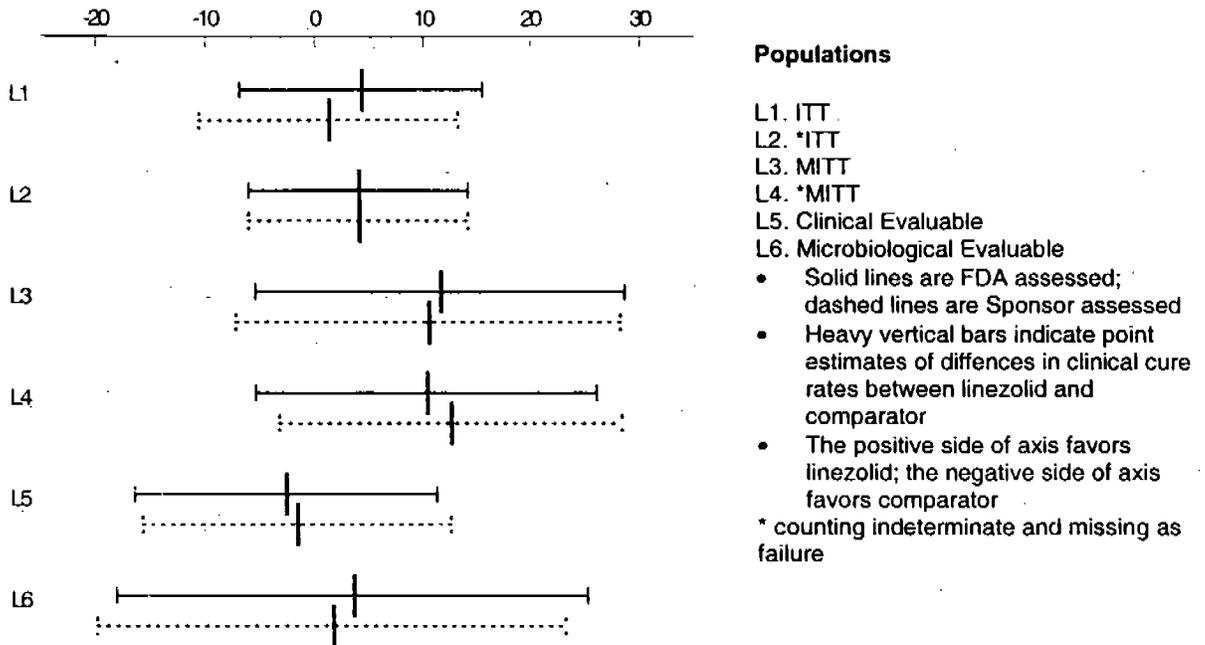


An overview of clinical cure rates for patients in Study 48a is presented in Figure 3 and Table 77.

FIGURE 3: STUDY 48a: 95% CONFIDENCE INTERVALS IN DIFFERENCES IN CLINICAL CURE RATES.



Population	Linezolid	Vancomycin	C.I.
	n/N (%)	n/N (%)	
ITT	85/174 (48.9%)	73/164 (44.5%)	-6.9%, 15.6%
*ITT	85/203 (41.9%)	73/193 (37.8%)	-6.1%, 14.2%
MITT	47/82 (57.3%)	33/72 (45.8%)	-5.5%, 28.5%
*MITT	47/94 (50.0%)	33/83 (39.8%)	-5.5%, 26.0%
FDA Clin. Evaluable	70/122 (57.4%)	62/103 (60.2%)	-16.6%, 11.0%
FDA Micro. Evaluable	36/54 (66.7%)	26/41 (63.4%)	-18.3%, 24.8%

* counting indeterminate and missing as failure

Reviewer's Summary For The Results Of One Study Regarding This Indication:

- The pretreatment characteristics were comparable between two treatments across all analysis groups.
- The confidence interval for the difference in clinical cure rates of linezolid minus vancomycin in clinically evaluable subjects were 122, 103(-16.6%, 11.0%)_{57.4%, 60.2%}. The efficacy analyses demonstrated the cure rate of linezolid was comparable to that of vancomycin. The results from ITT, MITT, and microbiologically evaluable populations were similar to those from clinically evaluable population.

- Results from the clinical response showed the treatment effects less favored linezolid in races other than white.
- Linezolid and vancomycin had similar microbiologic success rates against the target pathogens, which was however prohibited from meaningful difference detection due to small sample sizes.
- In this study, two treatment groups were not remarkably different in safety variables.

