
"The pediatric clinical development strategy was designed to include the following considerations:

- Provide sufficient clinical safety data to meet the requirements of the Pediatric Rule for the age-specific recommended dose regimens.
- Provide sufficient clinical data to make dosing recommendations for all pediatric age groups.
- Conduct clinical trials in pediatric patients to obtain safety and efficacy data to supplement adult data for pediatric indications where the disease process is similar in adults and children, i.e., community- and hospital-acquired pneumonia, vancomycin-resistant enterococcal infections, and complicated skin and skin structure infections.
- Conduct at least one adequate and well-controlled clinical trial in pediatric patients to obtain safety and efficacy data sufficient for a new indication of uncomplicated skin and skin structure infections in children."

The submission included two controlled clinical studies (skin and skin structure and resistant gram-positive infections) and three uncontrolled clinical studies (community-acquired pneumonia, otitis media, and compassionate use in patients with significant resistant bacterial infections).

The controlled clinical trial of resistant gram-positive infections is the subject of this statistical review. Dr. Nancy Silliman has reviewed the study of skin and skin structure infections.

2.2 DATA ANALYZED AND SOURCES

The studies included in this submission are described in Table 1.

Table 1. Studies Included in the Submission

Study	Indication	Design	Sample Size	Electronic Archive
0045	Community Acquired Pneumonia	• One-arm • Multi-center		\\cdsesub1\N21130\S_003\2002-06-21\clinstat\communityacquiredpneumonia\0045.pdf
0049	Otitis Media	• One-arm • Multi-center		\\cdsesub1\N21130\S_003\2002-06-21\clinstat\otitismedia\0049.pdf
0065	Skin and Skin Structure	• Linezolid vs. Cefadroxil • Multi-center	Linezolid: Cefadroxil:	\\cdsesub1\N21130\S_003\2002-06-21\clinstat\skinandskinstructure\0065.pdf
0082	Resistant Gram-positive Infections	• Linezolid vs. vancomycin • Multi-center	Linezolid: Vancomycin:	\\cdsesub1\N21130\S_003\2002-06-21\clinstat\resistantgram-positiveinfections\0082.pdf
0025	Compassionate use (significant bacterial infections)			\\cdsesub1\N21130\S_003\2002-06-21\clinstat\compassionateuse\0025.pdf

The trial of resistant gram-positive infections, Study 0082, is the subject of this statistical review. For a statistical review of the skin trial, Study 0065, see Dr. Nancy Silliman's review.

The datasets of the original submission for Study 0082 can be found under \\cdsesub1\N21130\s_003\2002-06-21\crt\datasets\0082. Additional one-observation-per-subject SAS data sets were created at the FDA's request, the most updated data set appears at \\cdsesub1\N21130\s_003\2002-08-07\crt\datasets\0082\statplus.xpt. Several iterations were required before the data set appeared to be internally consistent.

A detailed description of the overall study design of Study 0082 appeared in Section 6.1 of the sponsor's Study Report:

> "This phase 3, randomized, open-label, comparator controlled, multicenter study was designed to compare the safety, tolerability, and clinical efficacy of linezolid and vancomycin in the treatment of antibiotic-resistant gram-positive bacterial infections in children from birth through 11 years of age, and to assess population pharmacokinetics of linezolid in these patients. Hospitalized pediatric patients and those in chronic care facilities were eligible for treatment if they had known or suspected infections due to resistant gram-positive bacteria, including hospital-acquired pneumonia (HAP), complicated skin and skin structure infections, catheter-related bacteremia, bacteremia of unidentified source, and other infections. Patients with endocarditis, CNS infections, and skeletal infections (including osteomyelitis/septic arthritis) were excluded. The planned enrollment of 300 patients was

stratified by age as follows: birth through 90 days (60 patients), 91 days through 4 years (120 patients), and 5 years through 11 years (120 patients). Enrolled patients were randomized in a 2:1 ratio to receive linezolid or vancomycin, respectively.
During the first 3 days of treatment, patients were required to receive either linezolid IV 10 mg/kg (up to 600 mg/dose) every 8 hours or vancomycin IV at varying doses (10-15 mg/kg) and intervals (6-24 hours) depending on age and weight. Patients with documented VRE (on or before Day 3) who were randomized to vancomycin were switched to linezolid. After 3 days of treatment, the study patients could be switched from IV to oral study medication at the discretion of the investigator if they were ≥91 days of age. Patients randomized to linezolid treatment and switched to oral linezolid received a linezolid _____ (10 mg/kg) approximately every 8 hours. Patients randomized to vancomycin could receive an appropriate oral step-down medication (based on susceptibility of the infecting o organism) if they were ≥91 days of age. Planned duration of therapy for the study was at least 10 days and up to 28 days.

Screening activities included collection of suitable specimens (including blood culture) for Gram's stain, culture and identification, and antibiotic susceptibility testing; a chest radiograph for patients with a clinical diagnosis of pneumonia; blood sampling for laboratory assays; collection of medical history and demographic information; and a physical examination. Patients were allowed to receive the initial 72 hours of study medication before microbiological laboratory assay results were obtained; however, they were not allowed to continue if entry criteria were not met. Post-baseline visits comprised scheduled visits on days 3, 10, 17, and 24 during treatment (depending on treatment duration), an end-of-treatment (EOT) visit to take place within 72 hours after the last dose of study medication, and a follow-up (F-U) visit to take place between 12 and 28 days after treatment completion. Assessments performed at study visits included site culture and Gram's stain (as clinically indicated and at EOT and F-U), blood culture if positive at baseline, chest radiograph (as clinically indicated and at F-U for pneumonia patients), vital signs, clinical observations, sampling for laboratory assays and linezolid pharmacokinetic (PK) analysis, concomitant therapy, and adverse events. Clinical response was evaluated at EOT and F-U; the F-U evaluation was considered the test of cure."

The protocol states that the primary efficacy variables will be the test-of-cure (i.e., from the follow-up visit) clinical outcome as assessed by the investigator and by the sponsor. The sponsor's assessment is described below (from Section 6.5.2.1.2 of the Study Report), where a patient's clinical outcome is a cure unless he falls into any of the following categories

- "Failed
  - If a patient was given a non-investigational antibiotic for lack of efficacy at any time between Day 2 and the day after the investigator's clinical assessment, inclusive, (if the assessment was made), then the outcome was classified as Failed for that assessment and all assessments that followed. If no investigator's clinical assessment was made in the F-U window and the patient was given an antibiotic for lack of efficacy at any time between Day 2 and the upper limit of the F-U window, inclusive, then the outcome was classified as Failed for the F-U visit.
  - If a patient had no post-Baseline assessment in the EOT and F-U window (or the assessments were indeterminate at both time points), that patient was classified as a clinical failure at both visits.
  - If a patient had no data (or if the outcome was Indeterminate) at the F-U visit, an outcome of Failed at EOT was carried forward to the F-U visit.
- Indeterminate: If a patient was assessed by the sponsor as Clinically Improved or Cured at the EOT visit and had no assessment at the F-U visit (or the assessment was indeterminate), the outcome was Indeterminate at the Test-of-Cure visit.

- Missing: Patients who received fewer than 2 days of treatment or received fewer than 6 doses had an outcome of Missing."

Thus, the sponsor's algorithm is a function of the investigator's assessment at the EOT and TOC visits, the duration of study drug use, and whether effective concomitant drug use has been administered.

The study report indicates in Section 6.1.7.1 that the non-inferiority margin is –10%; however this does not appear to be addressed in the protocol. While the protocol is not explicit, it suggests that the overall population, regardless of clinical diagnosis and/or pathogen presence and type, is the primary population of interest for this non-inferiority comparison.

2.3 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY / SAFETY

This section is the heart of the review. A detailed summary of the sponsor's results and conclusions is presented. This is followed by a discussion of concerns about the sponsor's approach, and thus, the rationale for approach used by the FDA statistical reviewer. The FDA statistical review's results are presented, along with conclusions.

2.3.1 SPONSOR'S RESULTS AND CONCLUSIONS

The sponsor presented results can be summarized as follows:

- There were 215 patients in the Linezolid treatment group and 101 in the Vancomycin treatment group. (Note that four of the patients randomized to Vancomycin appear in the Linezolid treatment arm in all of the sponsor's tables.)
- The rate of 22% of the Linezolid patients who were discontinued was similar to 25% in Vancomycin. Both groups lost about 7% to adverse events. The Vancomycin group did experience a higher rate of lost-to-follow-up (10% vs. 3%).
- Approximately 60% of patients were in the MITT population for both arms. Approximately 70% were in the CE population for both arms, and about 45% in the ME population for both arms. The most common exclusion for the PP populations was "no postbaseline clinical outcome". The sponsor's report of reasons for exclusion was very similar across the arms.
- Approximately 65% of children were over the age of 1 year, 40% were white race, 55% were male, and 45% were North American in both groups. The only apparent slight imbalance was a larger percentage of black children in the Vancomycin group (23% vs. 12%). In addition, the Linezolid group had a larger percentage of children who were under 20 days at randomization.
- Median treatment duration was 11 days in both groups
- The sponsor's assessment of clinical outcome at the TOC visit was very similar between the two groups for ITT, MITT, CE, and ME populations (see table below for presented results.)
- Clinical success rates were fairly similar for the two groups using the following subgroups: baseline diagnosis, diagnosis by pathogen, race, and pathogen. However small sample size limits the strength of this conclusion.
- The reported adverse events were somewhat more prevalent in the Vancomycin arm for almost every category, and this difference was marked for those adverse events that were judged to be drug-related. However, the Linezolid arm did have a somewhat higher incidence of serious adverse events (20% versus 16%.) Adverse events with a difference associated with a nominal p-value of .01 were all more prevalent in the Vancomycin arm: anaphylaxis (10% vs. 0%), tachycardia (3% vs. 0%), monilia oral (7% vs. 1%), and hyperventilation (3% vs. 0%).
- A higher death rate was observed in the Linezolid group (6% vs. 3%).

- Comparisons of mean change in various lab values such as platelets and hemoglobin did not reveal important differences between the treatment arms.

The following set of tables, Table 2 - Table 10, present some key details excerpted from the sponsor's Study Report.

Statistical Reviewer's Comment: Note that all tables excerpted from the sponsor's Study Report classify patients by treatment received; there were four patients randomized to Vancomycin who received Linezolid – three according to the protocol because they had VRE, and one in error. This approach is not consistent with the intent-to-treat principle.

Table 2. Sponsor Result: Demographic characteristics from ITT population (excerpted from Study Report Table 14)

Demographic Characteristic	Category or Statistic	Treatment Group	
		Linezolid N = 215†	Vancomycin N = 101†
Age category, n (%)	Total patients reported	215	101
	0-7 days, pre-term*	1 (0.5)	2 (2.0)
	0-7 days, full term*	1 (0.5)	0
	8-90 days, pre-term*	25 (11.6)	6 (5.9)
	8-90 days, full term*	16 (7.4)	10 (9.9)
	8-90 days, unknown term	0	2 (2.0)
	91-182 days	10 (4.7)	5 (5.0)
	183 days - <1 year	24 (11.2)	11 (10.9)
	1 year-4 years	88 (40.9)	42 (41.6)
	5 years-11 years	50 (23.3)	23 (22.8)
Age, years	Total patients reported	215	101
	Mean ± SD	2.91 ± 3.16	2.94 ± 3.13
	Median	1.50	1.80
Race, n (%)	Total patients reported	214	101
	White	9	
	Black	26 (12.1)	23 (22.8)
	Asian or Pacific Islander	4 (1.9)	2 (2.0)
	Mixed/multiracial	91 (42.5)	38 (37.6)
Sex, n (%)	Total patients reported	215	101
	Male	117 (54.4)	59 (58.4)
	Female	98 (45.6)	42 (41.6)
Geographic region, n (%)	Total patients reported	215	101
	North America	95 (44.2)	46 (45.5)
	Latin America	120 (55.8)	55 (54.5)

Abbreviations: ITT = intent-to-treat, SD = standard deviation

* Pre-term=gestational age at delivery <34 weeks; full term=gestational age at delivery □

† All percentages and statistics are based on the number of patients reported

‡ P-value for mean age is based on ANOVA; other p-values are based on a chi-square test.

Table 3. Sponsor Result: Sponsor's Assessment of TOC Clinical Outcomes (#Cured/#Assessed)

Pop'n	Linezolid			Vancomycin			95% Confidence Interval of Treatment Diff
	Rate	Number Assessed	Total N	Rate	Number Assessed	Total N	
ITT	.791	196	215	.741	85	101	(-.060, .159)
MITT	.808	125	137	.811	53	62	(-.129, .123)
CE	.893	150	151	.845	71	73	(-.049, .146)
ME	.882	93	93	.870	46	46	(-.105, .130)

Table 4. Sponsor Result: Sponsor's Assessment of TOC Clinical Outcome by Diagnosis of Primary Infection in ITT Population (excerpted from Study Report Table 35)

Baseline Diagnosis	Assessment	Linezolid N = 215 n (%)*	Vancomycin N = 101 n (%)*	95% CI‡
Hospital-acquired pneumonia	Cured	13 (68.4)	11 (84.6)	-44.9, 12.5
	Failed	6 (31.6)	2 (15.4)	
	No. Assessed§	19 (100.0)	13 (100.0)	
Skin/skin structure infection	Cured	64 (86.5)	28 (82.4)	-10.9, 19.1
	Failed	10 (13.5)	6 (17.6)	
	No. Assessed§	74 (100.0)	34 (100.0)	
Bacteremia (catheter-related)	Cured	31 (73.8)	8 (72.7)	-28.4, 30.6
	Failed	11 (26.2)	3 (27.3)	
	No. Assessed§	42 (100.0)	11 (100.0)	
Bacteremia (unknown source)	Cured	23 (69.7)	10 (58.8)	-17.3, 39.0
	Failed	10 (30.3)	7 (41.2)	
	No. Assessed§	33 (100.0)	17 (100.0)	
Other infection	Cured	24 (85.7)	6 (60.0)	-7.3, 58.7
	Failed	4 (14.3)	4 (40.0)	
	No. Assessed§	28 (100.0)	10 (100.0)	

* All percentages are based on the number of patients assessed.
‡ Confidence interval (percentage) for the difference in cure rates based on normal approximation
§ Excludes patients with Indeterminate or Missing outcomes.

Table 5. Sponsor Result: Sponsor Assessment of Clinical Outcome at TOC by Selected Diagnosis and Pathogen in ME Population (Excerpted from Study Report Table 37)

Diagnosis / Pathogen	Assessment at F-U	Linezolid n (%)*	Vancomycin n (%)*	95% CI‡
Hospital-acquired pneumonia *Staphylococcus aureus*	Cured	3 (100.0)	2 (100.0)	--
	No. Assessed§	3	2	
Skin/skin structure infection *Staphylococcus aureus*	Cured	27 (93.1)	18 (94.7)	-15.3, 12.0
	No. Assessed§	29	19	
Skin/skin structure infection *Streptococcus pyogenes*	Cured	2 (100.0)	1 (50.0)	-19.3, 100
	No. Assessed§	2	2	
Catheter-related bacteremia *Staphylococcus epidermidis*	Cured	14 (77.8)	6 (85.7)	-40.2, 24.3
	No. Assessed§	18	7	

* All percentages are based on the number of patients assessed.
‡ Confidence interval (percentage) for the difference in cure rates based on normal approximation
§ Excludes patients with Indeterminate or Missing outcomes.

Table 6. Sponsor Result: Collapsed Pathogen Microbiologic Outcome at TOC by Baseline Susceptibility for MITT Population (Excerpted from Study Report Table 42)

Baseline Pathogen	Suscept. Profile	Assessment	Linezolid N = 137 n (%)†	Vancomycin N = 62 n (%)†	95% CI§
Enterococcus faecalis	V:S	Eradication	10 (66.7)	3 (75.0)	-57.0, 40.3
		No. Assessed¶	15 (100.0)	4 (100.0)	
Enterococcus faecium	V:R	Eradication	2 (66.7)	0	
		No. Assessed¶	3 (100.0)	0	
	V:S	Eradication	4 (100.0)	0	
		No. Assessed¶	4 (100.0)	0	
Staphylococcus aureus	M:R	Eradication	15 (83.3)	9 (75.0)	-21.6, 38.3
		No. Assessed¶	18 (100.0)	12 (100.0)	
	M:S	Eradication	25 (78.1)	17 (94.4)	-34.1, 1.5
		No. Assessed¶	32 (100.0)	18 (100.0)	
Staphylococcus epidermidis	M:R	Eradication	25 (80.6)	10 (90.9)	-32.2, 11.7
		No. Assessed¶	31 (100.0)	11 (100.0)	
	M:S	Eradication	2 (100.0)	1 (50.0)	-19.3, 100
		No. Assessed¶	2 (100.0)	2 (100.0)	
Staphylococcus hemolyticus	M:R	Eradication	4 (100.0)	1 (100.0)	
		No. Assessed¶	4 (100.0)	1 (100.0)	
	M:S	Eradication	1 (100.0)	0 (0.0)	
		No. Assessed¶	1 (100.0)	1 (100.0)	
Staphylococcus hominis	M:R	Eradication	11 (91.7)	0 (0.0)	76.0, 100
		No. Assessed¶	12 (100.0)	1 (100.0)	
Staphylococcus warneri	M:R	Eradication	0	1 (50.0)	
		No. Assessed¶	0	2 (100.0)	
	M:S	Eradication	1 (100.0)	1 (100.0)	
		No. Assessed¶	1 (100.0)	1 (100.0)	
Streptococcus pneumoniae	P2:R	Eradication	3 (75.0)	0	
		No. Assessed¶	4 (100.0)	0	
	P:I	Eradication	1 (100.0)	1 (100.0)	
		No. Assessed¶	1 (100.0)	1 (100.0)	
Streptococcus pyogenes	All	Eradication	3 (100.0)	1 (33.3)	13.3, 100
		No. Assessed¶	3 (100.0)	3 (100.0)	

* Antibiotic code:Susceptibility code
Antibiotic codes: M=Oxacillin, P=Penicillin, V=Vancomycin
Susceptibility codes: R=Resistant, I=Intermediate, S=Susceptible
P2:R= Resistance to penicillin and at least 1 other antibiotic
† All percentages are based on the number of patients assessed.
§ Confidence interval (percentage) for difference in eradication rates based on normal approximation
¶ Excludes patients with Indeterminate or Missing outcomes.