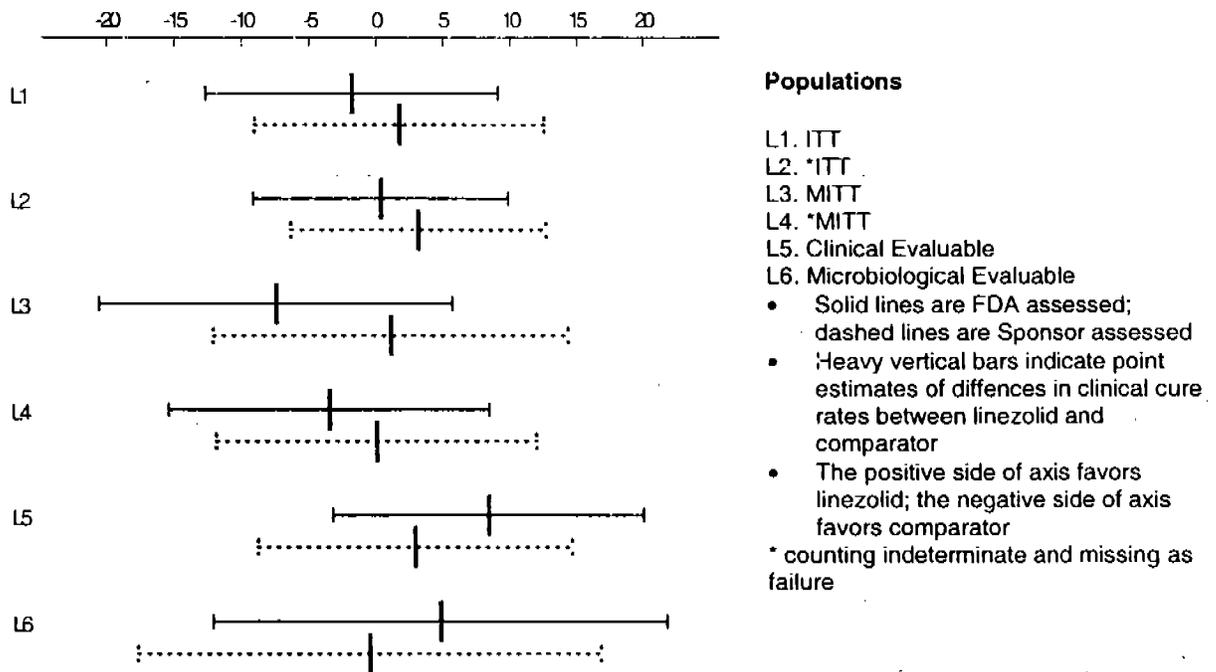
Methicillin-Resistant *Staphylococcus* Species (MRSS)

One controlled study was conducted to demonstrate the efficacy and safety of linezolid regarding this treatment.

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

An overview of clinical cure rates for patients in Study 31 is presented in Figure 4 and Table 78.

FIGURE 4: STUDY 31: 95% CONFIDENCE INTERVALS IN DIFFERENCES IN CLINICAL CURE RATES.



Population	Linezolid	Vancomycin	C.I.
	n/N (%)	n/N (%)	
ITT	111/181 (61.3%)	101/160 (63.1%)	-12.7%, 9.1%
*ITT	111/240 (46.3%)	101/220 (45.9%)	-9.2%, 9.9%
MITT	75/128 (58.6%)	74/112 (66.1%)	-20.5%, 5.6%
*MITT	75/157 (47.8%)	74/144 (51.4%)	-15.6%, 8.3%
FDA Clin. Evaluable	93/116 (80.2%)	90/125 (72.0%)	-3.4%, 19.7%
FDA Micro. Evaluable	45/59 (76.3%)	48/67 (71.6%)	-12.3%, 21.5%
FDA Bacteremia ME	10/17 (58.8%)	10/14 (71.4%)	-52.4%, 27.2%

* counting indeterminate and missing as failure

Reviewer's Summary For The Results Of One Study Regarding This Treatment:

- The pretreatment characteristics were comparable between two treatments across all analysis groups.
- The lower bound of 95% confidence interval in MITT population was notably lower than those of other populations which implied the performance of linezolid versus vancomycin was not consistent among the evaluation groups. Compared with the results from clinically evaluable and microbiologically evaluable populations, linezolid underperformed in ITT and MITT populations.
- Results from the clinical response showed the treatment effects were consistent across all demographic aspects.
- The rate of drug related adverse event was higher in the linezolid group than in the vancomycin group (18.3% vs. 8.2%).

Reviewer's General Comments:

- Therapeutic equivalence between linezolid and its comparators was evaluated by the two-tailed 95% confidence intervals and judged by clinically pertinent delta values. The review team will be deciding to choose and define the corresponding delta values for each indication in terms of the nature of studies and in compliance with the clinical perspective and relevant documents in order to determine whether the therapeutic efficacy of linezolid is clinically acceptable with respect to each indication.
- Conclusions should be cautiously drawn from the outcomes of microbiologically evaluable population due to its small sample size and resulting loss in power.
- The results by FDA assessment from ITT, MITT, FDA clinically evaluable, and FDA microbiologically evaluable populations were not always consistent with each other. This is partly attributed to a considerable amount of missing/indeterminate outcomes and/or different causes of death, and their reclassification by the Medical Officer based on different scenarios.
- The results from clinical outcomes and microbiological outcomes were fairly comparable.
- The sensitivity analysis conducted by this reviewer only applied one strategy to impute the missing data, which was not necessarily the worst case scenario and consequentially did not ensure the results of the protocol-specified method improperly favoring linezolid due to unforeseen patterns of the missing outcome.
- The post-hoc subset analyses, including for baseline pathogens and baseline disease characteristics, should be taken as exploratory and should be cautiously interpreted, since they were not corrected

for multiple comparisons and the sample sizes were notably small.

- *Results from the safety analysis suggested that linezolid and its comparator generally had comparable safety results, however, only in a few aspects, linezolid was observed remarkably poorer than its comparator.*

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/S/

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Archival: NDAs: 21-130, 21-131, 21-132

HFD-520

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HFD-344/Dr.Thomas

HFD-725/Chron.

This review contains 60 pages, 78 tables, and 4 figures.

MicrosoftWord 7.0/NDAszyvox

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APR 10 2000

Statistical Review and Evaluation

NDA: 21-130/21-131/21-132
Drug Name: Zyvox (Linezolid) Tablets, IV, and oral suspension
Applicant: Pharmacia and Upjohn
Indications covered in this review:

- Uncomplicated Skin and Skin Structure Infections
- Complicated Skin and Skin Structure Infections
- Vancomycin-resistant Enterococcal Infections

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- Uncomplicated Skin and skin structure Infections
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- Vancomycin-resistant Enterococcal Infections

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Action Goal Date: April 18, 2000

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1 Executive Summary

This statistical review considers NDA 21-130/21-131/21-132 for Linezolid, a new antibacterial agent developed to treat gram positive organisms. The three indications covered in this review are 1) uncomplicated skin and skin structure infections, 2) complicated skin and skin structure infections, and 3) vancomycin-resistant enterococcal (VRE) infections.

1.1 Overall approach to evaluation of efficacy

The sponsor applied a series of rules to the investigator clinical assessments to determine the sponsor's primary clinical outcome. This set of rules, or *algorithm*, was not pre-specified in the protocol. Since both the failure and indeterminate category generated by this algorithm appeared to be a mixture of poor outcomes and unknown outcomes, the FDA developed its own approach. The rationale behind the FDA approach was to distinguish bad outcomes from unknown outcomes; furthermore, deaths were considered bad outcomes. For ITT and MITT analyses, the FDA considered deaths prior to the end of the TOC window as failures, except for a few isolated cases where the TOC visit was completed prior to death and the assessment was cure. In contrast, the sponsor did not consider mortality status directly. Under the sponsor's algorithm, patients who died during treatment were likely to be counted as failures, whereas patients who died during the follow-up period were likely to be counted as indeterminates and excluded from most analyses.

This different approach to death was potentially very critical in the VRE trials where the death rate was substantial. However, even though many individual patient assessments were changed, the overall comparisons were only modestly impacted, as many changes cancelled each other out. In the skin trials, the difference with respect to death was inconsequential because of the extremely low death rate, and the other differences between the two approaches had only a small impact on the overall results.

1.2 Skin and skin structure trials

There were two trials of uncomplicated skin and skin structure infections that compared Linezolid to Clarithromycin. The domestic trial, Study 39a, had more than 300 patients per arm; the foreign trial, Study 39, had about 150 patients per arm. There was also one trial of complicated infections, Study 55, which compared Linezolid to Oxacillin, with about 400 patients per arm.

1.2.1 Summary of results of the skin and skin structure trials

Pivotal uncomplicated skin and skin structure trial, Study 39a

- Overall estimated cure rates for the Linezolid group were slightly numerically greater than for the comparator, Clarithromycin, regardless of whether the sponsor's or FDA's algorithm was used, or whether the ITT or evaluable populations were considered. For example, the cure rates for the ITT analysis were .86 for Linezolid and .84 for the control when missing values are excluded (95% CI: (-.03, .08)). The corresponding cure rates when missing values are counted as failures were .77 and .73.
- The lower bound of the 95% confidence interval of the treatment difference was typically in the -.05 range.
- The most favorable result was the ITT analysis which only included patients with documented selected pathogens (*Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Enterococcus faecium*, or *Enterococcus faecalis*) the potential advantage of Linezolid over the control drug approached statistical significance.
- About 12% of patients had missing data in both treatment groups.
- Patients with weight >75 kg had lower observed cure rates than those with lower weights; however, this is not a randomized comparison and should be considered cautiously.
- Study 39 yielded fairly similar results

Pivotal complicated skin and skin structure trial, Study 55

- The primary intent-to-treat population, ITT-PRIME, excluded patients without documented signs of complicated skin infection. The cure rates for this population were .86 for Linezolid and .82 for the control when missing values are excluded (95% CI: (-.02, .11)). The corresponding cure rates when missing values are counted as failures were .73 and .70.
- Overall estimated cure rates for the Linezolid group were generally about .05 higher than the estimates in the comparator, Oxacillin, regardless of analysis population or primary endpoint considered.

Executive Summary

- Aside from the microbiological evaluable populations, the lower bound of the confidence intervals were generally around -.02. Furthermore, for the ITT population, the lower bound was positive, indicating a statistically significant better result in the Linezolid group, but this population included patients without a documented complicated infection.
- Results weakened somewhat when patients without documented selected pathogens were excluded.
- About 15% of patients had missing data in both treatment groups.

1.2.2 Comments on the skin and skin structure trials

The lower bounds of the confidence intervals were generally not far from zero, for both of these pivotal trials. Indeed, there is even some suggestion of possible advantage of Linezolid over the comparators in both studies for certain analyses. However, there are two factors that cloud the interpretation: 1) missing data, and 2) possible lack of concrete information about the magnitude of the benefit over placebo in these populations. First, about 12-15% of the data are missing in these trials, and when worst-case sensitivity analyses are conducted, the lower bounds of the confidence intervals could reach as low as -.15. While this particular case is an extremely unlikely scenario, missing data always introduces uncertainty into the interpretation of the results. Second, it is unknown what data exist regarding the magnitude of the benefit that the comparators would almost always have over a placebo group in a hypothetical trial that mimics the conditions of the current trials. However, this second concern is somewhat minimal given the generally good performance of Linezolid relative to the respective comparators.

1.3 VRE trials

The sponsor originally planned a single trial with a total of about 500 patients. The sponsor has stated that in June 1999 they made a blinded, corporate decision to split the trial into two components. A protocol amendment in July stated that the components were 54a, which was comprised of patients already enrolled by June 20, 1999 and would be the pivotal trial, and the ongoing trial, designated 54, which was comprised of patients enrolled after this date, and would be a supportive trial. (However, it was discovered late in the review period that some patients enrolled before June 20 were submitted as part of Study 54; more details about the history of this trial can be found in Section 6.) This unplanned split of the original trial created a difficult and awkward situation with respect to interpretation of p-values. FDA considered a number of options for interpretation, but primarily adopted the sponsor's premise that Study 54a was the study of interest, and other data were ancillary, as described in Section 7.