Table 7. Sponsor Result: Collapsed Pathogen Microbiologic Outcome at TOC by Baseline Diagnosis and Baseline Susceptibility in MITT Population (Excerpted from Study Report Table 43)

Baseline Pathogen	Suscept. Profile*	Assessment	Linezolid n (%)†	Vancomycin n (%)†	95% CI§
Baseline Diagnosis: Hospital-acquired Pneumonia					
Staphylococcus aureus	M:R	Eradication	2 (66.7)	1 (100.0)	-86.7, 20.0
		Non-eradication	1 (33.3)	0 (0.0)	
		No. Assessed¶	3 (100.0)	1 (100.0)	
	M:S	Eradication	1 (100.0)	2 (100.0)	
		Non-eradication	0 (0.0)	0 (0.0)	
		No. Assessed¶	1 (100.0)	2 (100.0)	
Baseline Diagnosis: Skin / Skin Structure Infection					
Staphylococcus aureus	M:R	Eradication	9 (90.0)	6 (75.0)	-20.3, 50.3
		Non-eradication	1 (10.0)	2 (25.0)	
		No. Assessed¶	10 (100.0)	8 (100.0)	
	M:S	Eradication	21 (84.0)	13 (100.0)	-30.4, -1.6
		Non-eradication	4 (16.0)	0 (0.0)	
		No. Assessed¶	25 (100.0)	13 (100.0)	

* Antibiotic code:Susceptibility code
Antibiotic codes: M=Oxacillin
Susceptibility codes: R=Resistant, S=Susceptible
† All percentages are based on the number of patients assessed.
‡ P-value is based on a chi-square test.
§ Confidence interval (percentage) for difference in eradication rates based on normal approximation
¶ Excludes patients with Indeterminate or Missing outcomes.

Table 8. Sponsor Result: Adverse Event Summary (Excerpted Study Report Table 53)

Adverse Event Category	Linezolid N = 215 n (%)*	Vancomycin N = 101 n (%)*	p-Value†
Total Patients Reported*	213	99	
Patients with ≥1 AE	155 (72.8)	78 (78.8)	0.2552
Patients with ≥1 drug-related AE	40 (18.8)	34 (34.3)	0.0026
Patients with ≥1 AE leading to D/C	15 (7.0)	7 (7.1)	0.9927
Patients with ≥1 drug-related AE leading to D/C	2 (0.9)	6 (6.1)	0.0077
Patients with ≥1 serious AE	42 (19.7)	16 (16.2)	0.4523

Abbreviations: AE = adverse event, D/C = discontinuation of medication
* All percentages are based on the number of patients reported.
† P-value is based on a chi-square test.

Table 9. Sponsor Result: Adverse Events by Body System (excerpted from Study Report Table 54)

COSTART Body System Classification*	Treatment Group		p-Value‡
	Linezolid N = 215 n (%)†	Vancomycin N = 101 n (%)†	
Total Patients Reported	213	99	
Body	89 (41.8)	47 (47.5)	0.3454
Cardiovascular	27 (12.7)	13 (13.1)	0.9109
Digestive	64 (30.0)	29 (29.3)	0.8922
Hemic and Lymphatic	36 (16.9)	15 (15.2)	0.6972
Metabolic and Nutritional	31 (14.6)	9 (9.1)	0.1791
Musculo-skeletal	3 (1.4)	1 (1.0)	0.7710
Nervous	17 (8.0)	4 (4.0)	0.1960
Respiratory	47 (22.1)	19 (19.2)	0.5629
Skin	35 (16.4)	28 (28.3)	0.0152
Special Senses	12 (5.6)	3 (3.0)	0.3171
Urogenital	8 (3.8)	8 (8.1)	0.1070

* The information represents the number (%) of patients who reported at least one adverse event in the body system. Any patient who reported more than one event in a given body system was counted only once for that body system.
† All percentages are based on the number of patients reported.
‡ P-value is based on a chi-square test.

Table 10. Sponsor Result: Change from Baseline to Follow-up in Selected Hematology Assay Results (Excerpted from Study Report Table 64)

Assay	Statistic	Treatment Group		p-Value‡
		Linezolid N = 215†	Vancomycin N = 101†	
Hemoglobin, g/dL	Total reported*	181	78	0.596
	Baseline mean	10.82	10.8	
	Mean change from baseline	0.2	0.33	
	Standard deviation	1.95	1.52	
	p-value, within treatment (t-test)	0.164	0.056	
Hematocrit,%	Total reported*	183	78	0.340
	Baseline mean	32.55	32.42	
	Mean change from baseline	0.88	1.61	
	Standard deviation	6	4.73	
	p-value, within treatment (t-test)	0.049	0.004	
WBC, $x10^3$ / µL	Total reported*	183	78	0.248
	Baseline mean	12.48	14.71	
	Mean change from baseline	-3.17	-4.37	
	Standard deviation	6.98	9.04	
	p-value, within treatment (t-test)	<0.001	<0.001	
Neutrophil count, $x10^3$ / µL	Total reported*	173	70	0.224
	Baseline mean	7.34	8.7	
	Mean change from baseline	-3.3	-4.36	
	Standard deviation	5.96	6.49	
	p-value, within treatment (t-test)	<0.001	<0.001	
Band neutrophils, %	Total reported*	134	57	0.817
	Baseline mean	4.06	4.85	
	Mean change from baseline	-2.12	-1.85	
	Standard deviation	8.23	5.6	
	p-value, within treatment (t-test)	0.003	0.016	
Platelet count, $x10^3$ / µL	Total reported*	182	78	0.380
	Baseline mean	291	292.1	
	Mean change from baseline	61.4	38.5	
	Standard deviation	195.7	184.6	
	p-value, within treatment (t-test)	<0.001	0.069	

Abbreviations: F-U = follow-up (test-of-cure visit)
* Patients having non-missing values at both Baseline and Follow-up
† All percentages and statistics are based on the number of patients reported for each characterstic
‡ P-value is based on ANOVA.

The Study Report draws this overall conclusion:

> "The primary objectives of this study included assessment and comparison of the efficacy and safety of linezolid (IV and oral) and IV vancomycin in the treatment of infections due to antibiotic-resistant gram-positive bacterial pathogens in children from birth through 11 years of age. (The study's objectives relating to pharmacokinetic/pharmacodynamic assessments

are discussed in a separate report.) The enrollment criteria were successful in producing a study population with a representative set of relevant clinical characteristics including diagnosis and pathogen, and the randomization procedure allocated the patients into 2 groups with comparable demographic and clinical profiles. The study completion rates and overall patient disposition were similar between treatment groups.

Both clinical and microbiological endpoints were used to evaluate the efficacy of linezolid and vancomycin. In this study, both treatments were effective in the treatment of the types of infections studied. At the test-of-cure assessment (the follow-up visit) in the clinically evaluable population, the clinical cure rate in both treatment groups was ≥95% by the investigators' assessment and ≥84% by the sponsor's assessment. This effect was consistent across all primary and secondary efficacy assessments, for all age groups (including neonates), and across all primary sources of infection.

The overall safety profiles of linezolid and vancomycin were comparable in the patient population studied. No study-emergent adverse events or drug-related adverse events were reported statistically more frequently in linezolid recipients than in vancomycin recipients. The experience of linezolid-treated pediatric patients in this study with respect to hematologic adverse events was generally similar to that reported in linezolid adult clinical trials.

Increasing rates of antibiotic-resistant bacterial pathogens are now severely limiting the available choice of effective antibiotics in many areas. This study demonstrated that linezolid is well tolerated and equally as effective as vancomycin in treating infections in children due to suspected or proven resistant gram-positive pathogens, including hospital-acquired pneumonia, complicated skin and skin structure infections, catheter-related bacteremia, bacteremia of unknown source, and other infections."

2.3.2 STATISTICAL METHODOLOGIES

It is noted that the protocol did not pre-specify non-inferiority margins, nor compute a sample size with a specific stated goal, that is, apparently, this study was not designed to provide formal statistical evidence. On the surface, the statistical methodologies used by the sponsor are very elementary and straightforward; these primarily include the use of 95% confidence intervals and p-values to compare various rates of the treatment arms. While the results presented in the Study Report are, for the most part, consistent with the protocol, there are a number of more subtle concerns about the way that results are presented in the Study Report. This is partly because of potential weaknesses in the procedures established in the protocols. An alternate approach as conducted by the reviewer is described in this section.

2.3.2.1 Concerns about the Sponsor's Study Report

Concerns in the Study Report include:

- Many comparisons are made, and the nominal p-values and confidence intervals are listed without explanation about the difficulty in interpreting so many multiple comparisons.
- All tables are presented by treatment received, rather than by the randomized treatment. This impacts four patients who were randomized to Vancomycin who were treated with Linezolid. One of these patients was treated with Linezolid in error. On the other hand, three of these patients were diagnosed with VRE shortly after randomization on the basis of the baseline culture, and according to the protocol should be put on Vancomycin. However, even in this situation, one can argue that some other approach should have been used in presenting ITT and MITT results, such as separating out the VRE cases, since these patients were not really

randomized. One might argue that presenting results by "treatment received" for the CE and ME populations is less of a concern, especially in view of the relatively small number of cases.

- The sponsor uses a complex algorithm to determine assessment of the primary outcome (this algorithm can be found in Section 2.2 of this review). This assessment is a function of the length of time on study drug. It also makes judgments about the extent of incomplete information, and thereby classifies patients into failures, indeterminates, or missing for all analyses. Thus, the Study Report never distinguishes between a clear-cut failure and a patient with the sort of missing data pattern that gets classified into a failure. Thus, there are two concerns about this approach. First, its dependence on study drug compliance duration makes it inappropriate for ITT and MITT results. Second, while this algorithm is one reasonable approach as a type of sensitivity analysis that allocates specific outcomes for patterns of missing data, since it is always used, it does not allow the reader to distinguish clearly between good, bad, and unknown outcomes.
- This is a non-inferiority type study of a drug that has potential activity only against gram-positive organisms. Thus, antibiotics with gram-negative coverage were allowed to cover this potential. Even though the investigators enrolled patients with presumed gram-positive infections, in reality, randomized patients could have a) a documented gram-positive infection, b) no documented bacterial infection, c) a documented gram-negative infection, or d) a documented mixed infection (both gram-positive and gram-negative). In the case of a mixed infection, the infection might be due to one pathogen and the patient merely "colonized" with the other pathogen. In a non-inferiority trial, assay sensitivity is highest when only patients who are appropriately treated by the active control are included in the primary analysis. Thus, the cleanest analysis of these patients would include only those patients with documented gram-positive-only infections, thus this population should be considered in a sensitivity analysis. If Linezolid were actually worse than Vancomycin in the treatment of gram-positive patients, the inclusion of all the other patients might tend to obscure the treatment difference.
- The sponsor includes all patients with *coagulase-negative staphylococcus* as members of the MITT population. However, this organism is only considered a true pathogen if the patient has a catheter-related bloodstream infection or if the patient is a neonate (≤28 days old).
- The study report presents most results of the study overall. However, in this unusual study that mixes a number of indications, the results are probably most meaningful presented by baseline indication, and then further divided by pathogen. In addition, overall analyses that are stratified by baseline diagnosis and by age, which was a randomization stratification factor, should be conducted, at least as sensitivity analyses.
- The sponsor's CE (and ME) population included patients received antibiotics with gram-positive activity right before the trial or during the trial, in apparent violation of the protocol.
- The Study Report presents microbiologic outcomes. However, these data are almost always imputed from the clinical outcomes. Since this variable is a mixed bag of clinical outcome and a very small number of actual microbiologic assessments, it does not have a straightforward interpretation.
- This clinical trial was not blinded to treatment assignment. Since most assessments made in this trial have at least some subjective elements, this lack of blinding must be considered in the interpretation of the results.

2.3.2.2 Reviewer's Approach to address Concerns

Because of these concerns, this review will present a variety of alternative analyses. The ITT and MITT analyses ignore the duration of study therapy, and presents results by true cure, true failure,

and unknown and then consider alternate approaches to missing data. The results will focus on patients with documented gram-positive infections. Furthermore, much of the focus of the efficacy analyses will be by baseline diagnosis, and sometimes further subgrouped into pathogen type.

2.3.2.2.1 Reviewer's Clinical Cure Assessment

Because of concerns about highly derived nature of the sponsor's algorithm of clinical assessment, the reviewer will present many analyses using an alternate approach. The sponsor's assessment assigns some patients, for whom there is no outcome information, as failures, while some patients, who have outcome information or who were not assessed due to death, are assigned missing or indeterminate. The reviewer's alternate approach attempts to assign "cure" to patients with known good outcomes, "failure" to patients with known bad outcomes, and "missing" to patients with truly unknown outcomes, regardless of the duration of therapy. The reviewer will present some of these analyses with missing values excluded, as some with missing values analyzed as failures.

The reviewer's clinical assessment is as follows. Patients were assessed as failures if they were 1) assessed as a failure by the investigator at either the End of Treatment or Follow-up visit, 2) had died during the follow-up window unless they had a successful Follow-up visit, or 3) were prescribed an additional antibiotic for lack of efficacy, as stated by the investigator, during the study up to and including the Follow-up visit. Patients who did not meet any of the criteria for failure, and who were assessed as cures by the investigator at the Follow-up visit, were considered cures in the reviewer's analyses. Patients, who were neither failures nor cures, by the above criteria, were considered missing by the reviewer.

2.3.2.2.2 Reviewer's Population Criteria

The reviewer's ITT population differs slightly from the sponsor's. Those eight patients who were identified, by any source, at baseline, as having VRE (i.e., VREflag = 'Yes') were effectively not randomized, because all were treated with Linezolid. The solution used in the reviewer's analysis is to consider these patients separately. In addition, the additional non-VRE patient who was randomized to Vancomycin who received Linezolid instead, will appear in the Vancomycin group in the reviewer's analyses.

The reviewer's MITT population is based on the reviewer's ITT population. Those patients with *coagulase-negative staphylococcus* who were not diagnosed with catheter-related-bacteremia or were not neonates ($\leq$ 28 days old) and who did not have any other gram-positive pathogen were not considered part of the reviewer's MITT analysis population. (Note: patients with *S. Epidermidis, S. Warneri, S. Hominis, S. Hemolyticus* were all collapsed into *coagulase-negative staphylococcus.*)

The reviewer's CE population is based on the reviewer's ITT population. Patients who were excluded from the sponsor's CE population were also excluded by the reviewer's analysis. In addition, patient's use of the antibiotics with gram-positive coverage 24 hours in the 48-hour period prior to randomization, or during the study follow-up was a possible exclusion factor (considered antibiotics were listed in Table 27). Patients without a baseline pathogen, who received at least one of these antibiotics in the prior window or during the study (who were not re-prescribed due to lack of efficacy) were excluded from the reviewer's CE. In addition, the following five patients with baseline pathogens were excluded, because the FDA Medical Reviewer, Dr. Sumathi Nambiar, determined that they received concomitant drugs during the study that were effective therapy for their baseline pathogen: 8211115, 821154, 8222179, 8233161, and 8222232. Note that all four

patients who were randomized to Vancomycin but treated with Linezolid were excluded from the CE analysis for other reasons, so no decision was necessary about these patients.

The reviewer's ME population is based on the intersection of the reviewer's MITT and CE population.

FDA Statistical Reviewer's Comment: the reviewer's analysis population classifications will be referred to as FDA ITT, FDA MITT, FDA CE, and FDA ME for the rest of this review.

2.3.2.2.3 Additional comments about the reviewer's analysis

The reviewer's analysis did not consider microbiologic outcome. Very few patients had actual follow-up cultures, and only one of these had an outcome that was discordant with the clinical outcome. Thus, this endpoint contributed little, if any, new information.

The reviewer's analysis expanded somewhat on the sponsor's safety analysis. Again, all analyses are presented by randomized treatment, separating out the VREflag patients who effectively were not randomized. In addition, analysis of lab values was considered from slightly different angles.

2.3.3 DETAILED REVIEW OF STUDY 0082

This section presents the results of the FDA statistical reviewer's analysis, using the approaches described in Section 2.3.2.

2.3.3.1 Efficacy Results

Baseline characteristics are presented in Table 11. As expected, the treatment arms were reasonably comparable, in both populations. However, in the MITT population, the Linezolid group had more gram-positive coverage in the 48 hours prior to randomization and had a greater prevalence of CRB as the site of infection than the Vancomycin arm. In both arms, the mean age was around 3 years old. In addition, both arms were about 40% white, 55% male, 45% North American, 55% with baseline pathogen, 25% with baseline resistant pathogen. Approximately 40% of the patients had skin as the site of infection; this was the most prevalent site.