These trials used a novel design, in which the goal was to demonstrate efficacy by showing the superiority of the 600 mg dose to the 200 mg dose in the treatment of VRE infections. The sponsor and the FDA analyzed the data from the VRE trials quite differently. Because of the superiority trial design and the pathogen-specific indication, the FDA focused on the MITT population with documented VRE at baseline. In contrast, the sponsor did not require documented VRE for any of their major analyses; furthermore their major focus was on the clinically and microbiological analyses, which excluded most of the deaths.

1.3.1 Summary of results of the VRE trials

Pivotal VRE trial, Study 54a: for ITT patients with documented VRE (MITTVRE)

- FDA cure rates in the high dose arm were numerically higher than in the low dose arm for the combination of populations and clinical outcomes considered, but fell short of statistical significance.
- For example, the cure rate for the high dose arm was .67 versus .52 in the low dose arm (p=.16) when the FDA clinical outcome was used, and missing data excluded.
- Sponsor p-value results were similar, but the respective estimated cure rates were higher (high dose: .75 versus low dose: .59).
- Post-hoc multivariate adjustment of baseline mortal score, sex, age, and primary site of infection yielded p-values of treatment difference that approached statistical significance. However, when body weight was added to the covariates, the p-value returned to the unadjusted level, suggesting a lack of robustness of covariate adjustment.

Executive Summary

- Approximately 10% of the patients had missing values on the primary endpoint, adding to uncertainty in the results.
- Death rates were .35 in the low dose arm as opposed to .25 in the high dose arm ($p=.31$). However, when this analysis was restricted to bacteremic patients, the respective death rates were .56 versus .22 ($p=.08$)
- When patients without documented VRE were included, p-values for the ITT population approached statistical significance. However, this was not the case with the sponsor's analysis.
- There is a greater use of aminoglycosides in the high dose arm than the low dose arm. It is difficult to understand the implications of this finding. However, it does introduce some uncertainty into the results if there is any possibility that this therapy provided a benefit to the clinical outcome endpoint.
- Results from supportive Study 54 were quite consistent with those obtained in Study 54a, though generally not close to statistical significance due to very small sample size. However, a statistically significant difference was approached for the VRE bacteremic population in both studies. It is noted that the bacteremia population was pre-specified as the subgroup of particular interest.
- Collapsed data from 54a and 54 yield a nominally statistically significant result for the primary endpoint. However, the interpretation of this particular p-value is problematic as discussed in Sections 7.3 and 8.3.
- Enrollment into Study 54 has been terminated. Data from 104 patients have yet to be submitted. Given that the follow-up on these patients is completed, it is critical to analyze the results from these remaining patients to determine that results from these patients are consistent with previous results.
- Note: a more detailed summary of VRE results is presented in Section 8.

1.3.2 Comments on the VRE trials

The protocol does not explicitly state a primary analysis population or a method for handling deaths and missing values in the analysis. However, if one takes the FDA's view that the MITTVRE population is the clear first choice for the primary analysis in this trial, and that the FDA approach to clinical outcome assessment is the preferred primary endpoint, then this could be viewed as forming the basis of the primary analysis. Using this framework, the only test of statistical significance that has a clear interpretation is the one yielded from this primary analysis; this p-value is about .15. All other p-values must be viewed cautiously because of multiple comparisons and, in some cases, lack of specification in the protocol. However, the favorable results for mortality in the VRE bacteremic population, some covariate adjusted analyses, and the ITT analysis are notable.

If one accepts the premise that all α has been spent on Study 54a, then use of the results of Study 54 to bolster the results of Study 54a is problematic. It is well understood that if one tests for statistically significant differences more than once during the course of a study, the type I error will be inflated. In contrast, one might think it would be appropriate to cite the similar results of Study 54 to support the promising, but not statistically significant results of Study 54a. However, these two approaches are roughly equivalent. While it is not clear exactly how data from Study 54 may be used without compromising the statistical integrity, there are several legitimate pieces of information. First, it can be said that there is nothing apparent in Study 54 that contradicts the results that suggest potential benefit of the higher dose seen in Study 54a. Second, the nearly statistical significant difference, found in the VRE bacteremic population in both studies, is worthy of consideration, although even this must be viewed cautiously.

It is not surprising that Study 54a failed to demonstrate a statistically significant difference between the two arms in the primary analysis given that it has less than one third of the originally planned sample size. While one can only speculate what would have happened had the trial been conducted as originally planned, if the true treatment group difference is similar to that observed in Study 54a, then a clear-cut treatment difference probably would have been detected. As a side comment, this study does illustrate the feasibility of the dose-comparative design. However, the potential differences seen in mortality and the primary endpoint between the two groups also suggest the importance of careful a priori interim monitoring.

Finally, it is critical that the sponsor submit the results from the completed 54a/54 trial to be analyzed by the FDA. Enrollment into the trial was terminated in 12/99 after 331 patients were randomized; no formal submission citing a reason has been submitted. Data from 104 patients remains outstanding. It would be very important to determine if the results from these 104 patients are consistent or not with the previously submitted data. Furthermore, one could have taken the contrary view that the decision to split 54 into two

Executive Summary

components was unplanned and largely irrelevant, given that the trial continued and nothing changed as a result of this decision. That is, the data of interest is the totality of data obtained from all patients randomized into 54a/54, including patients whose data have not yet been submitted to the FDA. While interim results of current 54a/54 database combined are very promising, it remains to be seen what final results would be obtained from this approach. Under this scenario, results at the interim tests cannot provide the basis for establishing statistical significance, unless they had been prespecified. In any event, regardless of one's position on interpretation of the p-value, it is still important to see the final and complete results of Study 54a/54.