Table 11. Baseline Characteristics in ITT and FDA MITT Populations (VRE Patients Excluded)

	FDA ITT				FDA MITT			
	Linezolid		Vancomycin		Linezolid		Vancomycin	
	MEAN	N	MEAN	N	MEAN	N	MEAN	N
Prior Gram+ Drug	0.282	206.00	0.294	102.00	0.288	118.00	0.182	55.000
Age in Years	2.957	206.00	2.933	102.00	2.825	118.00	2.471	55.000
White	0.413	206.00	0.382	102.00	0.432	118.00	0.400	55.000
Male	0.539	206.00	0.588	102.00	0.534	118.00	0.473	55.000
North American	0.417	206.00	0.461	102.00	0.458	118.00	0.473	55.000
FDA MITT	0.573	206.00	0.539	102.00	1.000	118.00	1.000	55.000
Resistant Pathogen	0.272	206.00	0.235	102.00	0.475	118.00	0.436	55.000
CRBSI	0.218	206.00	0.127	102.00	0.314	118.00	0.182	55.000
BUO	0.155	206.00	0.186	102.00	0.110	118.00	0.145	55.000
HAP	0.112	206.00	0.157	102.00	0.076	118.00	0.091	55.000
SKIN	0.374	206.00	0.402	102.00	0.398	118.00	0.491	55.000
OTHER Diagnosis	0.141	206.00	0.127	102.00	0.102	118.00	0.091	55.000

CRBSI denotes Catheter Related Bloodstream Infection
BUO denotes Bacteremia of Unknown Origin

Comparison of success rates across all clinical sites and pathogens are presented in Table 12. While this overall comparison is difficult to interpret due to the large heterogeneity of the study population, analyses that suggest overall differences might be meaningful. This table suggests a potential difference between the two arms in the FDA MITT population, which does not reach statistical significance at the .05 level, with an approximate success rate of .80 in the Linezolid arm and .90 in the Vancomycin arm, when missing outcomes are excluded with a lower bound of the 95% confidence interval of -.23. On the other hand, the analyses in the other populations yield point estimates that are very similar across the two arms. Apparently, the Linezolid arm had a numeric advantage over Vancomycin in the patients with no pathogen isolated, whereas this flipped in the patients with pathogens. In general, if a difference exists, it will be easier to detect in patients who have strong evidence of bacterial disease (i.e., the patients with documented pathogens), and thus, this might be an explanation for the difference. However, given the size of the study, all of these findings may simply be due to chance. In addition, apparently a disproportionate number of Linezolid failures were excluded from the Per-Protocol (PP, i.e., CE and ME) analyses, which diminished the observed treatment effects in these populations. The primary concern about ITT and MITT analyses in the non-inferiority setting is that they may bias the treatment difference towards no difference. However, in this study, the MITT treatment difference is larger than the corresponding ME population, thus, there is no reason to embrace the ME result out of fear that the MITT is underestimating the treatment difference. Thus, in conclusion, the MITT result that suggests a possible treatment difference is an important finding.

Table 12. Analysis of Reviewer's Clinical Endpoint in FDA Primary Analysis Populations

Reviewer's Clinical Endpoint								
Population	Missing Data	Linezolid		Vancomycin		Diff (L-V)	95% Confidence Interval	
		Cure Rate	N	Cure Rate	N		Lower	Upper
FDA ITT	*Excluded*	0.806	186	0.831	83	-.025	-.132	0.082
FDA MITT	*Excluded*	0.796	108	0.898	49	-.102	-.230	0.027
FDA CE	*Excluded*	0.906	117	0.907	54	-0.001	-.109	0.106
FDA ME	*Excluded*	0.888	80	0.905	42	-.017	-.148	0.113

The results of sensitivity analyses presented in Table 13 tend to be consistent with the primary results. Considering missing outcomes as failures as one approach that is sometimes used. However, the value of comparing two arms, using this approach, is unclear, unless it is reasonable to assume missing data, indeed tends to represent patients who would have failed, had they been measured. It is not clear that this is such a situation, however, the point estimates for each arm are conservative. Note that in the FDA MITT population the approximately 10% of the observations are missing, in both arms. However, in the ITT population, the Vancomycin arm is missing about 20% of the observations; this differential has an unknown impact on ITT results. The sensitivity analysis that excluded patients with mixed infections (i.e., gram positive and gram negative) as represented by FDA MITT2 was nearly identical to the FDA MITT analysis, because there were few patients with mixed infections.

It is further noted that stratified confidence intervals that controlled for age category, which was the randomization stratification factor, as well as site of infection, yielded results that were nearly identical to the unstratified analyses presented in this review.

Table 13. Sensitivity Analyses of Reviewer's Clinical Endpoint: Alternate Populations and Strategies for Missing Data

Reviewer's Clinical Endpoint								
Population	Missing Data	Linezolid		Vancomycin		Diff (L-V)	95% Confidence Interval	
		Cure Rate	N	Cure Rate	N		Lower	Upper
FDA ITT	*Failures*	0.728	206	0.676	102	0.052	-.065	0.168
FDA MITT	*Failures*	0.729	118	0.800	55	-.071	-.217	0.075
FDA MITT2	*Excluded*	0.794	102	0.894	47	-.099	-.233	0.034
FDA MITT2	*Failures*	0.730	111	0.808	52	-.078	-.227	0.071
FDA ME alt	*Excluded*	0.877	81	0.905	42	-.028	-.160	0.104

FDA MITT2 deletes MITT patients with gram-negative infections at baseline
FDA ME alt does not exclude failures who received concomitant antibiotics

The sponsor's clinical endpoint is analyzed using FDA populations in Table 14, as another sensitivity analysis. While the pattern between populations is somewhat similar to the results using the reviewer's clinical outcome, the results almost all are more favorable to Linezolid than the FDA results. Concerns about the sponsor's clinical outcome algorithm are discussed in Section 2.3.2.

Table 14. Sponsor's Clinical Endpoint using FDA Analysis Populations

Sponsor Clinical Endpoint								
Population	Missing Data	Linezolid		Vancomycin		Diff (L-V)	95% Confidence Interval	
		Cure Rate	N	Cure Rate	N		Lower	Upper
FDA ITT	*Excluded*	0.791	187	0.744	86	0.047	-.070	0.165
FDA ITT	*Failures*	0.718	206	0.627	102	0.091	-.028	0.210
FDA MITT	*Excluded*	0.796	108	0.837	49	-.040	-.184	0.103
FDA MITT	*Failures*	0.729	118	0.745	55	-.017	-.170	0.137
FDA CE	*Excluded*	0.898	118	.875	56	0.023	-.092	0.139
FDA ME	*Excluded*	0.877	81	.884	43	-.007	-.145	0.130

The reviewer's clinical endpoint is analyzed by site of infection with the ITT population in Table 15. Perhaps only HAP and skin infections are appropriately considered without regard to pathogens. When missing values are excluded for both of these indications, again, there is a numerical advantage of Vancomycin; however, these sample sizes are much too small to be conclusive.

Table 15. Analysis of Reviewer's Clinical Endpoint by Baseline Diagnosis in ITT Population

Reviewer's Clinical Endpoint (FDA ITT Population)								
	Site	Linezolid		Vancomycin		Diff (L-V)	95% Confidence Interval	
		Cure Rate	N	Cure Rate	N		Lower	Upper
Missing Values Excluded	BUO	0.759	29	0.688	16	0.071	-.253	0.395
	CRB	0.732	41	0.667	12	0.065	-.288	0.418
	HAP	0.722	18	0.917	12	-.194	-.523	0.134
	OTH	0.923	26	0.889	9	0.034	-.270	0.338
	SKN	0.847	72	0.912	34	-.065	-.213	0.084
Missing Values Counted as Failures	BUO	0.688	32	0.579	19	0.109	-.207	0.424
	CRB	0.667	45	0.615	13	0.051	-.296	0.399
	HAP	0.565	23	0.688	16	-.122	-.480	0.235
	OTH	0.828	29	0.615	13	0.212	-.142	0.566
	SKN	0.792	77	0.756	41	0.036	-.142	0.214

The reviewer's clinical endpoint is analyzed by site of infection with the FDA MITT population in Table 16. With the exception of CRB which shows very similar success rates in both arms, the other sites show a numerical advantage for Vancomycin; although, again, the study sizes are far too small to be conclusive.

Table 16. Analysis of Reviewer's Clinical Endpoint by Baseline Diagnosis in FDA MITT Population

Reviewer's Clinical Endpoint (FDA MITT Population)								
	Site	Linezolid		Vancomycin		Diff (L-V)	95% Confidence Interval	
		Cure Rate	N	Cure Rate	N		Lower	Upper
Missing Values Excluded	BUO	0.667	12	0.875	8	-.208	-.664	0.247
	CRB	0.714	35	0.700	10	0.014	-.371	0.400
	HAP	0.833	6	1.000	4	-.167	-.673	0.340
	OTH	0.917	12	1.000	4	-.083	-.406	0.240
	SKN	0.860	43	0.957	23	-.096	-.262	0.070
Missing Values Counted as Failures	BUO	0.615	13	0.875	8	-.260	-.711	0.191
	CRB	0.676	37	0.700	10	-.024	-.409	0.361
	HAP	0.556	9	0.800	5	-.244	-.878	0.389
	OTH	0.917	12	0.800	5	0.117	-.409	0.642
	SKN	0.787	47	0.815	27	-.028	-.244	0.189

Since the skin infections arguably can be considered with and without pathogens, Table 17 presents the reviewer's clinical success rates for patients with skin infection by presence or absence of baseline pathogen. It is interesting to note that the observed rates are very similar without documented pathogens, with a suggestion of a difference with documented bacterial disease. Again, the sample sizes are too small to draw conclusions.

Table 17. Reviewer's Clinical Endpoint in FDA ITT Population by Presence or Absence of Baseline Pathogen in Skin Infections

Skin Infections, FDA ITT Population, Reviewer's Clinical Assessment, Missing Values Excluded				
Baseline Pathogen	Linezolid		Vancomycin	
	Cure Rate	N	Cure Rate	N
Present	.860	43	.957	23
Absent	.828	29	.818	11

Reviewer's clinical success rates are presented by pathogen in Table 18. An advantage of Vancomycin that is statistically significant at the nominal .05 level is seen for patients with MRSE; however, given the large number of multiple comparisons; this should only be interpreted as a possible advantage, and not truly statistically significant. A potential advantage is also seen for *S. Aureus* patients. In fact, in the MITT analyses with missing values excluded, for most pathogens considered, the observed success rate in the Vancomycin arm is larger than that of the Linezolid arm. Estimates of success rates in the Linezolid arms are between .70 and .90 for most pathogens. Observed treatment differences are generally smaller in the FDA ME population.

Table 18. Reviewer's Clinical Endpoint by Baseline Pathogen

Reviewer's Clinical Endpoint								
	Baseline Pathogen	Linezolid		Vancomycin		Diff (L-V)	95% Confidence Interval	
		Cure Rate	N	Cure Rate	N		Lower	Upper
FDA MITT Missing Values Excluded	*S Aureus*	0.851	47	0.966	29	-.114	-.264	0.035
	Coag-Neg Staph	0.778	36	0.769	13	0.009	-.310	0.327
	E Faecium	0.833	6	.	.	.	.	.
	E Faecalis	0.643	14	0.800	5	-.157	-.724	0.410
	S Pneumo	0.800	5	1.000	1	-.200	-1.15	0.751
	S Pyogenes	1.000	3	0.667	3	0.333	-.533	1.200
	PRSP	0.750	4	.	.	.	.	.
	MRSA	0.889	18	1.000	9	-.111	-.340	0.117
	MRSE	0.741	27	1.000	9	-.259	-.499	-.020
	MRSS	0.781	32	0.818	11	-.037	-.367	0.293
FDA MITT Missing Values Counted as Failures	*S Aureus*	0.727	55	0.824	34	-.096	-.294	0.102
	Coag-Neg Staph	0.737	38	0.769	13	-.032	-.352	0.288
	E Faecium	0.833	6	.	.	.	.	.
	E Faecalis	0.643	14	0.667	6	-.024	-.596	0.548
	S Pneumo	0.800	5	1.000	1	-.200	-1.15	0.751
	S Pyogenes	1.000	3	0.500	4	0.500	-.282	1.282
	PRSP	0.750	4	.	.	.	.	.
	MRSA	0.842	19	0.692	13	0.150	-.215	0.514
	MRSE	0.714	28	1.000	9	-.286	-.526	-.045
	MRSS	0.735	34	0.818	11	-.083	-.415	0.249
FDA ME	*S Aureus*	0.947	38	0.958	24	-.011	-.152	0.130
	Coag-Neg Staph	0.821	28	0.833	12	-.012	-.326	0.302
	E Faecium	1.000	3	.	.	.	.	.
	E Faecalis	0.625	8	0.750	4	-.125	-.853	0.603
	S Pneumo	1.000	3	1.000	1	0.000	-.667	0.667
	S Pyogenes	1.000	2	0.500	2	0.500	-.693	1.693
	PRSP	1.000	2	.	.	.	.	.
	MRSA	0.941	17	1.000	9	-.059	-.256	0.138
	MRSE	0.783	23	1.000	9	-.217	-.463	0.028
	MRSS	0.808	26	0.900	10	-.092	-.401	0.217

The reviewer's success rates are presented by both site of infection and pathogen in Table 19. While sample sizes are generally very small, a few site-by-pathogen samples are large enough to provide some limited information: *S. aureus* skin infections, *Coagulase Negative staphylococcus* CRB infections, MRSE CRB infections, and MRSS CRB infections. In these four subgroups, the observed success rates for Linezolid ranged from .737 to .833. The observed success rates were higher for Vancomycin for the *S aureus* skin infections and the MRSE CRB infections; however the reverse was true for *Coagulase-Negative staphylococcus* CRB infections and MRSS infections.

Table 19. Reviewer's clinical endpoint by pathogen and site of infection (FDA MITT population)

Reviewer's Clinical Endpoint (FDA MITT Population)									
		Missing Excluded				Missing Counted as Failures			
		Linezolid		Vancomycin		Linezolid		Vancomycin	
Pathogen	Site	Cure Rate	N	Cure Rate	N	Cure Rate	N	Cure Rate	N
S Aureus	BUO	1.000	2	0.667	3	0.667	3	0.667	3
	CRB	0.500	2	1.000	1	0.333	3	1.000	1
	HAP	1.000	3	1.000	3	0.600	5	0.750	4
	OTH	1.000	4	1.000	1	1.000	4	0.500	2
	SKN	0.833	36	1.000	21	0.750	40	0.875	24
Coag Neg Staph	BUO	0.800	5	1.000	3	0.800	5	1.000	3
	CRB	0.769	26	0.667	9	0.741	27	0.667	9
	HAP	0.667	3	1.000	1	0.500	4	1.000	1
	OTH	1.000	1	.	.	1.000	1	.	.
	SKN	1.000	1	.	.	1.000	1	.	.
E Faecium	CRB	0.667	3	.	.	0.667	3	.	.
	OTH	1.000	1	.	.	1.000	1	.	.
	SKN	1.000	2	.	.	1.000	2	.	.
E Faecalis	BUO	0.333	3	0.500	2	0.333	3	0.500	2
	CRB	0.600	5	.	.	0.600	5	.	.
	HAP	.	.	1.000	1	.	.	1.000	1
	OTH	0.750	4	1.000	1	0.750	4	0.500	2
	SKN	1.000	2	1.000	1	1.000	2	1.000	1
S Pneumo	BUO	0.500	2	.	.	0.500	2	.	.
	CRB	1.000	1	.	.	1.000	1	.	.
	OTH	1.000	2	1.000	1	1.000	2	1.000	1
S Pyogenes	SKN	1.000	3	0.667	3	1.000	3	0.500	4
PRSP	BUO	0.500	2	.	.	0.500	2	.	.
	CRB	1.000	1	.	.	1.000	1	.	.
	OTH	1.000	1	.	.	1.000	1	.	.
MRSA	BUO	1.000	1	1.000	1	1.000	1	1.000	1
	HAP	1.000	2	1.000	1	0.667	3	1.000	1
	OTH	1.000	4	1.000	1	1.000	4	0.500	2
	SKN	0.818	11	1.000	6	0.818	11	0.667	9
MRSE	BUO	0.667	3	1.000	3	0.667	3	1.000	3
	CRB	0.737	19	1.000	5	0.737	19	1.000	5
	HAP	0.667	3	1.000	1	0.500	4	1.000	1
	OTH	1.000	1	.	.	1.000	1	.	.
	SKN	1.000	1	.	.	1.000	1	.	.
MRSS	BUO	0.800	5	1.000	3	0.800	5	1.000	3
	CRB	0.773	22	0.714	7	0.739	23	0.714	7
	HAP	0.667	3	1.000	1	0.500	4	1.000	1
	OTH	1.000	1	.	.	1.000	1	.	.
	SKN	1.000	1	.	.	1.000	1	.	.

A summary of variables measured during the course of the study is presented in Table 20. Of particular interest, the number of drug doses taken was very similar across the two arms.

Table 20. On Study variables in FDA ITT and FDA MITT Populations

	FDA ITT				FDA MITT			
	Linezolid		Vancomycin		Linezolid		Vancomycin	
	MEAN	N	MEAN	N	MEAN	N	MEAN	N
Completed Study	0.782	206.00	0.755	102.00	0.797	118.00	0.855	55.000
Adverse Event	0.709	206.00	0.775	102.00	0.763	118.00	0.764	55.000
Related Adverse Event	0.180	206.00	0.343	102.00	0.229	118.00	0.400	55.000
Serious Adverse Event	0.191	204.00	0.170	100.00	0.179	117.00	0.127	55.000
Total # Doses meds taken	30.117	206.00	31.624	101.00	32.331	118.00	31.673	55.000
Discontinued due to AE	0.068	206.00	0.069	102.00	0.085	118.00	0.055	55.000
Gram+ Drug During	0.379	206.00	0.431	102.00	0.390	118.00	0.364	55.000
Drug for lack efficacy	0.112	206.00	0.078	102.00	0.144	118.00	0.073	55.000
FDA CE	0.578	206.00	0.559	102.00	0.695	118.00	0.782	55.000
FDA Clinical Cure	0.806	186.00	0.831	83.000	0.796	108.00	0.898	49.000
FDA Clinical Cure Missing as Failure	0.728	206.00	0.676	102.00	0.729	118.00	0.800	55.000

Patients, who were identified at some point as having VRE, were treated with Linezolid, regardless of randomized assignments, and thus were removed from the reviewer's analyses that compared the randomized groups. A summary of these eight patients appears in Table 21. Only three of these patients actually had VRE on the study baseline culture. Of these, one failed, and two were cures. The two cures also had other gram-positive coverage during the treatment period.

Table 21. Summary of patients who were treated with Linezolid regardless of treatment assignment because of VRE infection (VREFLAG='Y')

VRE on baseline culture (*E Faecium*)	Other Baseline Pathogens	Site	Number of Doses	Gram+ Drug Prior*	Other Gram+ Drug During	Sponsor CE	FDA CE	Reviewer's Clinical Outcome
Yes		Other	10	Yes				Failed
Yes		BUO	52	Yes	Yes	Yes	Yes	Cured
Yes		SKIN	32	Yes	Yes			Cured
		CRB	26	Yes	Yes	Yes		Cured
	S Aureus; E faecalis	CRB	40			Yes	Yes	Cured
		Other	51	Yes	Yes	Yes		Cured
		CRB	21			Yes	Yes	Failed
		SKIN	30	Maybe	Yes	Yes		Cured

- More than 24 hours during 48 hours prior to randomization

2.3.3.2 Safety Results

This trial provides the only safety data on patients exposed to TID dosing. The information presented in this section is intended to augment the information provided by the sponsor, and to consider some of the data from slightly different angles.