1.4 Safety

The sponsor conducted extensive safety analyses. Changes in hematologic variables was an area that was studied substantially. There appears to be some evidence that platelet counts are suppressed with Linezolid therapy. However, this appears to be a temporary effect. In the skin infection trials, overall adverse event rates were generally larger in the linezolid arms. In the VRE trial, the low dose actually had more adverse events than the high dose; however, it is presumed that some adverse events actually represented failures of the drug's efficacy such as death.

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2 Introduction

Linezolid represents a member of a new class of antibacterial agents developed to treat gram-positive organisms. Phase III trials have been conducted, and results were submitted for several indications for adults. This review considers the trials that studied the following indications:

- Uncomplicated skin and skin structure infections
- Complicated skin and skin structure infections
- Infections due to vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium*

The following indications were included in this NDA submission, but are not covered in this review (see Dr. Jiang's review):

- Hospital Acquired Pneumonia
- Community Acquired Pneumonia

2.1 Comparison of FDA's and the sponsor approach to the analysis

There were several key differences in the approach that the FDA and the sponsor took to the analysis. First, the assessment of clinical outcome were quite dissimilar, especially in the way that failures and unknown outcomes were distinguished. Second, some of the key analysis populations considered differed in the two approaches.

2.1.1 Assessment of clinical outcome

The sponsor's clinical assessment applied a number of modifications to the investigator's raw assessment. This approach was not presented in the protocol and its amendments (for example, see section 9.9.2 for Study 54a under the heading "Changes in Planned Analyses"). The FDA had concerns that the sponsor's approach would obscure the difference between some bad and unknown outcomes, and thus applied a somewhat different set of modifications.

The rationale behind the FDA approach was to distinguish "bad" outcomes from unknown outcomes. Thus, if a patient died by the end of the TOC window, he was classified as a failure, except for a few isolated cases where the patient did have a TOC assessment of cure prior to death. Furthermore, if a patient did not have a TOC outcome and did not die, nor have any other signs of lack of efficacy, he was classified as missing. However, for analyses of clinically evaluable and microbiologically evaluable populations, the FDA did not classify patients who died, who were otherwise missing, as failures, unless the FDA Medical Officer strictly judged the infection as the direct cause of the death. Among the indications covered in this review, the issue of handling deaths had a large impact only on the VRE trials, because of significant number of deaths. Since these trials employed a superiority design, the per protocol analyses were not emphasized.

In contrast, the approach of the sponsor, did not consider deaths directly. Patients with unknown outcomes at both the end of treatment (EOT) visits and the TOC visits were classified as failures for all ITT and MITT analyses. Patients with unknown outcome at TOC, and a good outcome at EOT were classified as indeterminate. The sponsor excluded indeterminate outcomes for almost all of their analyses.

The sponsor also required that failures have at least two days of drug to be considered a failure, and cures to have at least five days of drug to be considered a cure; if these requirements were not met, the patient was considered missing. In contrast, the FDA did not consider study drug use at all in the assessment of clinical outcome. However, insufficient drug use was used to exclude patient from the PP analyses under both approaches. The sponsor's requirement for some minimal period on drug did not have a major impact on the difference, because there were relatively few patients that the sponsor regarded as missing for this reason, who were not also missing in the FDA analyses.

The details of the two algorithms are provided in Table 1.

Table 1. Comparison of assessment of clinical outcome between the sponsor and FDA

Step 1. Both approaches start with the investigator's assessment at TOC. However, if the investigator's TOC assessment was missing or indeterminate, the two approaches differed:

If investigator assessment was missing or indeterminate at TOC:	Sponsor-defined outcome	FDA outcome
Missing or indeterminate at EOT and alive at follow-up	Failure	Missing
Missing or indeterminate at EOT and dead at follow-up	Failure	Failure
Improved or cure at EOT and alive at follow-up	Indeterminate	Missing
Improved or cure at EOT and dead at follow-up	Indeterminate	Failure
Failure at EOT	Failure	Failure

Step 2. Revise outcome if there was evidence of lack of efficacy

Evidence of lack of efficacy	Sponsor-defined outcome	FDA outcome
New antibiotic given for lack of efficacy	Failure	Failure
Investigator stated patient discontinued from study due to lack of efficacy	Generally failure	Failure

Step 3. Revise outcome if duration of drug exposure was too short

Study drug exposure	Sponsor Outcome	FDA Outcome
Investigator TOC assessment was failure and drug use < 2 days or 4 doses	Missing	Failure
Investigator TOC assessment was cure and drug use < 5 days or 10 doses	Missing	Cure

2.1.1.1 Review of investigator assessment by FDA Medical Officers

Using the principles described above, FDA Medical Officer, blinded to treatment assignment, classified the outcomes of a random sample of patients in the trials of complicated and uncomplicated skin and skin structure trials. These outcomes were compared to those generated by the study investigators with the FDA algorithm applied. Since there was sufficient agreement between the two sets of outcomes in the random sample, the investigator assessment (modified by the FDA algorithm) were accepted as valid.

The FDA Medical Officer conducted a complete review of all patients in studies 54a/54. In a few cases there was a clear-cut need to change the assessment of the investigator (modified by the FDA algorithm). These revised assessments were used in the FDA's primary assessment of clinical outcome.

2.1.1.2 Summary of important differences in assessment of clinical outcome

The major consequences:

- Almost all deaths were considered failures in the FDA ITT and MITT analyses.
- In the sponsor's ITT and MITT analyses, deaths by the end of treatment were likely to be counted as failures, and deaths that occurred between treatment and the end of follow-up were likely to be considered indeterminate and thus excluded from the primary analyses.
- Patients with no information at either EOT or TOC, and had no other signs of failure, were generally failures in the sponsor's analyses, and were generally missing in the FDA analyses.
- Some patients in studies 54a/54 were reclassified by the FDA Medical Officer

Since most of the difference related to how failures and missing outcomes were distinguished, analyses that reclassified missing outcomes into the failure category had similar outcomes under both approaches.

2.1.2 Differences in major analysis populations

There were some differences with respect to populations analyzed. There were some minor differences in the populations for CE populations. Some patients who were failures due to evidence of lack of efficacy (see Table 1) or whose deaths were judged by the MO to be due to infection, and who had at least two days on drug, were not included in the sponsor's PP populations because of insufficient drug or lack of assessment. These patients were generally included in the FDA's PP populations. In addition, patients who had a missing outcome on the FDA's clinical outcome were excluded from the FDA's PP populations.

Other differences unique to particular trials will be addressed in the sections describing these trials.

2.1.3 Intent-to-treat analyses vs. per protocol analyses

There is wide consensus amongst statisticians that superiority trials should be primarily analyzed using populations that follow the intent-to-treat principle, that is the main analysis population should not make any exclusions on the basis of post-baseline characteristics. This is somewhat in contrast to equivalence trials, where there is some concern that the intent-to-treat approach may sometimes tend to diminish the treatment difference found in truly compliant patients, and thus lead to a false conclusion of similarity. However, "per protocol" analysis populations that exclude on the basis of post-baseline characteristics, such as the clinically evaluable subset, are known to be subject to bias. Thus, the FDA's approach to interpretation of equivalence trial results is to focus on both types of analyses, and try to reconcile any conclusions that are at odds.

In contrast, while the sponsor presented ITT and MITT results, the primary focus was on the per protocol analyses which excluded patients for post-baseline characteristics.

2.2 Statistical methods

The following analyses were performed for all trials.

- Comparison of treatment groups at baseline
- Distribution of disposition of patients
- Comparison of treatment groups on primary endpoint for key analysis populations
- Sensitivity analyses related to missing data

It is noted that the protocol did not include a provision that the analyses be stratified by randomization strata (i.e., center). Neither the sponsor nor FDA considered such stratification in the primary analyses.

The larger the percentage of primary endpoint data that are missing, the greater the uncertainty about the results. The robustness of the results with differing assumptions about missing data were considered. Primary analyses were performed each of two ways: a) with missing outcomes excluded, and b) with missing data regarded as failures. However, the missing data particularly distort the outcome when the true (but unobserved) cure rates in the missing category differ between the two groups. Thus, as sensitivity analyses "worst case scenarios" were considered, where all missing data are classified

Primary methods of treatment assessment differed by trial design.

2.2.1 Equivalence trials

Evaluation of treatment difference was based on 95% confidence intervals of the difference in cure rates. These confidence intervals were based on the normal approximation, and used a standard continuity correction. It is noted that the confidence intervals presented in the sponsor's submission were not continuity corrected, and thus may not be sufficiently wide.

Conclusions regarding efficacy cannot be based solely on these confidence intervals, and other data from these equivalence trials. As described in the E10 guidance document, demonstration of efficacy requires external evidence that the active control would have a benefit over a hypothetical placebo group in the population studied. Furthermore, a conservative assessment of this benefit is needed to provide a basis for determining

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whether the experimental therapy would have been found superior to placebo, if such an arm could have been included in the trial ethically. Secondly, a judgement about the acceptable loss in efficacy from existing therapy is also necessary.

2.2.2 Superiority trials

Because of the relatively small sample size, evaluation of treatment was based on Fisher's exact tests. It is noted that the p-values presented in the sponsor's submission are based on Chi-square tests, without a continuity correction. With the small sample sizes of Study 54a and Study 54, such an approach will tend to underestimate the p-value.

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3 Pivotal trial of uncomplicated skin and skin structures infection: Study 39a

The pivotal trial of uncomplicated skin and skin structures (USST) infection was Study 39a. Original Study 39 was split; patients seen in North American sites comprised Study 39a, other patients comprised Study 39, which was deemed supportive. This trial was a double blind, randomized, multicenter equivalence trial comparing Linezolid 400 mg BID to Clarithromycin 250 mg BID. These skin and skin structure trials only allowed five pathogens when designating the microbiologically evaluable populations (FDA ME). These were *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Enterococcus faecium*, and *Enterococcus faecalis*. Another microbiologically evaluable population was designated as well (FDA ME2) which included only patients with *Staphylococcus aureus* and *Streptococcus pyogenes*.

3.1 Baseline comparisons

Baseline comparisons for the ITT population are presented below in Table 2 and Table 3. The treatment groups appear to be fairly comparable. Baseline comparisons for the FDA CE population were similar.