Adverse events are summarized in Table 22. This table differs from the sponsor tables only by the way the arms are grouped. Patients are presented as randomized, except for the 8 VREFLAG patients who are presented separately. Overall, the Vancomycin arm had a higher rate of declared adverse events: .775 versus .709. The Vancomycin arm also had far more adverse events that were considered related. It should be kept in mind, that this study was unblinded, and thus there is a potential bias in the assessment of some soft adverse events. The observed death rate was higher in the Linezolid arm; however, this may simply be a chance finding, because of the small sample size.

Similarly, the observed serious adverse event rate was slightly larger in the Linezolid arm. It is noted that the very small VREflag data base had a higher observed rate of adverse events.

Table 22. Adverse Events by Randomized Treatments

	Randomized Treatment					
	Linezolid		Vancomycin		Vreflag	
	RATE	N	RATE	N	RATE	N
Death during Follow-up	0.058	206.000	0.020	102.000	0.125	8.000
Death	0.058	206.000	0.029	102.000	0.125	8.000
Adverse Event	0.709	206.000	0.775	102.000	1.000	8.000
Related Adverse Event	0.180	206.000	0.343	102.000	0.250	8.000
Serious Adverse Event	0.191	204.000	0.170	100.000	0.250	8.000

Lab values are presented as rates that fall above or below certain cut-offs in Table 23; for example, the proportion of Linezolid patients with End of Treatment Platelet values less than 50 was .066. Examination, of the data in this table, does not suggest any apparent areas of concern about Linezolid with respect to these lab values, in that the results seem very similar to Vancomycin. (Note: these cut-offs were not pre-specified).

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Table 23. Rates of Lab Values Above and Below Cut-offs by Randomized Treatment (ITT Population)

	Randomized Treatment					
	Linezolid		Vancomycin		Vreflag	
	RATE	N	RATE	N	RATE	N
B Platelets < 100	0.166	199.000	0.152	99.000	0.286	7.000
B Platelets < 50	0.106	199.000	0.071	99.000	0.143	7.000
EOT Platelets < 100	0.109	183.000	0.082	85.000	0.429	7.000
EOT Platelets < 50	0.066	183.000	0.082	85.000	0.143	7.000
FU Platelets <100	0.055	181.000	0.111	81.000	0.333	6.000
FU Platelets < 50	0.022	181.000	0.062	81.000	0.000	6.000
B Bands > 0	0.538	160.000	0.593	81.000	0.800	5.000
B Bands > 5	0.275	160.000	0.296	81.000	0.400	5.000
EOT Bands > 0	0.385	148.000	0.370	73.000	0.600	5.000
EOT Bands > 5	0.095	148.000	0.137	73.000	0.200	5.000
FU Bands > 0	0.312	141.000	0.313	67.000	0.500	6.000
FU Bands > 5	0.106	141.000	0.149	67.000	0.000	6.000
B Neutrophils < 1	0.077	195.000	0.065	93.000	0.143	7.000
B Neutrophils > 9	0.297	195.000	0.398	93.000	0.286	7.000
EOT Neutrophils < 1	0.029	175.000	0.063	80.000	0.429	7.000
EOT Neutrophils > 9	0.103	175.000	0.138	80.000	0.143	7.000
FU Neutrophils < 1	0.029	172.000	0.067	75.000	0.000	6.000
FU Neutrophils > 9	0.052	172.000	0.053	75.000	0.167	6.000
B White Bl Cell < 4	0.125	200.000	0.110	100.000	0.286	7.000
B White Bl Cell < 6	0.175	200.000	0.190	100.000	0.286	7.000
EOT White Bl Cell < 4	0.055	183.000	0.069	87.000	0.429	7.000
EOT White Bl Cell < 6	0.175	183.000	0.184	87.000	0.571	7.000
FU White Bl Cell < 4	0.077	182.000	0.062	81.000	0.167	6.000
FU White Bl Cell < 6	0.181	182.000	0.210	81.000	0.333	6.000
B Hematocrit < 20	0.020	200.000	0.020	100.000	0.000	7.000
B Hematocrit < 25	0.105	200.000	0.100	100.000	0.000	7.000
EOT Hematocrit < 20	0.005	184.000	0.000	87.000	0.000	7.000
EOT Hematocrit < 25	0.109	184.000	0.057	87.000	0.143	7.000
FU Hematocrit < 20	0.000	182.000	0.000	81.000	0.000	6.000
FU Hematocrit < 25	0.044	182.000	0.037	81.000	0.500	6.000
B Hemoglobin < 10	0.338	198.000	0.360	100.000	0.429	7.000
B Hemoglobin < 7	0.025	198.000	0.020	100.000	0.000	7.000
EOT Hemoglobin < 10	0.317	183.000	0.310	87.000	0.286	7.000
EOT Hemoglobin < 7	0.027	183.000	0.011	87.000	0.000	7.000
FU Hemoglobin < 10	0.280	182.000	0.272	81.000	0.833	6.000
FU Hemoglobin < 7	0.000	182.000	0.000	81.000	0.000	6.000
B ALT > 30	0.302	192.000	0.295	95.000	0.500	6.000
B ALT > 50	0.146	192.000	0.147	95.000	0.333	6.000
EOT ALT > 30	0.361	180.000	0.279	86.000	0.286	7.000
EOT ALT > 30	0.133	180.000	0.116	86.000	0.143	7.000
FU ALT > 30	0.337	169.000	0.289	76.000	0.833	6.000
FU ALT > 50	0.172	169.000	0.184	76.000	0.500	6.000

B denotes Baseline; EOT denotes End of Treatment; FU denotes Follow-up;
Neutrophil and Platelet counts are x1000/µl
Hemoglobin is expressed as g/dl; White Blood Cell counts are x1000/µl

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Table 24 considers the distribution of EOT and FU platelet, neutrophil, and hemoglobin values among patients who were not low at baseline. These tables also show little difference between the treatment groups, although there were slightly higher prevalence of low hemoglobin values in the Linezolid arm than the Vancomycin arm. That is, at FU 14% of Linezolid patients with baseline values at least 10 were now below 10, whereas this was the case for only 10% of Vancomycin patients who baseline values were at least 10. However, the Vancomycin group had proportionately more missing values, which might have biased the comparison.

Table 24. Distribution of Patient's Lab Values at End of Treatment and Follow-up among Patients whose Baseline Values were Not Low (Non-randomized VRE patients excluded)

Population: Patients whose baseline platelet count ($x10^3/\mu l$) was at least 100				
Platelet Value	End of Treatment		Follow-up	
	Linezolid	Vancomycin	Linezolid	Vancomycin
<100	6	2	4	2
≥100	145	71	143	65
Missing	15	11	19	17
Population: Patients whose baseline neutrophil count ($x10^3/\mu l$) was at least 1.2				
Neutrophil Value	End of Treatment		Follow-up	
	Linezolid	Vancomycin	Linezolid	Vancomycin
<1.2	4	3	6	4
≥1.2	152	67	143	62
Missing	20	15	25	19
Population: Patients whose baseline Hemoglobin g/dl value was at least 10				
Hemoglobin Value	End of Treatment		Follow-up	
	Linezolid	Vancomycin	Linezolid	Vancomycin
<10	17	7	16	5
≥10	97	46	97	45
Missing	12	9	13	13

Plots of baseline lab values versus end of treatment and follow-up lab values were examined for three key lab values: platelets, neutrophils, and hemoglobin. These plots provided another perspective of how lab values change over time. Examination of these plots failed to detect any concerns about Linezolid patient lab values. For example, when considering baseline versus end of treatment for platelets: one notes that Linezolid proportionately had slightly more values below 100 than Vancomycin at EOT, which is consistent with the information in Table 23. However, many of the Linezolid patients with EOT platelet values below 100 actually improved from baseline, whereas all Vancomycin patients with EOT platelet values below 100 fell from baseline.

2.3.4 STATISTICAL REVIEWER'S FINDINGS

Since this review is based on a single study, the findings are described in the collective evidence section (see Section 2.6).

2.4 SPECIAL/SUBGROUP POPULATIONS

Generally, subgroup analysis is an integral part of the review. However, given the extremely small number of patients within a baseline diagnosis, any attempt to further subdivide the patients with respect to gender, race and geographical regions is not practical. The following tables present the reviewer's clinical success rates, but only consider patients across all sites of infection and pathogens. The point-estimates of success rates are similar across subgroups. However, the North American subgroup appeared to have somewhat lower observed FDA success rates than the Latin American success rates. Furthermore, in the MITT population, there was a potential difference between the arms in North America. In this population, the FDA success rate was .62 (n=47) in the Linezolid arm, and .81 (n=21) in the Vancomycin arm; the nominal p-value associated with this difference was .10. This difference was decreased when missing values were analyzed as failures.

Table 25. Reviewer's Clinical Success Rates in ITT Population by Special Populations

	Reviewer's Clinical Cure Missing Excluded				Reviewer's Clinical Cure Missing as Failures			
	Randomized Treatment				Randomized Treatment			
	Linezolid		Vancomycin		Linezolid		Vancomycin	
	Rate	N	Rate	N	Rate	N	Rate	N
AGEGRP								
< 90 days	0.81	36.00	0.79	14.00	0.71	41.00	0.55	20.00
91 days - <1 year	0.81	32.00	0.86	14.00	0.81	32.00	0.75	16.00
1-4 years	0.84	74.00	0.86	35.00	0.75	83.00	0.70	43.00
5-11 years	0.75	44.00	0.80	20.00	0.67	49.00	0.70	23.00
Sex								
Female	0.81	84.00	0.86	37.00	0.72	95.00	0.76	42.00
Male	0.80	102.00	0.80	46.00	0.75	110.00	0.62	60.00
Race								
Asian or Pacific Islander	1.00	3.00	0.00	2.00	0.75	4.00	0.00	2.00
Black	0.76	21.00	0.88	17.00	0.64	25.00	0.65	23.00
Mixed/Multiracial	0.85	88.00	0.90	29.00	0.82	91.00	0.68	38.00
White	0.76	74.00	0.80	35.00	0.66	85.00	0.72	39.00
Geographic Region								
North America	0.68	72.00	0.76	38.00	0.58	85.00	0.62	47.00
Latin America	0.89	114.00	0.89	45.00	0.84	120.00	0.73	55.00

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Table 26. Reviewer's Clinical Success Rates in FDA MITT Population by Special Populations

	Reviewer's Clinical Cure Missing Excluded				Reviewer's Clinical Cure Missing as Failures			
	Randomized Treatment				Randomized Treatment			
	Linezolid		Vancomycin		Linezolid		Vancomycin	
	Rate	N	Rate	N	Rate	N	Rate	N
AGEGRP								
< 90 days	0.82	28.00	0.90	10.00	0.74	31.00	0.75	12.00
91 days - <1 year	0.65	17.00	0.82	11.00	0.65	17.00	0.82	11.00
1-4 years	0.87	39.00	0.95	19.00	0.79	43.00	0.86	21.00
5-11 years	0.75	24.00	0.89	9.00	0.69	26.00	0.73	11.00
Sex								
Female	0.78	50.00	0.89	28.00	0.71	55.00	0.86	29.00
Male	0.81	58.00	0.90	21.00	0.76	62.00	0.73	26.00
Race								
Asian or Pacific Islander	1.00	2.00	0.00	1.00	1.00	2.00	0.00	1.00
Black	0.71	14.00	0.90	10.00	0.63	16.00	0.64	14.00
Mixed/Multiracial	0.89	46.00	0.94	17.00	0.85	48.00	0.89	18.00
White	0.72	46.00	0.90	21.00	0.65	51.00	0.86	22.00
Geographic Region								
North America	0.62	47.00	0.81	21.00	0.55	53.00	0.65	26.00
Latin America	0.93	61.00	0.96	28.00	0.89	64.00	0.93	29.00

2.5 STATISTICAL AND TECHNICAL ISSUES

This study was not designed to provide formal statistical evidence. Thus, the inability to draw a clear conclusion about the efficacy of Linezolid in this population is not surprising. In addition, there is no direct comparison with placebo, nor any precise information about how a placebo arm would have performed in this population; however, clinical colleagues have indicated that there would probably be little spontaneous resolution in a population this sick. Thus, if this assumption is correct, the relatively high point estimates of clinical success provide good assurance that both arms are far superior to placebo. According to the reviewer's analysis, only 108 Linezolid patients and 49 Vancomycin patients have known outcomes in the MITT population; there are 10 and 6 missing outcomes respectively. Thus, the number of patients in this sample was small and drawn from a heterogeneous mix of indications; in addition, about 10% of the outcomes are unknown. This missing rate is not very excessive; however, it is still large enough, that the true outcome, if all values were known, could be considerably different from what was observed. A sensitivity analysis in which all unknown values were counted as failures yielded fairly similar results; however, this certainly does not cover all possible alternatives.

The lack of blinding in this trial is also troubling, given that many outcomes are at least somewhat subjective. Thus, reports of adverse events and assessments of efficacy were made with complete knowledge of treatment assignment, and thus were potentially subject to some bias.

The sign of a possible Vancomycin advantage was suggested by only the reviewer's MITT analysis; that is the reviewer's other analysis populations and the sponsor's analyses did not suggest this at all. However, the reviewer's MITT analysis is arguably the most appropriate analysis. This is because it is intended as a true ITT analysis that also excluded patients who may be obscuring treatment difference. In addition, one should not discount the MITT result if the ME observed difference is smaller, because the a priori concern is that the MITT analysis will underestimate the treatment difference, not overestimate. In addition, the reviewer's MITT results are remarkably consistent across MITT subgroups.

On the other hand, the sponsor's analysis was pre-specified in the protocol. Furthermore, the sample sizes are small, and confidence intervals of differences are wide and do not exclude zero. In addition, since the study was not powered to rule out a difference of certain size, it is hard to interpret the importance of the lower bounds of the reviewer's primary MITT confidence intervals, which tend to be quite low. Thus, while the potential that Linezolid may be somewhat less effective than Vancomycin does exist, this observation is far from conclusive, and can only be considered a suggestion. It probably is worthy of little concern by itself, and would only be meaningful if coupled with serious safety concerns found outside this study.

2.6 STATISTICAL REVIEWER'S FINDINGS AND EVALUATION OF COLLECTIVE EVIDENCE

This review considers a single study, Study 0082, which enrolled pediatric patients with suspected resistant gram positive infections.

All of the results cited in this section are based on the analyses conducted by the FDA statistical reviewer.

While the sponsor's analysis, for the most part, was faithful to the protocol, there were a number of potential weaknesses in this analytic strategy. The reviewer's analysis was designed to address these weaknesses; the reviewer's analysis used a different algorithm for clinical assessment, and slightly different definitions for population inclusion (see Section 2.3.2 for details). The goal of this alternate clinical assessment was to distinguish patients with good outcomes, poor outcomes, and unknown outcomes without regard to duration of therapy in the ITT and MITT analyses. The alternate definition of analysis populations classified patients as randomized, rather than as treated, and furthermore separated out those VRE patients who were effectively not part of the randomized experiment, because they were all treated with Linezolid from the start, despite treatment assignment. Finally, some additional patients were excluded from the per-protocol populations, if their concomitant gram-positive drug use just prior to or during the study appeared to be in violation of the protocol.

When all diagnoses are collapsed, the reviewer's analysis found very similar rates between the two arms for the ITT, CE, and ME populations; however, for the FDA MITT population, there was a hint of a potential advantage of Vancomycin, although this difference did not reach statistical significance (i.e., $p>.05$). Analysis of the reviewer's clinical assessment in the FDA MITT population, when missing values were excluded, found the observed cure rate for Linezolid was .796 (n=108) versus .898 (n=49) in the Vancomycin arm, with the corresponding 95% confidence interval for the difference of (-.230, .027). The lower bounds for the confidence intervals of the other three analysis populations ranged from -.109 for it FDA CE to -.148 for the FDA ME. The observed cure rates for the Linezolid arm was about .80 for ITT/MITT analyses and .90 for per-protocol analyses. When missing values were analyzed as failures, observed Linezolid success rates in the ITT/MITT analyses were about .73. (For details see Table 12 and Table 13.)

In the reviewer's FDA MITT population analysis, numerically larger clinical success rates in the Vancomycin arm was consistently seen in most key subgroups, although the sample size in these subgroup analyses, was small to very small, and differences were not statistically significant and should be interpreted very cautiously. For example, the observed Vancomycin clinical success rate was larger than the Linezolid clinical success rate for four of the five baseline diagnosis categories in the FDA MITT population; the exception was catheter-related bacteremia, in which case the estimates were nearly identical (Table 16.) Similarly, the observed rates by pathogen were generally higher in the Vancomycin group by pathogen. One of these differences was nominally statistically significant at the .05 level (with no adjustment for multiple comparisons): in MRSE patients the

observed FDA MITT cure rate for Linezolid was .741 (n=27) versus 1.00 (n=9) in Vancomycin. A noticeable difference was also observed in the S. Aureus patients with Linezolid's cure rate of .851 (n=47) versus .966 (n=29) in Vancomycin patients (see Table 18). Analyses of diagnosis-by-pathogen subgroups were generally based on extremely small numbers; however, several of these subgroups had sizeable samples. For example, there was a clear suggestion of a Vancomycin advantage among patients with complicated skin and skin structure infections with a documented S. Aureus pathogen. On the other hand, the patients with catheter-related bacteremia with coagulase-negative staphylococcus infections in Linezolid had numerically better results than the Vancomycin arm (see Table 19). Finally, the FDA statistical review found higher observed success rates in the Vancomycin arm than the Linezolid arm in virtually every demographic category considered (see Table 26).

In contrast to the above, the sponsor's results and the reviewer's analyses of all populations other than FDA MITT generally did not yield concerns about the efficacy of Linezolid. However, the reviewer's analysis in the FDA MITT population is arguably the most appropriate analysis presented. It is the only true intent-to-treat analysis that excluded patients who may not have the disease of interest, inclusion of patients without documented bacterial disease can obscure true treatment differences. Since, the major concern about a ITT/MITT analysis in a non-inferiority is that it may tend to underestimate treatment effect by including non-compliers and so forth, one should always pay attention to an ITT/MITT analysis that suggests a *larger* difference than the per-protocol analyses. In classic superiority trials, there is consensus that ITT/MITT analyses are the most appropriate. However, there is some concern about ITT and MITT analyses in non-inferiority trials is that they may tend to underestimate treatment differences, and what is usually a conservative approach in a superiority trial can lead to false demonstration of efficacy in the non-inferiority setting. This concern has lead to some reliance on per-protocol analyses in non-inferiority studies, even though researchers also worry about bias in these analyses, and it is less clear whether the estimate will be an under- or overestimate of the treatment difference. However, in a case where the ITT or MITT analysis is detecting a possible difference, but the corresponding per-protocol analysis is not, this alleviates concerns that the ITT/MITT approach is underestimating the true treatment difference, and thus one should pay attention to this potential difference.

That said, even the reviewer's MITT analysis, because of the small sample sizes and wide confidence intervals, provides no more than a hint that Vancomycin might have an edge in treating these patients. While the results are consistent with Vancomycin advantage as large as .20, or so, there is a reasonable chance that no difference exists. Furthermore, if one can assume that patients in this study population and design would have a poor outcome (e.g., less than .50 cured) if not treated with any antibiotic, then one can be confident that Linezolid is superior to placebo. Even in the worst case scenario, when missing values are counted as failures, the exact 95% confidence interval for in Linezolid arm in the FDA MITT overall population is (.639, .807).

The FDA statistical review considered some slightly different analysis of safety than those presented in the sponsor's Study Report, but no new safety concerns emerged. However, the higher observed death rate in the Linezolid arm than in the Vancomycin arm, while not statistically significant, does raise some concern.

2.7 CONCLUSIONS AND RECOMMENDATIONS

This clinical trial provides reasonable assurance that the safety and efficacy of Linezolid and Vancomycin are roughly comparable in pediatric patients with documented gram-positive infections. While the sponsor's analysis and some FDA analyses showed very similar outcomes in the two

treatment groups, there are some hints in the FDA MITT analysis that Linezolid might possibly be slightly less effective than Vancomycin, although this difference is not statistically significant. In addition, since no non-inferiority margin appeared to be specified in the protocol, it is not straightforward to interpret the confidence interval results from the trial. Nonetheless, under the presumption that the clinical success rates with no treatment in this patient population would be much lower than .50, then one can conclude easily that Linezolid has efficacy when compared to placebo. The sponsor concludes "This study demonstrated that linezolid is well tolerated and equally as effective as vancomycin in treating infections in children due to suspected or proven resistant gram-positive pathogens, including hospital-acquired pneumonia, complicated skin and skin structure infections, catheter-related bacteremia, bacteremia of unknown source, and other infections." However, such a strong conclusion is not warranted because the number of patients with documented gram-positive infections is small, and within each diagnostic category is very small, and because no non-inferiority margin appeared to be specified in the protocol. Furthermore, analyzing patients across indications may not provide a meaningful comparison. Even though this is billed as a trial of resistant gram-positive infections, only a minority of enrolled patients has such infections. Conclusions about resistant gram-positive infections must, of course, be limited to these patients. Finally, an important weakness of this design was that it was open-label, and that most assessments were at least partially subjective.

Adverse events were reported in a larger proportion of Vancomycin than Linezolid patients; however, the significance of this is muted by the open-label nature of the trial. Secondly, deaths and serious adverse events were more frequent in the Linezolid group. The differences are not statistically significantly different in this small sample size, thus it is impossible to know whether this imbalance was due to chance, or could represent a slightly higher risk of mortality in the Linezolid group. Of course, death is one variable in this data set was not impacted by the open-label design.

In sum, there appears to be rough similarity in efficacy between Linezolid and Vancomycin in this patient population. However, the strength of this conclusion is limited by: a) some key results in the FDA MITT analysis suggesting a possible, though statistically insignificant, Vancomycin advantage, b) the very small sample size for each indication with gram positive infections, and c) the open-label design. With respect to safety, no clear concerns emerged from this trial, except for the higher observed death rate in the Linezolid patients, which could easily be due to chance. Ultimately, the results of this clinical trial need to be interpreted in the context of all available information: results from the clinical trials in adults and the PKPD data in children.

2.8 APPENDIX 1

Table 27. Drugs with Gram Positive Coverage Considered in Reviewer's Classification of Clinically Evaluable Patients

- AMOXICILLIN W/CLAVULANIC ACID
- AUGMENTIN
- AMPICILLIN
- BACTRIM
- CEFOTAXIME
- CEFTRIAXONE
- CEPHALEXIN
- CEPHRADINE
- CLAFORAN
- CLINDAMYCIN
- IMIPENEM (THIENAMYCIN)
- MEROPENEM
- OXACILLIN SODIUM
- PIPERACILLIN
- PIPERACILLIN SODIUM & TAZOBACTAM SODIUM
- SMZ-TMP
- VANCOCIN
- ZOSYN
- CEFUROXIME
- RIFAMPIN
- LINEZOLID
- VANCOMYCIN
- CHLORAMPHENICOL (CLORANFENICOL)
- DOXYCYCLINE
- VIBRAMYCIN
- AMPICILLIN SODIUM W/SULBACTAM SODIUM
- TIMENTIN

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Erica Brittain
12/20/02 10:06:53 AM
BIOMETRICS

Please sign off

Daphne Lin
12/20/02 11:19:32 AM
BIOMETRICS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS
DIVISION OF BIOMETRICS III

Statistical Review and Evaluation

NDA(s):	21-130 SE5-003, 21-131 SE5-003, 21-132 SE5-003
Date Received by Center:	06/21/02
Name of drug:	Zyvox™ (linezolid) tablets, I.V. for injection, and oral suspension
Sponsor:	Pharmacia & Upjohn Company
Indication:	Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains) or *Streptococcus pyogenes*
Documents reviewed:	Electronic submission found under \\CDSESUB1\N21130\S_003
Statistical reviewer:	Nancy Silliman, Ph.D. (SGE)
Statistical team leader:	Daphne Lin, Ph.D. (HFD-725)
Biometrics division director:	Mohammad Huque, Ph.D. (HFD-725)
Clinical Reviewer:	Sumathi Nambiar, M.D. (HFD-520)
Project Manager:	Beth Duvall-Miller (HFD-520)
Keywords:	Clinical Studies, NDA review, Active-control/Non-inferiority

1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS AND RECOMMENDATIONS

This application includes efficacy and safety data from two Phase 3 comparator-controlled clinical trials in pediatric patients: Study M/1260/0065 (Study 0065) in children with uncomplicated skin and skin structure infections (uSSSI) and Study M/1260/0082 in children with resistant gram-positive bacterial infections, including nosocomial pneumonia, community-acquired pneumonia, complicated SSSI, catheter-related bacteremia, and bacteremia of unidentified source. This review focuses on Study 0065. For discussion of the other controlled study, please see the statistical review by Dr. Erica Brittain.

Study 0065 was a randomized, blinded, active-controlled, multi-center, multinational trial conducted in children ages 5-17 with uSSSI. Efficacy of linezolid was shown to be not inferior to that of the comparator cefadroxil, an approved product, using an acceptable clinical difference of 10 percentage points. In addition, the safety profile of the two regimens was shown to be similar. Based upon this study and previous controlled clinical studies in uSSSI in adults receiving linezolid, this reviewer feels that it would be appropriate to include information from Study 0065 in the Zyvox label. As subjects were dosed bid in Study 0065, however, this reviewer does not agree with the sponsor's suggestion in the proposed label for tid dosing for children with uSSSI. Instead, this reviewer feels that the label should reflect the dosing regimen studied for Zyvox in children with uSSSI, which was 10 mg/kg oral, up to [redacted], every 12 hours for patients aged 5 through 11 years, and 600 mg oral, every 12 hours, for patients from 12 through 17 years of age. The reviewer does not object to the sponsor's suggestion in the label for dosing to range from 10 to 14 days, if the medical reviewer thinks this is acceptable. While study 0065 allowed for dosing to range from 10 to 21 days, 75% of ITT patients were dosed between 10 and 14 days.

1.2 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

Pharmacia & Upjohn (P&U) has developed a new class of antibacterial agents called oxazolidinones that have shown in vitro and in vivo activity against gram-positive organisms, including organisms resistant to other antibiotics. Linezolid (ZYVOX™), the first of these to be marketed, has demonstrated in vitro and in vivo antibacterial activity against staphylococci (including methicillin-resistant strains), streptococci (including penicillin- and/or cephalosporin-resistant *Streptococcus pneumoniae*), and enterococci (including vancomycin-resistant strains). Approved indications in adult patients include nosocomial pneumonia, community-acquired pneumonia, complicated and uncomplicated skin and skin structure infections (SSSI), and resistant enterococcal infections.

P&U is currently pursuing a registration initiative for pediatric indications. Consistent with guidance provided in the FDA Final Pediatric Rule (21 CFR 314.55a) to support pediatric labeling, approval is being sought for treatment of the following indications in pediatric patients:

Supported by pharmacokinetic, efficacy, and safety data in pediatric patients plus efficacy data from adequate well-controlled adult trials:

- Nosocomial pneumonia
- Community-acquired pneumonia
- Vancomycin-resistant enterococcal infections
- Complicated skin and skin structure infections

Supported by adequate and well-controlled trials in children:

- Uncomplicated skin and skin structure infections.

Efficacy and safety data from 2 new Phase 3 comparator-controlled clinical trials in pediatric patients are included in this submission: Study M/1260/0065 (Study 0065) in children with uncomplicated SSSI and Study M/1260/0082 in children with resistant gram-positive bacterial infections, including nosocomial pneumonia, community-acquired pneumonia, complicated SSSI, catheter-related bacteremia, and bacteremia of unidentified source. In addition, efficacy and safety data are provided from 2 uncontrolled Phase 2 trials of linezolid in pediatric patients in the treatment of community-acquired pneumonia (M/1260/0045) and acute otitis media (M/1260/0049) that were included in the original linezolid NDA. This review focuses on the controlled uncomplicated SSSI study, Study 0065, conducted in children ages 5-17. For discussion of the other controlled study and indications, please see the statistical review by Dr. Erica Brittain.

Study 0065 was a randomized, blinded, active-controlled, multi-center, multinational trial conducted in children ages 5-17 with uSSSI. Linezolid was dosed q12 hours, 10 mg/kg oral suspension (up to 600 mg/dose) for patients 5 - 11 years old, and 600 mg oral tablets for patients 12 - 17 years of age. The comparator, cefadroxil, was dosed q12 hours, 15 mg/kg oral suspension (up to 500 mg/dose) for patients 5 - 11 years old, and 500 mg oral capsules for patients 12 - 17 years of age. Both treatment regimens were to be given for 10-21 days. The primary efficacy measures were the investigators' and sponsor's evaluation of patient clinical outcome at the follow-up (F-U) visit. Secondary efficacy measures included patient microbiological outcome, individual pathogen outcomes, an evaluation of the patients' clinical signs and symptoms, body temperature, white blood cell counts (WBC), and size and involvement of the lesion. Safety assessments were based on the evaluation of data from laboratory assays, vital sign measurements, and recorded adverse events and concomitant medications. Safety data was analyzed using the intent-to-treat (ITT) population, while efficacy data was analyzed using the ITT, modified ITT (MITT), clinically evaluable (CE), and microbiologically evaluable (ME) populations.

Study 0065 was conducted at 91 centers: 68 in the U.S. (enrolling 70% of ITT patients), 8 in Canada (enrolling 4% of ITT patients), 5 in Argentina (enrolling 9% of ITT patients), 3 in Brazil (enrolling 2% of ITT patients), 3 in Chile (enrolling 3% of ITT patients), 2 in Mexico (enrolling 3% of ITT patients), and 2 in Peru (enrolling 10% of ITT patients). The majority of investigators enrolled only a few patients; 11 investigators enrolled 10 or more patients (the maximum number of patients enrolled at a site was 30). A total of 508 subjects were randomized to either linezolid (252) or cefadroxil (256). Ninety-eight percent of all subjects

were included in the ITT population, 66% were included in the MITT population, 87% were included in the CE population, and 61% were included in the ME population. The distribution of subjects in each of these patient populations was similar across treatment arms, as were the reasons for exclusion from a patient population.

1.3 PRINCIPAL FINDINGS

The primary efficacy measures were the investigators' and sponsor's evaluation of patient clinical outcome at the follow-up visit, classified as either cure or failure. Cure rates were to be considered similar if the 95% confidence interval around the difference ruled out a 10% decrease in cure rates for linezolid compared to cefadroxil (i.e., if the lower limit of the confidence interval around the difference in rates, linezolid minus cefadroxil, was greater than -10%). Note that since the sponsor specified two endpoints as primary and they do not adjust the analysis for multiple endpoints, both endpoints will have to satisfy the criteria for non-inferiority for the study to be considered proof of efficacy for linezolid in the treatment of uSSSI.

Results for the primary efficacy variables can be found in Tables 3 and 4 (pages 16 and 18, respectively). The cure rates at the F-U visit for the Investigators' Assessment of Clinical Outcome were 93.3% for linezolid versus 92.9% for cefadroxil [95% CI for the difference of (-4.3%, 5.2%)] in the ITT population, and 93.6% for linezolid versus 94.1% for cefadroxil [95% CI for the difference of (-5.0%, 4.1%)] in the CE population. The cure rates at the F-U visit for the Sponsor's Assessment of Clinical Outcome were 88.7% for linezolid versus 86.2% for cefadroxil [95% CI for the difference of (-3.5%, 8.7%)] in the ITT population, and 91.0% for linezolid versus 90.0% for cefadroxil [95% CI for the difference of (-4.6%, 6.5%)] in the CE population. In general, the effectiveness of the 2 treatments was similar for all subgroups including age, gender, race, diagnosis, pathogen, and geographic regions. Results for secondary efficacy variables were also supportive of similar efficacy for linezolid compared to cefadroxil. Taken as a whole, the results suggest that the efficacy of linezolid in the treatment of uSSSI in children is similar to that of cefadroxil.

Overall, safety results were similar for linezolid and cefadroxil. In the linezolid arm, 45% of subjects experienced at least one adverse event (AE). In the cefadroxil arm, 47% of subjects experienced at least one adverse event. Five (2.0%) linezolid-treated patients discontinued the study due to an AE, while 9 (3.6%) cefadroxil -treated patients discontinued the study due to an AE. Two (0.8%) linezolid-treated patients experienced a serious AE, while 4 (1.6%) cefadroxil -treated patients experienced a serious AE. No patients died during this study.

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 INTRODUCTION AND BACKGROUND

Pharmacia & Upjohn (P&U) has developed a new class of antibacterial agents called oxazolidinones that have shown in vitro and in vivo activity against gram-positive organisms, including organisms resistant to other antibiotics. Linezolid (ZYVOX™), the first of these to

be marketed, has demonstrated in vitro and in vivo antibacterial activity against staphylococci (including methicillin-resistant strains), streptococci (including penicillin- and/or cephalosporin-resistant *Streptococcus pneumoniae*), and enterococci (including vancomycin-resistant strains). Approved indications in adult patients include nosocomial pneumonia, community-acquired pneumonia, complicated and uncomplicated skin and skin structure infections (SSSI), and resistant enterococcal infections.

P&U is currently pursuing a registration initiative for pediatric indications. Consistent with guidance provided in the FDA Final Pediatric Rule (21 CFR 314.55a) to support pediatric labeling, approval is being sought for treatment of the following indications in pediatric patients:

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- Uncomplicated skin and skin structure infections.

Efficacy and safety data from 2 new Phase 3 comparator-controlled clinical trials in pediatric patients are included in this submission: Study M/1260/0065 (Study 0065) in children with uncomplicated SSSI and Study M/1260/0082 in children with resistant gram-positive bacterial infections, including nosocomial pneumonia, community-acquired pneumonia, complicated SSSI, catheter-related bacteremia, and bacteremia of unidentified source. In addition, efficacy and safety data are provided from 2 uncontrolled Phase 2 trials of linezolid in pediatric patients in the treatment of community-acquired pneumonia (M/1260/0045) and acute otitis media (M/1260/0049) that were included in the original linezolid NDA. This review focuses on the controlled uncomplicated SSSI study, Study 0065, conducted in children ages 5-17. For discussion of the other controlled study and indications, please see the statistical review by Dr. Erica Brittain.

Study 0065 was a randomized, blinded, active-controlled, multi-center, multinational trial conducted in children ages 5-17 with uSSSI. Linezolid was dosed q12 hours, 10 mg/kg oral suspension (up to 600 mg/dose) for patients 5 - 11 years old, and 600 mg oral tablets for patients 12 - 17 years of age. The comparator, cefadroxil, was dosed q12 hours, 15 mg/kg oral suspension (up to 500 mg/dose) for patients 5 - 11 years old, and 500 mg oral capsules for patients 12 - 17 years of age. Both treatment regimens were to be given for 10-21 days. The primary efficacy measures were the investigators' and sponsor's evaluation of patient clinical outcome at the follow-up (F-U) visit. Secondary efficacy measures included patient microbiological outcome, individual pathogen outcomes, an evaluation of the patients' clinical signs and symptoms, body temperature, white blood cell counts (WBC), and size and involvement of the lesion. Safety assessments were based on the evaluation of data from

laboratory assays, vital sign measurements, and recorded adverse events and concomitant medications. Safety data was analyzed using the intent-to-treat (ITT) population, while efficacy data was analyzed using the ITT, modified ITT (MITT), clinically evaluable (CE), and microbiologically evaluable (ME) populations.

2.2 DATA ANALYZED AND SOURCES

Data sets for Study 0065 were submitted electronically. Data sets used in the review process were found in the following directories in the Electronic Document Room:
\\Cdsesub1\n21130\S_003\2002-06-21
\\Cdsesub1\n21130\S_003\2002-08-07
\\Cdsesub1\n21130\S_003\2002-10-02

The reviewer has found all data sets to be well organized and of good quality.