Table 2. Baseline comparison between two treatment groups: ITT Population

	Treatment Decode			
	Clarithromycin 250 mg BID		Linezolid 400 mg BID	
	N	MEAN	N	MEAN
Selected 5 Pathogens	371.00	0.46	382.00	0.40
Male sex	371.00	0.53	382.00	0.57
Age >=65	371.00	0.13	382.00	0.16
White race	370.00	0.87	381.00	0.83
Lesion < 1.5 sq cm for certain diagnoses	368.00	0.12	381.00	0.11
OEEP	370.00	0.14	382.00	0.13
Weight (kg)	364.00	84.07	377.00	83.49

	Treatment Decode					
	Clarithromycin 250 mg BID			Linezolid 400 mg BID		
	N	MEAN	STD	N	MEAN	STD
Age (years)	371.00	43.87	17.00	382.00	44.14	17.14
Sum Sign/Symptom score	371.00	10.89	3.75	382.00	11.19	3.76
LESAREA at baseline	368.00	46.37	131.61	381.00	56.54	246.81
LOG (Lesion area)	368.00	1.98	2.02	381.00	1.87	2.13
INFECBUR at baseline	370.00	9.60	17.98	382.00	8.54	11.64

Table 3. Distribution of clinical diagnosis for two treatment groups: ITT Population

Col Pct	DX(Patient Baseline Clinical Diagnosis)		Total
	TRTMNT(Treatment Decode)		
	Clarithr omycin 2 50 mg BI D	Linezoli d 400 mg BID	
Infected Wound	10.51	14.92	
Cellulitis	26.15	22.25	
Erysipelas	1.89	0.52	
Folliculitis	6.20	8.38	
Carbuncle	2.16	2.36	
Furuncle	5.39	7.33	
Skin Ulcer	2.70	1.83	
Skin Abscesses	18.33	13.61	
Impetigo	5.12	4.19	
Infected bite	5.93	7.07	
Infected Surgica l Incision	2.96	2.62	
Paronychia	6.74	6.81	
Other	5.93	8.12	
Total	371	382	753

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3.2 Disposition of patients

The investigators reported the primary reason for discontinuation from treatment or study follow-up. The following table present this information.

Table 4. Reason discontinued from treatment according to study investigator (Sponsor's Table)

Reasons for Discontinuations	Linezolid N=382		Clarithromycin N=371	
	n	%	n	%
Discontinued Patients	52	13.6	40	10.8
Lack of Efficacy	7	1.8	4	1.1
Adverse Event (Serious)	5	1.3	2	0.5
Adverse Event (Non-Serious)	22	5.8	16	4.3
Ineligible, but Started Study Medication	1	0.3	0	0.0
Protocol Violation	4	1.0	1	0.3
Withdrawn Consent (Patient's Personal Request)	3	0.8	4	1.1
Lost to Follow-up	7	1.8	10	2.7
Other‡	3	0.8	3	0.8

‡Not specified

(Sponsor's table) Reference: Section 14, Table 1.2, Appendix 14, Table E-1

Table 5. Reason discontinued from study follow-up according to study investigator (Sponsor's Table)

Reasons for Discontinuations	Linezolid N=382		Clarithromycin N=371	
	n	%	N	%
Discontinued Patients	40	10.5	46	12.4
Lack of Efficacy	3	0.8	7	1.9
Death	1	0.3	0	0.0
Adverse Event (Serious)	4	1.0	1	0.3
Adverse Event (Non-Serious)	15	3.9	12	3.2
Withdrawn Consent (Patient's Personal Request)	2	0.5	6	1.6
Lost to Follow-up	13	3.4	14	3.8
Other‡	2	0.5	6	1.6

‡ Not specified

(Sponsor's table) Reference: Section 14, Table 1.6, Appendix 14, Table E-1

3.3 Results for major populations

Differences in primary endpoint results when using FDA as opposed to sponsor endpoints were negligible for this trial. The results from most populations were quite consistent. Generally, the lower bounds of the confidence intervals were in the vicinity of -.05. For most populations, the estimated cure rate of the Linezolid group was between .85 and .90; the cure rates for the control group were a few percentage points lower.

Table 6. Comparison of clinical outcome between treatment groups in major analysis populations

Population	Endpoint	Linezolid		Clarithromycin		95% confidence interval of difference in cure rates with continuity correction		
		Cure rate	n	Cure rate	n	Diff	Lower bound	Upper bound
ITT	FDA	0.859	341	0.835	322	0.024	-.034	0.082
ITT	Sponsor	0.845	343	0.830	323	0.016	-.043	0.075
ITT	FDA-MF	0.767	382	0.725	371	0.042	-.023	0.107
Sponsor CE	FDA	0.913	310	0.873	300	0.040	-.013	0.092
Sponsor CE	Sponsor	0.913	310	0.870	301	0.042	-.010	0.095
FDA CE	FDA	0.884	320	0.853	307	0.031	-.025	0.087
FDA CE	Sponsor	0.884	320	0.859	305	0.025	-.030	0.081
Sponsor ME	FDA	0.881	143	0.871	140	0.010	-.074	0.093
Sponsor ME	Sponsor	0.881	143	0.865	141	0.016	-.069	0.100
FDA ME	FDA	0.880	108	0.835	121	0.045	-.054	0.144
FDA ME	Sponsor	0.880	108	0.835	121	0.045	-.054	0.144
FDA ME2	FDA	0.866	97	0.858	113	0.008	-.095	0.111

- FDA-MF is the FDA clinical outcome where missing values are analyzed as failures

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3.4 Results for subgroups

Comparison of treatment groups for important subgroups are presented in Table 7. For most subgroups considered the Linezolid cure rates are numerically higher than those of Clarithromycin; even with these small sample sizes, the lower bounds of the confidence intervals is generally no lower than -.10. The one subgroup in which Linezolid fares somewhat less well than Clarithromycin, is the subgroup with weight <75 kg. However, in both treatment groups, the observed cure rates of patients with lower weight are higher than higher weight patients. These analyses were exploratory and were not designed with sufficient power to provide precise estimates of treatment differences.