2.3 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY / SAFETY

Study 0065 is reviewed in further detail in this section.

2.3.1 SPONSOR'S RESULTS AND CONCLUSIONS

The sponsor and reviewer were in general agreement about how to proceed in evaluating the results from Study 0065. The sponsor's results may be found under *Detailed Review of Individual Studies* (pg. 8). Slight disagreements about the statistical methodology to be used and several additional analyses by the reviewer are discussed under *Statistical Reviewer's Findings* (pg. 24). Both sponsor and reviewer concluded from this study that efficacy and safety for linezolid are similar to that of cefadroxil in pediatric patients with uSSSI.

2.3.2 STATISTICAL METHODOLOGIES

All data listings, summaries, and statistical analyses performed by the sponsor were generated using SAS® Version 6.12. The reviewer used SAS® Version 6.12, JMP Version 3.2.5, and Splus 2000 Professional Release 1 for all tabulations and analyses. All statistical tests were 2-sided. P-values less than or equal to 0.05 were considered statistically significant. All 95% confidence intervals were based on the normal approximation to the binomial distribution. Patients who received the wrong study medication (i.e., the treatment other than the one they were randomized to receive) were included in their actual treatment group (i.e., the one representing the medication they actually received) for both safety and efficacy analyses. Key efficacy results were presented by investigator/center. Due to the expected small number of evaluable patients at each center, terms for investigator effect and treatment group-by-investigator interaction were not included in the statistical models used for analysis. However, consistency of treatment effects across centers was investigated for those centers with appreciable numbers of evaluable patients.

The comparability of the treatment groups with respect to age, height, weight, vital signs,

selected quantitative laboratory assays, duration of infection, and size of lesion at the baseline visit was assessed using an F-test derived from the usual one-way analysis of variance (ANOVA) fixed-effects model with a factor for treatment group for the ITT and CE populations. The comparability of the treatment groups with respect to the categorical variables gender, race, geographic region, medical history, physical examination, diagnosis, degree of involvement, and clinical signs and symptoms was assessed using a chi-square test for 2-way contingency tables for the ITT and CE populations.

The primary efficacy measures were the investigators' and sponsor's evaluation of patient clinical outcome at the follow-up visit, classified as either cure or failure. Cure rates were to be considered similar if the 95% confidence interval around the difference ruled out a 10% decrease in cure rates for linezolid compared to cefadroxil (i.e., if the lower limit of the confidence interval around the difference in rates, linezolid minus cefadroxil, was greater than -10%). Note that since the sponsor specified two endpoints as primary and they do not adjust the analysis for multiple endpoints, both endpoints will have to satisfy the criteria for non-inferiority for the study to be considered proof of efficacy for linezolid in the treatment of uSSSI. The primary efficacy measures were summarized for the ITT, MITT, CE, and ME populations. Populations of most interest to this reviewer are the ITT and CE populations. The sponsor did not specify an analysis population as primary, but they did power the study to show non-inferiority in the CE population.

The sponsor calculated confidence intervals using the normal approximation to the binomial distribution without the continuity correction. The reviewer calculated confidence intervals for the primary efficacy endpoints in two ways: (1) using the normal approximation to the binomial distribution, incorporating the continuity correction, and (2) stratified by age group (5-11 and 12-17 years old) using a Mantel-Haenszel approach (Koch GG, Carr GJ, Amara IA, Stokes ME, and Uryniak TJ [1989]. *Categorical Data Analysis.* In *Statistical Methodology in the Pharmaceutical Sciences* (Berry, ed.). Marcel Dekker: New York, pp. 389-473.).

2.3.3 DETAILED REVIEW OF INDIVIDUAL STUDIES

2.3.3.1 Study 0065

Study 0065 was a randomized, blinded, active-controlled, multi-center, multinational trial conducted in children ages 5-17 with uSSSI. Patients were randomized in a 1:1 ratio to receive either linezolid or cefadroxil for 10-21 days. Linezolid was dosed q12 hours, 10 mg/kg oral suspension (up to 600 mg/dose) for patients 5 - 11 years old, and 600 mg oral tablets for patients 12 - 17 years of age. The comparator, cefadroxil, was dosed q12 hours, 15 mg/kg oral suspension (up to 500 mg/dose) for patients 5 - 11 years old, and 500 mg oral capsules for patients 12 - 17 years of age. The primary efficacy measures of interest were the investigators' and sponsor's evaluation of patient clinical outcome (cure, failure) at the follow-up (F-U) visit. Assuming that both treatment groups would obtain 90% cure rates, a total of 474 patients were to be enrolled to provide 80% power for a conclusion of non-inferiority for linezolid compared to cefadroxil (i.e., the lower limit of the two-sided 95% confidence interval around the difference in clinical cure rates, linezolid minus cefadroxil, at follow-up should be greater than –10%); the sample size was calculated first for clinically

evaluable patients, and then increased under the assumption that only 60% of patients enrolled would be considered clinically evaluable. As there was no adjustment for the multiple primary endpoints, each endpoint would have to satisfy the criteria for non-inferiority for the study to be considered a success.

A total of 189 investigators in the United States, Canada, Argentina, Brazil, Chile, Mexico, and Peru were recruited to perform this study and received study medication. Of these, 91 investigators enrolled patients in the study: 68 in the U.S. (enrolling 70% of ITT patients), 8 in Canada (enrolling 4% of ITT patients), 5 in Argentina (enrolling 9% of ITT patients), 3 in Brazil (enrolling 2% of ITT patients), 3 in Chile (enrolling 3% of ITT patients), 2 in Mexico (enrolling 3% of ITT patients), and 2 in Peru (enrolling 10% of ITT patients). The majority of investigators enrolled only a few patients; 11 investigators enrolled 10 or more patients (the maximum number of patients enrolled at a site was 30).

The study consisted of 4 visits: a baseline visit, a day 7 visit, an end of treatment (EOT) visit within 72 hours of the last dose of study medication, and a follow-up (F-U) visit 10 - 21 days after the last dose of study medication. The F-U visit was considered the test-of-cure (TOC) visit (note that for analysis, a window of 7- to 28-days post-treatment was used for the F-U visit). Clinical assessments were performed at each visit. At the EOT and F-U visits, investigators made efficacy assessments based on the change in clinical signs and symptoms, including vital signs, compared with those at the baseline visit. Microbiologic assessments were performed as clinically indicated throughout the study. Safety was evaluated throughout the study with vital sign measurements, laboratory assays, and by the analyses of concomitant medication and adverse event reporting.

Pediatric patients (aged 5 through 17 years) with suspected gram-positive skin or skin structure infection (e.g., simple abscesses, impetigo, erysipelas, folliculitis, carbunculosis, cellulitis, wound infection, and infected burns) were eligible for enrollment if they had an infection site that was accessible for Gram's stain and culture and at least 2 of the following symptoms: drainage/discharge, erythema, fluctuance, heat/localized warmth, pain/tenderness to palpation, or swelling/induration. If the primary site of infection was an abscess, in addition to surgical draining, systemic antibiotic treatment must have been required to effect a cure at the time of enrollment.

Patients were to be excluded from the study if they had any of the following diagnoses: infections cured by surgical incision alone; medical conditions in which inflammation could have been prominent for an extended period even after successful bacterial eradication; infections requiring potentially effective concomitant antimicrobial therapy; decubitus, ischemic ulcers (unless an associated cellulitis), necrotizing fascitis, gas gangrene, or burns covering more than 20% of the total body surface; orbital, buccal, or facial cellulitis suspected to be due to *Haemophilus influenzae* type B or other gram-negative species; infection due to organisms known to be resistant to the study medications; in HIV infected patients, a CD4 cell count $\leq$200 cells/mm^3; an infected device that was not removed; endocarditis, osteomyelitis/septic arthritis, central nervous system (CNS) infection; pheochromocytoma, carcinoid syndrome, untreated hyperthyroidism, or uncontrolled hypertension; known or suspected leukemia. Patients were also to be excluded from participation in the study for the

following reasons: more than 24 hours of previous antibiotic treatment within 48 hours of study entry (unless the treatment failed or the pathogen showed drug resistance); hypersensitivity to linezolid or cefadroxil or one of the excipients in either drug formulation; previous enrollment in this or another linezolid protocol; concurrent use of another investigational medication; females with childbearing potential who were unable to take adequate contraceptive precautions, pregnant, or breastfeeding.

A patient was to be withdrawn from the study if, in the investigators' opinion, it was medically necessary or if it was the wish of the patient or patient's parent or legal guardian. In addition, a patient was to be withdrawn from the study if the isolated pathogen was not susceptible to any of the study medications and the patient was not improving, gram-negative bacterial pathogen(s) were present that required gram-negative coverage, their disease progressed (e.g., septic shock, acute renal failure) and the patient required therapy with other antimicrobials, administrative reasons (e.g., patient noncompliance or a major protocol violation), request of the sponsor or regulatory agency, lack of clinical improvement within 72 hours, or lack of microbiological improvement. Patients who were withdrawn from the study were to undergo a clinical assessment, including the appropriate EOT activities on the day that study medication was discontinued. A F-U visit was also to be completed. If a patient did not return for a scheduled visit, every effort was to be made to document the patient's response to the study medication.

As is consistent with a blinded study, supply labeling did not include drug identification. Encapsulation of the oral solid dosage forms was not attempted, since this would increase the size of the study medication and limit the number of children who were able to swallow the dosage form. The cefadroxil liquid dosage form was provided in the original manufacturer bottles but was overlabeled to hide the product name. Because of the limitations of the blinding of the study medications used in this study, it was likely that some study coordinators (through distribution of study medication) and some patients/guardians knew the group assignment of specific patients. Study coordinators, patients, and parents were instructed not to reveal the physical characteristics of the study medication or the medication name to the investigator.

The primary efficacy measures were investigators' assessment of clinical outcome and sponsor's assessment of clinical outcome. Linezolid was expected to show non-inferior cure rates compared to cefadroxil for each of these primary endpoints.

At the EOT and F-U visits, the investigator assessed each patient and assigned a clinical outcome as follows:

- Cured - Resolution of the clinical signs and symptoms of infection, when compared with baseline.
- Improved - Incomplete resolution of the clinical symptoms (only used at EOT).
- Failed - Persistence, incomplete resolution (at F-U) or worsening of the baseline clinical signs and symptoms of infection, or the development of new clinical signs and symptoms consistent with an active infection that required additional antimicrobials therapy. If a patient experienced an adverse event(s) and the discontinuation of study medication was required, the patient was to be considered a

clinical Failure. In addition, patients who withdrew from the study due to lack of clinical improvement after at least 48 hours of treatment were to be classified as clinical Failures.

- Indeterminate - Extenuating circumstances precluded classification to one of the above outcomes. Patients whose infection required an incision and drainage more than 48 hours after the first dose of study medication were also to be classified as Indeterminate. (Note: The reviewer would have preferred to classify such patients as failures. There was 1 such linezolid patient and 6 such cefadroxil patients. The linezolid patient and 1 of the cefadroxil patients were actually classified as failures by the investigator. The remaining 5 cefadroxil patients were classified as indeterminate. Note that reassigning these 5 patients to be failures would actually make linezolid's comparative efficacy look slightly better.)

The investigators' assessment of clinical outcome was summarized for the ITT, MITT, and CE populations.

The sponsor's evaluation of clinical outcome at the EOT and F-U visits was based on the global evaluations made by the investigator, the number of days and doses of study medication received, and whether a concomitant antibiotic had been administered. The patient must have received at least 5 days (10 doses) of study medication to be classified as a Cure or Improved and the patient must have received at least 2 days (4 doses) of study medication to be classified as a Failure. The algorithm used by the sponsor to classify outcomes is described below.

1. Failed:
   - If a patient was given an antibiotic for lack of efficacy any time between day 2 and the day after the investigators' clinical assessment, inclusive (if an assessment was made), then the outcome was classified as Failed for that assessment and all assessments that followed. If no investigators' clinical assessment was made in the F-U window and the patient was given an antibiotic for lack of efficacy at any time between day 2 and the upper limit of the F-U window, inclusive, then the outcome was classified as Failed for the F-U visit.
   - If a patient had no post-baseline assessment in the EOT and F-U window (or the assessments were Indeterminate in both), the patient was classified as a clinical Failure at both visits.
   - If a patient had no data (or if the outcome was Indeterminate) for the F-U visit, an outcome of Failed at the EOT visit was carried forward to the F-U visit.
2. Indeterminate:
   - If a patient was assessed by the sponsor as clinically Improved or Cured at the EOT visit and had no assessment at the F-U visit (or the assessment was Indeterminate), the outcome was Indeterminate at the TOC visit. (Note: Recall that patients whose infection required an incision and drainage more than 48 hours after the first dose of study medication were to be included in this category. While the reviewer would have preferred to classify such patients as failures, the sponsor's analysis was conservative with regard to conclusions about non-inferiority. Of the 7 such patients in this study (1 linezolid, 6 cefadroxil), the sponsor actually classified the linezolid patient and 3 of the cefadroxil patients as failures. The remaining 3

cefadroxil patients were classified as indeterminate. Reassigning these latter 3 patients to be failures would actually make linezolid's comparative efficacy look slightly better.)

3. Missing:
   - If a patient received less than 2 days of treatment or received less than 4 doses, an outcome of Missing was assigned.

The sponsor's assessment of clinical outcome was summarized for the ITT, MITT, CE, and ME populations.

The sponsor classified microbiologic outcomes for each patient at the F-U visit as either eradication (documented or presumed), persistence (documented or presumed; patients must have received at least 2 days and 4 doses of study drug to be given this outcome), superinfection, colonization, indeterminate (if no microbiological data were available at F-U and the patient's clinical outcome was indeterminate), or missing. If multiple visits occurred in the F-U window, the worst outcome was used. Selection of the worst outcome followed the order: Documented Persistence, Presumed Persistence, Superinfection, Colonization, Presumed Eradication, and Documented Eradication. The above microbiologic outcome categories were then collapsed into the following categories:

- Microbiologic Success - Any patient who had a Documented or Presumed Eradication or Colonization.
- Microbiologic Failure - Any patient who had a Documented or Presumed Persistence or Superinfection.
- Indeterminate - Any patient who was classified as Indeterminate.
- Missing - Any patient who was classified as Missing.

Analyses of efficacy variables were done separately for intent-to-treat (ITT), modified intent-to-treat (MITT), clinically evaluable (CE), and microbiologically evaluable (ME) populations. Assignments of patients to the CE and ME populations were reviewed and approved by the sponsor before the study blind was broken. The subsets are described below.

ITT Patients - The ITT population included all patients who received one or more doses of study medication. This population of patients was used for the analyses of safety and primary efficacy variables.

MITT Patients - The MITT population included all ITT patients who had a baseline pathogen isolated from a culture taken in the ITT window from the infected site or blood. This population was used for the analyses of primary and secondary efficacy variables.

CE Patients - The CE population included all patients in the ITT population unless they met 1 or more of the following criteria:

- Eligibility criteria not met.
- Prior antibiotic usage - if the antibiotic was started before the start of study medication and was potentially effective against the condition under study. Patients whose prior antibiotics were stopped on day 1 were not excluded.

- Insufficient therapy - a patient who discontinued study medication for any reason other than lack of efficacy before the minimum requirement of 7 days.
- Noncompliance with study medication regimen - a patient who did not take at least 80% of the prescribed study medication based on their study medication record or who had noncompliance documented elsewhere in the CRF.
- Concomitant antibiotics given for inter-current illness - a patient who was prescribed an antibiotic for an adverse event or inter-current illness after day 1 and before the F-U visit if the antibiotic was potentially effective against the condition under study. The use of concomitant antibiotic therapy due to a lack of efficacy in the treatment of baseline pathogens was not a reason for exclusion from the CE population.
- No post-baseline assessment - a patient without an assessment (Indeterminate is an assessment) in the F-U visit analysis window was not evaluable unless they met either of the following criteria:
    - The investigators' Clinical Outcome was a Failure at EOT.
    - The patient was given an antibiotic due to lack of efficacy any time between day 2 and the last day of the F-U analysis window, inclusive.

This population was used for the analyses of primary and secondary efficacy variables.

ME Patients - The ME population included all CE patients unless they met either of the following criteria:

- No baseline pathogen was isolated from a culture taken in the evaluable window from the infected site or blood.
- All baseline pathogens in the evaluable window were resistant to linezolid or cefadroxil.

This population was used for the analyses of primary and secondary efficacy variables.

A total of 508 patients, enrolled by 91 investigators, were randomized in a 1:1 ratio to receive treatment with either linezolid or cefadroxil. Nine patients were randomized but were withdrawn from the study before receiving study medication. A total of 499 patients received study medication and were included in the ITT population. Of these patients, 232 (93.5%) of the 248 patients in the linezolid group and 229 (91.2%) of the 251 patients in the cefadroxil group completed the study. Reasons for discontinuing the study were similar between treatment groups. The two most common reasons for not completing the study were "lost to follow-up" and "adverse event".

Table 1 summarizes the distribution of subjects in each study population. Reasons for exclusion from a study population were generally similar among treatment groups.

Table 1. Summary of Patient Populations and Reasons for Exclusion

Population Reasons for Exclusion*	Linezolid n (%)	Cefadroxil n (%)
All Randomized Patients	252 (100)	256 (100)
ITT Population	248 (98.4)	251 (98.0)
Never received study medication	4 (1.6)	5 (2.0)
MITT Population	171 (67.9)	166 (64.8)
No baseline pathogen	77 (30.6)	85 (33.2)
CE Population	224 (88.9)	216 (84.4)
Prior antibiotic usage	1 (0.4)	0 (0)
Insufficient therapy	5 (2.0)	12 (4.7)
Concomitant antibiotics for inter-current illness	3 (1.2)	6 (2.3)
Noncompliant with therapy regimen	3 (1.2)	3 (1.2)
No post-baseline clinical outcome	15 (6.0)	22 (8.6)
ME Population	159 (63.1)	150 (58.6)
Not clinically evaluable	24 (9.5)	35 (13.7)
No baseline pathogen	78 (31.0)	85 (33.2)

*Patients could have had more than one reason for exclusion.

There were 2 patients incorrectly randomized in this study. Investigator Carrascal (#45780) enrolled patients #6500578 and #6500579 after receiving the study medication but before an initiation visit had been completed by the field monitor. The investigator was not aware that the patients' randomization had to come from the central interactive voice response system (IVRS), therefore, the investigator selected "Treatment B" for these patients. Once the field monitor was notified that patients had been enrolled at the site, the patients were entered into the IVRS. When the blind was broken, the patients were found to have received the incorrect treatment (they were both randomized to linezolid but received cefadroxil). An additional patient at this site (#6500595) was enrolled in the study without correct use of IVRS, but was given the correct treatment. This patient was not considered misrandomized. All patients are included in the analyses according to the medication they actually received.

In the ITT population, the average patient age was 10.9 years (range from 4.9 to 17.9 years). Approximately 50% of ITT patients were female and 50% were male. Most of the patients were white (72%), and from North America (74%). The treatment groups were comparable in demographics and did not differ significantly in baseline measurements of age, weight, height, race, or geographic region. However, there were significantly more females in the linezolid group than in the cefadroxil group (56% v. 44%, p=0.01). Similar trends in the baseline measurements of age, gender, weight, height, race, and geographic region were observed in the MITT, CE, and ME populations. However, in the MITT and ME populations, the difference between the groups in the percentages of male and female patients was no longer statistically significant.

In the ITT population, medical history and baseline physical examination findings were generally similar among treatment groups, as were baseline vital signs and baseline clinical signs and symptoms of disease. Over two thirds of the patients in each treatment group had erythema, tenderness, swelling, and heat/localized warmth at the baseline visit. All patients had at least 2 clinical signs and symptoms of skin and skin structure infection (as required for inclusion by the protocol) and nearly 75% of patients in each treatment group had 5 or more

signs and symptoms. Table 2 summarizes the primary diagnosis of the skin infections for ITT patients.

Table 2. Clinical Diagnosis: ITT Patients

Diagnosis	Linezolid N=248 n (%)	Cefadroxil N=251 n (%)
Infected Wound	11 (4.4)	10 (4.0)
Cellulitis	46 (18.5)	50 (19.9)
Folliculitis	9 (3.6)	10 (4.0)
Carbuncle	3 (1.2)	3 (1.2)
Furuncle	7 (2.8)	6 (2.4)
Skin Ulcer	1 (0.4)	0 (0)
Skin Abscess	18 (7.3)	20 (8.0)
Impetigo	95 (38.3)	85 (33.9)
Infected Bite	11 (4.4)	16 (6.4)
Infected Surgical Incision	4 (1.6)	0 (0)
Paronychia	23 (9.3)	34 (13.5)
Burn	1 (0.4)	0 (0)
Other	19 (7.7)	17 (6.8)

In the ITT population, 77% of patients had a "superficial" degree of involvement of their infection, while the remaining 23% had a "deep" degree of involvement. The average duration of infection prior to treatment with study medication was 11.8 ± 18.7 days for the linezolid-treated patients and 14.9 ± 30.0 days for the cefadroxil-treated patients (p=0.17). The average area of the primary lesion at the baseline visit was 32.90 ± 111.63 cm^2 for the patients in the linezolid group and 18.52 ± 43.88 cm^2 for the patients in the cefadroxil group. Although the difference between the groups was not statistically significant (p = 0.07), the average lesion size for the linezolid group was nearly twice that of the cefadroxil group. However, the difference in average lesion area was probably caused by a few outlying values, since the median baseline lesion area for the treatment groups was similar (linezolid: 4.00 cm^2; cefadroxil: 3.75 cm^2).

In the ITT population, similar percentages of patients in both treatment groups took non-investigational antibiotics (linezolid: 16.1% [40/248], cefadroxil: 17.1% [43/251]) prior to or on the first day of study medication. The use of individual topical and systemic antibiotics was similar between treatment groups. Of the 248 patients in the linezolid group, 18 (7.3%) used topical antibiotics, 6 (2.4%) used penicillins, and 9 (3.6%) used cephalosporins. Of the 251 patients in the cefadroxil group, 16 (6.4%) used topical antibiotics, 12 (4.8%) used penicillins, and 8 (3.2%) used cephalosporins.

In the ITT population, similar percentages of patients in both treatment groups also started taking non-investigational antibiotics after the first day of study medication (linezolid: 9.7% [24/248], cefadroxil: 9.6% [24/251]). The use of individual topical and systemic antibiotics was similar between treatment groups. Of the 248 patients in the linezolid group, 5 (2.0%) used topical antibiotics, 6 (2.4%) used penicillins, and 6 (2.4%) used cephalosporins. Of the

251 patients in the cefadroxil group, 5 (2.0%) used topical antibiotics, 5 (2.0%) used penicillins, and 10 (4.0%) used cephalosporins.

The frequency of the use of concomitant medications, excluding antibiotics, started prior to or on the first day of study medication was also similar among treatment groups, as was the frequency of the use of concomitant medications, excluding antibiotics, started after the first day of study medication.

In the ITT population, 8% of linezolid patients were dosed less than 10 days, 75% were dosed between 10 and 14 days, and 17% were dosed more than 14 days. Similarly, 10% of cefadroxil patients were dosed less than 10 days, 72% were dosed between 10 and 14 days, and 18% were dosed more than 14 days. The average duration of treatment was 12.0 ± 3.6 days for the patients in the linezolid group and 11.9 ± 3.9 days for the patients in the cefadroxil group

Table 3 summarizes results for the first primary efficacy variable, the investigators' assessment of clinical outcome at F-U, by treatment group for the ITT, MITT, and CE populations. The sponsor's 95% confidence intervals for the treatment difference in cure rates are calculated using the normal approximation to the binomial distribution without the continuity correction. Confidence intervals calculated with the continuity correction, and stratified by age group, are given under the "Statistical Reviewer's Findings" section (page 24). As each of the lower CI limits are greater than -10%, linezolid cure rates may be considered similar to those of cefadroxil. Cure rates at EOT were also similar between the treatment groups for each of the populations summarized below (86.5% linezolid and 86.3% cefadroxil in the ITT population; 87.6% linezolid and 87.1% cefadroxil in the CE population).

Table 3. Investigators' Assessment of Clinical Outcome at F-U

Population	Assessment	Linezolid n (%)	Cefadroxil n (%)	95% CI for Difference in Cure Rates (Linezolid – Cefadroxil)
ITT	Number of Patients Assessed*	224 (100)	210 (100)	(-4.3%, 5.2%)
	Cured	209 (93.3)	195 (92.9)	
	Failed	15 (6.7)	15 (7.1)	
	Indeterminate	7	17	
	Missing	17	24	
MITT	Number of Patients Assessed*	160 (100)	146 (100)	(-5.0%, 6.2%)
	Cured	150 (93.8)	136 (93.2)	
	Failed	10 (6.3)	10 (6.8)	
	Indeterminate	3	7	
	Missing	8	13	
CE	Number of Patients Assessed*	219 (100)	202 (100)	(-5.0%, 4.1%)
	Cured	205 (93.6)	190 (94.1)	
	Failed	14 (6.4)	12 (5.9)	
	Indeterminate	4	12	
	Missing	1	2	

*Excludes patients with indeterminate or missing outcomes.

In the results summarized above, patients with indeterminate or missing outcomes are excluded when calculating cure rates. If these patients are included as failures (as they typically are in the ITT analysis), the results change as follows. In the ITT population, the cure rates are 84.3% for linezolid and 77.7% for cefadroxil (95% CI for the difference of (-0.3%, 13.4%)). In the MITT population, the cure rates are 87.7% for linezolid and 81.9% for cefadroxil (95% CI for the difference of (-1.9%, 13.4%)). In the CE population, the cure rates are 91.5% for linezolid and 88.0% for cefadroxil (95% CI for the difference of (-2.1%, 9.2%)). In each case, the lower limit of the CI is still well above –10%.

Subgroup analyses were performed for both the ITT and CE populations to determine if the investigators' assessment of clinical outcome differed by age, gender, race, or diagnosis. In the analyses by age, gender, and diagnosis, the results for each subgroup were similar to those observed in the primary analysis. There were no significant treatment differences for the subgroups in the percentages of patients considered cured at the F-U visit. In the analysis by race, the results for all races except black were similar to those observed in the primary analysis. There were no significant treatment differences in the subgroups in the percentages of patients considered cured at the F-U visit. In the ITT population, the percentage of black patients cured (linezolid: 87.5% [21/24], cefadroxil: 83.3% [10/12]) at the F-U visit was lower than those of patients of other races (linezolid: 93.5% - 100%, cefadroxil: 92.9% - 100%). However, the number of black patients studied was small. Similar results were obtained for the CE population.

Table 4 summarizes results for the second primary efficacy variable, the sponsor's assessment of clinical outcome at F-U, by treatment group for the ITT, MITT, CE, and ME populations. Results are similar to those found for the investigators' assessment of clinical outcome, except that cure rates are slightly lower for the sponsor's assessment. As with the investigators' assessment, the sponsor's 95% confidence intervals for the treatment difference in cure rates are calculated using the normal approximation to the binomial distribution without the continuity correction. Confidence intervals calculated with the continuity correction, and stratified by age group, are given under the "Statistical Reviewer's Findings" section (page 24). As each of the lower CI limits are greater than -10%, linezolid cure rates may be considered similar to those of cefadroxil. Cure rates at EOT were also similar between the treatment groups for each of the populations summarized below (85.0% linezolid and 83.0% cefadroxil in the ITT population; 87.2% linezolid and 85.8% cefadroxil in the CE population).

Table 4. Sponsor's Assessment of Clinical Outcome at F-U

Population	Assessment	Linezolid n (%)	Cefadroxil n (%)	95% CI for Difference in Cure Rates (Linezolid – Cefadroxil)
ITT	Number of Patients Assessed*	231 (100)	224 (100)	(-3.5%, 8.7%)
	Cured	205 (88.7)	193 (86.2)	
	Failed	26 (11.3)	31 (13.8)	
	Indeterminate	15	22	
	Missing	2	5	
MITT	Number of Patients Assessed*	164 (100)	155 (100)	(-4.5%, 9.6%)
	Cured	147 (89.6)	135 (87.1)	
	Failed	17 (10.4)	20 (12.9)	
	Indeterminate	7	11	
	Missing	0	0	
CE	Number of Patients Assessed*	221 (100)	210 (100)	(-4.6%, 6.5%)
	Cured	201 (91.0)	189 (90.0)	
	Failed	20 (9.0)	21 (10.0)	
	Indeterminate	3	6	
	Missing	0	0	
ME	Number of Patients Assessed*	157 (100)	147 (100)	(-6.6%, 6.6%)
	Cured	142 (90.4)	133 (90.5)	
	Failed	15 (9.6)	14 (9.5)	
	Indeterminate	2	3	
	Missing	0	0	

*Excludes patients with indeterminate or missing outcomes.

In the results summarized above, patients with indeterminate or missing outcomes are excluded when calculating cure rates. If these patients are included as failures (as they typically are in the ITT analysis; note that for the sponsor's assessment of clinical outcome most of the patients classified as "missing" by the investigator have already been reclassified as failures – "missing" in the above analysis was assigned only if a patient failed to complete two days or four doses of therapy), the results change as follows. In the ITT population, the cure rates are 82.7% for linezolid and 76.9% for cefadroxil (95% CI for the difference of (-1.3%, 12.8%)). In the MITT population, the cure rates are 86.0% for linezolid and 81.3% for cefadroxil (95% CI for the difference of (-3.3%, 12.5%)). In the CE population, the cure rates are 89.7% for linezolid and 87.5% for cefadroxil (95% CI for the difference of (-3.7%, 8.2%)). In the ME population, the cure rates are 89.3% for linezolid and 88.7% for cefadroxil (95% CI for the difference of (-6.3%, 7.6%)). In each case, the lower limit of the CI is still well above –10%.

Subgroup analyses were performed for the ITT, CE, and ME populations to determine if the sponsor's assessment of clinical outcome differed by age, gender, race, investigator (ITT and CE populations only; sites that enrolled ≥10 ITT, or CE, patients, respectively, were included in this analysis), or geographic region (CE population only). In the analysis by age, gender, investigator, and geographic region, the results for each of the subgroups were similar to those observed in the primary analysis. There were no significant treatment differences in the subgroups in terms of the percentages of patients considered cured at the F-U visit. In the analysis by race, the results for all races except black were similar to those

observed in the primary analysis, and there were no treatment differences by race subgroup. In the ITT population, the percentage of black patients (linezolid: 74.1% [20/27], cefadroxil: 76.9% [10/13]) cured at the F-U visit was lower than those of patients in other races (linezolid: 89.2 - 100%, cefadroxil: 85.6% - 100%). Again, the number of black patients studied was small. This trend was also observed in the CE population. In the ME population, the percentage of black patients in the linezolid group cured at the F-U visit was similar to those of patients in other races.

Table 5 summarizes the sponsor's assessment of clinical outcome by diagnosis for the CE population. There were no significant treatment differences in the cure rates by diagnosis. Results were similar for the ITT population.

Table 5. Sponsor's Assessment of Clinical Outcome at F-U by Baseline Diagnosis: CE Population

	Cure Rate	
Diagnosis	**Linezolid n/N (%)***	**Cefadroxil n/N (%)***
Burn	1/1 (100)	0
Carbuncle	1/3 (33.3)	3/3 (100)
Cellulitis	34/38 (89.5)	38/40 (95.0)
Folliculitis	9/9 (100)	7/9 (77.8)
Furuncle	7/7 (100)	4/5 (80.0)
Impetigo	78/86 (90.7)	69/74 (93.2)
Infected Bite	9/9 (100)	15/15 (100)
Infected Surgical Incision	2/2 (100)	0
Infected Wound (traumatic)	8/10 (80.0)	7/8 (87.5)
Other	18/19 (94.7)	11/13 (84.6)
Paronychia	20/22 (90.9)	24/29 (82.8)
Skin Abscess	13/14 (92.9)	11/14 (78.6)
Skin Ulcer	1/1 (100)	0

*All percentages are based on the number of patients assessed within each diagnosis.

Table 6 summarizes the sponsor's assessment of clinical outcome for patients with selected baseline pathogens in the MITT population. There were no significant treatment differences in the cure rates by baseline pathogen. Results were similar in the ME population.

Table 6. Sponsor's Assessment of Clinical Outcome at F-U For Patients with Selected Baseline Pathogens: MITT Population

	Cure Rate	
Pathogen	**Linezolid n/N (%)***	**Cefadroxil n/N (%)***
Staphylococcus aureus	123/136 (90.4)	113/133 (85.0)
Streptococcus pyogenes	33/36 (91.7)	26/27 (96.3)
Streptococcus agalactiae	1/1 (100)	2/2 (100)
Streptococcus dysgalactiae	2/2 (100)	3/3 (100)
Enterococcus faecalis	1/1 (100)	1/1 (100)

*All percentages are based on the number of patients assessed with each pathogen.

Secondary efficacy endpoints were also supportive of comparative efficacy of linezolid compared to cefadroxil. Table 7 summarizes patient microbiological outcome at the F-U visit for the MITT and ME populations. Success rates were comparable between the treatment groups in both populations.

Table 7. Patient Microbiological Outcome at F-U: MITT and ME Populations

Population	Assessment	Linezolid n (%)*	Cefadroxil n (%)*	95% CI for Difference in Success Rates (Linezolid – Cefadroxil)
MITT	Total Number of Patients	171	166	(-5.2%, 9.1%)
	Number of Patients Assessed**	164 (100)	155 (100)	
	Microbiological Success	146 (89.0)	135 (87.1)	
ME	Total Number of Patients	159	150	(-7.3%, 6.1%)
	Number of Patients Assessed**	158 (100)	147 (100)	
	Microbiological Success	142 (89.9)	133 (90.5)	

*All percentages are based on the number of patients assessed.
**Excludes patients with indeterminate or missing outcomes.

A supplementary analysis of the patient microbiological outcome was conducted in which indeterminate and missing outcomes were classified as failures. In the ME population, the microbiological success rates (89.3% in the linezolid group versus 88.7% in the cefadroxil group) were still considered comparable between the treatment groups (95% CI for the difference in success rates of (-6.3, 7.6)). In addition, analyses of the patient microbiological outcome were performed for the CE and ME populations by age, gender, race, diagnosis (CE population only), and geographic region (CE population only). In these analyses, the results for each of the subgroups were similar to those observed in the primary analyses. There were no significant differences between treatment groups in the percentages of patients with an outcome of success at the F-U visit.

Table 8 summarizes patient microbiological outcome at F-U by selected baseline pathogens in the MITT population. Note that in the MITT population, pathogen eradication rates for methicillin-resistant *S. aureus* (MRSA) were 92.9% (13/14) for linezolid and 77.8% (7/9) for cefadroxil. For methicillin-susceptible *S. aureus* (MSSA), eradication rates were 89.4% (110/123) for linezolid and 85.5% (106/124) for cefadroxil. There were no significant treatment differences in the success rates by baseline pathogen. Results were similar in the ME population.

Table 8. Patient Microbiological Outcome at F-U For Patients with Selected Baseline Pathogens: MITT Population

	Microbiological Success Rate	
Pathogen	Linezolid n/N (%)*	Cefadroxil n/N (%)*
Staphylococcus aureus	123/137 (89.8)	113/133 (85.0)
Streptococcus pyogenes	33/37 (89.2)	26/27 (96.3)
Streptococcus agalactiae	1/1 (100)	2/2 (100)
Streptococcus dysgalactiae	2/2 (100)	3/3 (100)
Enterococcus faecalis	1/1 (100)	1/1 (100)

*All percentages are based on the number of patients assessed with each pathogen.

All patients who received at least one dose of study medication (i.e., the ITT population) were included in the safety evaluation. Five patients (3 linezolid, 2 cefadroxil) were unable to be assessed for adverse events because they did not return to the clinic after their baseline visit. Table 9 summarizes the frequencies of adverse events in several overall categories. Rates were generally similar between treatment groups.

Table 9. Adverse Event Summary

Adverse Event Category	Linezolid N=248 n (%)	Cefadroxil N=251 n (%)
Total Patients Reported	245 (100)	249 (100)
Patients with ≥1 AE	111 (45.3)	117 (47.0)
Patients with ≥1 drug-related AE	47 (19.2)	35 (14.1)
Patients with ≥1 AE leading to D/C of medication	5 (2.0)	9 (3.6)
Patients with ≥1 drug-related AE leading to D/C of medication	4 (1.6)	6 (2.4)
Patients with ≥1 serious AE	2 (0.8)	4 (1.6)
Patients who died	0	0

Abbreviations: AE = adverse event, D/C=discontinuation

Table 10 displays the frequencies of adverse events reported in ≥1% of patients in either treatment group. Within each body system, events appear in decreasing order of their frequency in the linezolid group. Frequencies were generally similar between treatment groups.

Table 10. Frequencies of Study-Emergent Adverse Events Reported by ≥1% of Patients in Either Treatment Group

Body System	Adverse Event	Linezolid N=248 n (%)	Cefadroxil N=251 n (%)
Total Patients Reported		245 (100)	249 (100)
Body	Headache	16 (6.5)	10 (4.0)
	Upper respiratory infection	9 (3.7)	13 (5.2)
	Trauma	8 (3.3)	12 (4.8)
	Fever	7 (2.9)	9 (3.6)
	Abdominal pain generalized	6 (2.4)	7 (2.8)
	Abdominal pain localized	6 (2.4)	7 (2.8)
	Localized pain	5 (2.0)	4 (1.6)
	Allergic reaction	3 (1.2)	3 (1.2)
	Reaction unevaluable	3 (1.2)	2 (0.8)
Digestive	Diarrhea	19 (7.8)	20 (8.0)
	Nausea	9 (3.7)	8 (3.2)
	Vomiting	7 (2.9)	16 (6.4)
	Loose stools NEC	4 (1.6)	2 (0.8)
	Dyspepsia	3 (1.2)	1 (0.4)
Nervous	Dizziness	4 (1.6)	1 (0.4)
	Vertigo	3 (1.2)	1 (0.4)
Respiratory	Pharyngitis	7 (2.9)	4 (1.6)
	Cough	6 (2.4)	10 (4.0)
	Rhinitis	2 (0.8)	10 (4.0)
	Sinusitis	0	3 (1.2)
Skin	Disorder skin NEC	5 (2.0)	0
	Rash	4 (1.6)	3 (1.2)
	Skin infection	3 (1.2)	4 (1.6)
	Disorder nail	0	3 (1.2)
Special Senses	Ear pain	3 (1.2)	1 (0.4)

Abbreviation: NEC = not elsewhere classified

Table 11 displays the percentages of patients in each treatment group with at least one substantially abnormal selected hematology or chemistry assay values. Most of these abnormal laboratory values resolved by the end of the study (in the linezolid arm, all did).

Table 11. Patients with at Least One Substantially Abnormal Laboratory Assay Value

Assay (Criteria)	Linezolid		Cefadroxil	
	Substantially Abnormal n/N (%)	Resolved n/N (%)	Substantially Abnormal n/N (%)	Resolved n/N (%)
RBC (<75% of LLN)	1/243 (0.4)	1/1 (100)	0/246 (0.0)	--
WBC (<75% of LLN)	2/243 (0.8)	2/2 (100)	2/246 (0.8)	1/2 (50.0)
Neutrophil Count (<0.5 of LLN)	3/242 (1.2)	3/3 (100)	2/245 (0.8)	2/2 (100)
Platelet Count (<75% of LLN)	0/243 (0.0)	--	1/246 (0.4)	0/1 (0.0)
Creatinine (>2 x ULN)	1/243 (0.4)	1/1 (100)	0/246 (0.0)	--
Lipase (>2 x ULN)	1/244 (0.4)	1/1 (100)	3/244 (1.2)	1/3 (33.3)

At the EOT visit, there were statistically significant differences between the treatment groups in the mean change from baseline values in WBC count (p=0.006), percentage of neutrophils (p=0.015), neutrophil count (p=0.004), percentage of lymphocytes (p=0.003), monocyte count (p=0.040), basophil count (p=0.046), platelet count (p<0.001), and ALT (p=0.024). With the exception of basophil count (p=0.045), none of the above treatment differences remained significant at the follow-up visit.

For select laboratory assays, the possible range of values was divided into 5 grades. The sponsor then analyzed the change from baseline grade to the worst grade obtained during the study. Table 12 summarizes the shifts to a higher (worse) grade for these laboratory assay values. Hemoglobin was categorized as follows: Grade 1 (> 9.4 g/dL), Grade 2 (8.0 – 9.4 g/dL), Grade 3 (7.0 – 7.9 g/dL), Grade 4 (6.5 – 6.9 g/dL), or Grade 5 (< 6.5 g/dL). Platelet count was categorized as follows: Grade 1 (> 99 x $10^3/\mu L$), Grade 2 (75 - 99 x $10^3/\mu L$), Grade 3 (50 – 74.9 x $10^3/\mu L$), Grade 4 (20 – 49.9 x $10^3/\mu L$), or Grade 5 (< 20 x $10^3/\mu L$). Neutrophil count was categorized as follows: Grade 1 (> 1500 x $10^3/\mu L$), Grade 2 (1000 - 1500 x $10^3/\mu L$), Grade 3 (750 – 999 x $10^3/\mu L$), Grade 4 (500 – 749 x $10^3/\mu L$), or Grade 5 (< 500 x $10^3/\mu L$). For neutrophil count, the 12 linezolid and 8 cefadroxil patients with a shift of 1 grade all changed from Grade 1 to Grade 2, the 1 linezolid and 2 cefadroxil patients with a shift of 2 grades all changed from Grade 1 to Grade 3, and the 1 linezolid and 2 cefadroxil patients with a shift of 3 grades all changed from Grade 1 to Grade 4. AST and ALT were categorized as follows: Grade 1 (< 1.25 x ULN), Grade 2 (≥ 1.25 - < 2.5 x ULN), Grade 3 (≥ 2.5 - < 5 x ULN), Grade 4 (≥ 5 - < 10 x ULN), or Grade 5 (≥ 10 x ULN). For AST, the 9 linezolid and 12 cefadroxil patients with a shift of 1 grade all changed from Grade 1 to Grade 2. For ALT, the 9 linezolid patients with a shift of 1 grade all changed from Grade 1 to Grade 2; 5 of the cefadroxil patients with a shift of 1 grade changed from Grade 1 to Grade 2, the remaining cefadroxil patient changed from Grade 2 at baseline to Grade 3 during the study.

Table 12. Summary of Shifts in Select Laboratory Assay Values to Higher Grades

Assay	Shift Category	Linezolid n/N (%)	Cefadroxil n/N (%)
Hemoglobin	Any shift	0/214 (0)	0/213 (0)
Platelet Count	Any shift	0/197 (0)	1/197 (0.5)
	Shift of 1 grade	0/197 (0)	1/197 (0.5)
Neutrophil Count	Any shift	14/185 (7.6)	12/192 (6.3)
	Shift of 1 grade	12/185 (6.5)	8/192 (4.2)
	Shift of 2 grades	1/185 (0.5)	2/192 (1.0)
	Shift of 3 grades	1/185 (0.5)	2/192 (1.0)
AST	Any shift	9/233 (3.9)	12/226 (5.3)
	Shift of 1 grade	9/233 (3.9)	12/226 (5.3)
ALT	Any shift	9/233 (3.9)	6/227 (2.6)
	Shift of 1 grade	9/233 (3.9)	6/227 (2.6)

2.3.4 STATISTICAL REVIEWER'S FINDINGS

Table 13 summarizes results for the first primary efficacy variable, the investigators' assessment of clinical outcome at F-U, by treatment group for the ITT, MITT, and CE populations. (Note: Rates in this table are the same as those given in Table 3 above.) Confidence intervals for the treatment difference in cure rates are calculated (1) using the normal approximation to the binomial distribution with the continuity correction, and (2) stratified by age group (5-11 years old and 12-17 years old). As each of the lower CI limits are greater than -10%, linezolid cure rates may be considered similar to those of cefadroxil.

Table 13. Investigators' Assessment of Clinical Outcome at F-U

Population	Assessment	Linezolid n (%)	Cefadroxil n (%)	95% CI for Difference in Cure Rates (Linezolid – Cefadroxil) Method 1 (Normal approx. w/ cc) Method 2 (Stratified by age group)
ITT	# Patients Assessed*	224 (100)	210 (100)	
	Cured	209 (93.3)	195 (92.9)	(-4.8%, 5.7%)
	Failed	15 (6.7)	15 (7.1)	(-4.2%, 5.4%)
	Indeterminate	7	17	
	Missing	17	24	
MITT	# Patients Assessed*	160 (100)	146 (100)	
	Cured	150 (93.8)	136 (93.2)	(-5.6%, 6.8%)
	Failed	10 (6.3)	10 (6.8)	(-4.7%, 6.4%)
	Indeterminate	3	7	
	Missing	8	13	
CE	# Patients Assessed*	219 (100)	202 (100)	
	Cured	205 (93.6)	190 (94.1)	(-5.5%, 4.6%)
	Failed	14 (6.4)	12 (5.9)	(-5.0%, 4.2%)
	Indeterminate	4	12	
	Missing	1	2	

*Excludes patients with indeterminate or missing outcomes.

Table 14 summarizes results for the second primary efficacy variable, the sponsor's assessment of clinical outcome at F-U, by treatment group for the ITT, MITT, CE, and ME populations. Results are similar to those found for the investigators' assessment of clinical outcome, except that cure rates are slightly lower for the sponsor's assessment. (Note: Rates in this table are the same as those given in Table 4 above.) As with the investigators' assessment, confidence intervals for the treatment difference in cure rates are calculated (1) using the normal approximation to the binomial distribution with the continuity correction, and (2) stratified by age group (5-11 years old and 12-17 years old). As each of the lower CI limits are greater than -10%, linezolid cure rates may be considered similar to those of cefadroxil.

Table 14. Sponsor's Assessment of Clinical Outcome at F-U

Population	Assessment	Linezolid n (%)	Cefadroxil n (%)	95% CI for Difference in Cure Rates (Linezolid – Cefadroxil) Method 1 (Normal approx. w/ cc) Method 2 (Stratified by age group)
ITT	# Patients Assessed*	231 (100)	224 (100)	
	Cured	205 (88.7)	193 (86.2)	(-3.9%, 9.1%)
	Failed	26 (11.3)	31 (13.8)	(-3.5%, 8.7%)
	Indeterminate	15	22	
	Missing	2	5	
MITT	# Patients Assessed*	164 (100)	155 (100)	
	Cured	147 (89.6)	135 (87.1)	(-5.1%, 10.2%)
	Failed	17 (10.4)	20 (12.9)	(-4.4%, 9.7%)
	Indeterminate	7	11	
	Missing	0	0	
CE	# Patients Assessed*	221 (100)	210 (100)	
	Cured	201 (91.0)	189 (90.0)	(-5.1%, 7.0%)
	Failed	20 (9.0)	21 (10.0)	(-4.6%, 6.5%)
	Indeterminate	3	6	
	Missing	0	0	
ME	# Patients Assessed*	157 (100)	147 (100)	
	Cured	142 (90.4)	133 (90.5)	(-7.3%, 7.2%)
	Failed	15 (9.6)	14 (9.5)	(-6.5%, 6.7%)
	Indeterminate	2	3	
	Missing	0	0	

*Excludes patients with indeterminate or missing outcomes.

The reviewer conducted an additional analysis of the clinical outcome at follow-up using a slightly different algorithm to define cures, failures, and missing data. This analysis is similar to one conducted by Dr. Brittain in her review of Study 0082. Patients were considered cures if they were assessed as cures at F-U by the investigator; they were assessed as failures if either (1) they were assessed as failures by the investigator at either the EOT or F-U visit, (2) they had died by the F-U visit and were not assessed as a cure by the investigator at the F-U visit (note: no patients died in this study), or (3) they were prescribed an additional antibiotic for lack of efficacy at any time during the study up to and including the F-U visit; all other patients were assessed as missing. Patients are included in the analysis by the treatment to which they were randomized.

Table 15 summarizes results for this "reviewer's assessment of clinical outcome at F-U", by treatment group for the ITT, MITT, and CE populations. Cure rates are calculated excluding missing values, and confidence intervals for the treatment difference in cure rates are calculated using the normal approximation to the binomial distribution with the continuity correction. Results are similar to those found for the investigators' assessment of clinical outcome at F-U, except that cure rates are somewhat lower. Results are also similar to those found for the sponsor's assessment of clinical outcome at F-U, except that the treatment differences are somewhat smaller, mostly because the cure rates for cefadroxil are slightly higher in this analysis. As each of the lower CI limits are greater than -10%, the reviewer considers linezolid cure rates similar to those of cefadroxil.

Table 15. Reviewer's Assessment of Clinical Outcome at F-U

Population	Assessment	Linezolid n (%)	Cefadroxil n (%)	95% CI for Difference in Cure Rates (Linezolid – Cefadroxil)
ITT	# Patients Assessed*	229 (100)	217 (100)	(-5.1%, 7.2%)
	Cured	206 (90.0)	193 (88.9)	
	Failed	23 (10.0)	24 (11.1)	
	Missing	21	32	
MITT	# Patients Assessed*	163 (100)	149 (100)	(-6.3%, 8.1%)
	Cured	148 (90.8)	134 (89.9)	
	Failed	15 (9.2)	15 (10.1)	
	Missing	10	15	
CE	# Patients Assessed*	221 (100)	207 (100)	(-6.2%, 5.5%)
	Cured	201 (91.0)	189 (91.3)	
	Failed	20 (9.0)	18 (8.7)	
	Missing	3	9	

*Excludes patients with missing outcomes.

2.4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Investigators' Assessment of Clinical Outcome

Subgroup analyses were performed for both the ITT and CE populations to determine if the investigators' assessment of clinical outcome differed by age, gender, race, or diagnosis. In the analyses by age, gender, and diagnosis, the results for each subgroup were similar to those observed in the primary analysis. There were no significant treatment differences for the subgroups in the percentages of patients considered cured at the F-U visit. In the analysis by race, the results for all races except black were similar to those observed in the primary analysis. There were no significant treatment differences in the subgroups in the percentages of patients considered cured at the F-U visit. In the ITT population, the percentage of black patients cured (linezolid: 87.5% [21/24], cefadroxil: 83.3% [10/12]) at the F-U visit was lower than those of patients of other races (linezolid: 93.5% - 100%, cefadroxil: 92.9% - 100%). However, the number of black patients studied was small. Similar results were obtained for the CE population.

Sponsor's Assessment of Clinical Outcome

Subgroup analyses were performed for the ITT, CE, and ME populations to determine if the sponsor's assessment of clinical outcome differed by age, gender, race, diagnosis, investigator (ITT and CE populations only; sites that enrolled ≥10 ITT, or CE, patients, respectively, were included in this analysis), or geographic region (CE population only). In the analysis by age, gender, investigator, and geographic region, the results for each of the subgroups were similar to those observed in the primary analysis. There were no significant treatment differences in the subgroups in terms of the percentages of patients considered cured at the F-U visit. In the analysis by race, the results for all races except black were similar to those observed in the primary analysis, and there were no treatment differences by race subgroup. In the ITT population, the percentage of black patients (linezolid: 74.1% [20/27], cefadroxil: 76.9% [10/13]) cured at the F-U visit was lower than those of patients in other races (linezolid: 89.2 - 100%, cefadroxil: 85.6% - 100%). Again, the number of black patients studied was small. This trend was also observed in the CE population. In the ME

population, the percentage of black patients in the linezolid group cured at the F-U visit was similar to those of patients in other races.

Patient Microbiological Outcome

Subgroup analyses of the patient microbiological outcome were performed for the CE and ME populations by age, gender, race, diagnosis (CE population only), and geographic region (CE population only). In these analyses, the results for each of the subgroups were similar to those observed in the primary analyses. There were no significant differences between treatment groups in the percentages of patients with an outcome of success at the F-U visit.

2.5 STATISTICAL AND TECHNICAL ISSUES

There are no additional statistical and/or technical issues that need to be addressed.

2.6 STATISTICAL EVALUATION OF COLLECTIVE EVIDENCE

As there was only one controlled study conducted in pediatric patients with uSSSI, no meta-analytic methods were used in the review.

2.7 CONCLUSIONS AND RECOMMENDATIONS

This application includes efficacy and safety data from two Phase 3 comparator-controlled clinical trials in pediatric patients: Study M/1260/0065 (Study 0065) in children with uncomplicated skin and skin structure infections (uSSSI) and Study M/1260/0082 in children with resistant gram-positive bacterial infections, including nosocomial pneumonia, community-acquired pneumonia, complicated SSSI, catheter-related bacteremia, and bacteremia of unidentified source. This review focuses on Study 0065. For discussion of the other controlled study, please see the statistical review by Dr. Erica Brittain.

Study 0065 was a randomized, blinded, active-controlled, multi-center, multinational trial conducted in children ages 5-17 with uSSSI. Efficacy of linezolid was shown to be not inferior to that of the comparator cefadroxil, an approved product, using an acceptable clinical difference of 10 percentage points. In addition, the safety profile of the two regimens was shown to be similar. Based upon this study and previous controlled clinical studies in uSSSI in adults receiving linezolid, this reviewer feels that it would be appropriate to include information from Study 0065 in the Zyvox label.

As subjects were dosed bid in Study 0065, however, this reviewer does not agree with the sponsor's suggestion in the proposed label for tid dosing for children with uSSSI. Instead, this reviewer feels that the label should reflect the dosing regimen studied for Zyvox in children with uSSSI, which was 10 mg/kg oral, up to ———— every 12 hours for patients aged 5 through 11 years, and 600 mg oral, every 12 hours, for patients from 12 through 17 years of age. The reviewer does not object to the sponsor's suggestion in the label for dosing to range from 10 to 14 days, if the medical reviewer thinks this is acceptable.

While study 0065 allowed for dosing to range from 10 to 21 days, 75% of ITT patients were dosed between 10 and 14 days.

One other labeling suggestion that the reviewer would make in the Clinical Studies section is to include primary efficacy results for the ITT population from study 0065. The sponsor has already proposed including results for the clinically evaluable and microbiologically evaluable populations.

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/s/

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