Table 7. Comparison of FDA clinical outcome between treatment groups in important subgroups

		Linezolid		Clarithromycin		95% confidence interval of difference in cure rates with continuity correction		
Population	Subgroup	Cure rate	n	Cure rate	n	Diff	Lower	Upper
ITT	Important pathogen *	0.870	131	0.787	150	0.084	-.011	0.178
ITT	Age < 65	0.866	290	0.863	277	0.003	-.057	0.063
ITT	Age >= 65	0.824	51	0.667	45	0.157	-.037	0.351
ITT	Female	0.841	145	0.833	150	0.008	-.083	0.099
ITT	Male	0.872	196	0.837	172	0.035	-.043	0.113
ITT	Cellulitis	0.816	76	0.788	85	0.028	-.108	0.163
ITT	Weight<=75	0.886	123	0.911	124	-.025	-.108	0.058
ITT	Weight>75	0.850	214	0.798	193	0.053	-.026	0.132
ITT	Lesion Size >1.5**	0.862	304	0.838	284	0.024	-.037	0.085
FDA CE	Important pathogen *	0.889	126	0.803	142	0.086	-.007	0.179
FDA CE	Age < 65	0.886	272	0.869	268	0.017	-.042	0.076
FDA CE	Age >= 65	0.875	48	0.744	39	0.131	-.058	0.321
FDA CE	Female	0.875	136	0.854	144	0.021	-.066	0.108
FDA CE	Male	0.891	184	0.853	163	0.039	-.038	0.115
FDA CE	Cellulitis	0.857	70	0.823	79	0.034	-.097	0.165
FDA CE	Weight<=75	0.920	113	0.933	119	-.012	-.088	0.063
FDA CE	Weight>75	0.868	204	0.814	183	0.053	-.025	0.132
FDA CE	Lesion Size >1.5**	0.891	284	0.860	271	0.031	-.028	0.090

* Important pathogen denotes the following pathogens: *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Enterococcus faecium*, and *Enterococcus faecalis*.

**Excludes lesion Size<1.5 square centimeters for certain clinical diagnoses

3.5 Results by pathogen

Pathogen results indicate that *Staphylococcus aureus* was the most prevalent pathogen. Respective cure rates were .85 and .80 for the ITT population.

Table 8. Clinical outcome by pathogen subgroup for various populations

		ITT FDA		ITT Spon		ITT FDA_MF		FDA ME		Spon ME	
		Treatment Code		Treatment Code		Treatment Code		Treatment Code		Treatment Code	
		L	C	L	C	L	C	L	C	L	C
Pathogen											
ENTEROCOCCUS FAECALIS	N	10.00	17.00	10.00	17.00	11.00	18.00	8.000	13.00	8.000	12.00
	MEAN	0.900	0.588	0.900	0.588	0.818	0.556	1.000	0.615	1.000	0.667
ENTEROCOCCUS FAECIUM	N	1.000	.	1.000	.	1.000	.	1.000	.	1.000	.
	MEAN	1.000	.	1.000	.	1.000	.	1.000	.	1.000	.
STAPHYLOCOCCUS AUREUS	N	116.0	132.0	120.0	133.0	135.0	152.0	93.00	105.0	91.00	104.0
	MEAN	0.853	0.803	0.817	0.789	0.733	0.697	0.860	0.848	0.879	0.856
STAPHYLOCOCCUS EPIDERMIDIS	N	49.00	44.00	51.00	42.00	56.00	52.00	9.000	8.000	31.00	23.00
	MEAN	0.878	0.841	0.843	0.881	0.768	0.712	1.000	0.750	0.839	0.913
STAPHYLOCOCCUS LUGDUNENSIS	N	8.000	8.000	9.000	8.000	9.000	9.000	2.000	3.000	8.000	8.000
	MEAN	1.000	0.875	0.889	0.875	0.889	0.778	1.000	0.667	1.000	0.875
STREPTOCOCCUS AGALACTIAE	N	11.00	5.000	10.00	5.000	11.00	6.000	10.00	5.000	10.00	5.000
	MEAN	1.000	0.800	1.000	0.800	1.000	0.667	1.000	0.800	1.000	0.800
STREPTOCOCCUS PYOGENES	N	6.000	11.00	6.000	11.00	7.000	16.00	5.000	11.00	5.000	11.00
	MEAN	0.833	0.909	0.833	0.909	0.714	0.625	1.000	0.909	1.000	0.909

- L denotes Linezolid and C denotes control group

3.6 Missing data

Sensitivity analyses on missing data can provide insight into the degree of robustness of the results. As a general rule, studies with a low rate of missing data will be very robust with respect to these sensitivity analyses and visa versa. In the following table, it is seen that under the most extreme worst case scenario assumption about the missing data, the lower bound of the confidence interval is -.15.

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Table 9. Sensitivity analysis of missing data: treatment comparisons of FDA clinical endpoint under various imputation assumptions for missing data

Pop	Linezolid			Clarithromycin			95% confidence interval of difference in cure rates with continuity correction	
	Imputed cure rate	Cure rate	n	Imputed cure rate	Cure rate	n	Lower bound	Upper bound
ITT	none	.859	341	none	.835	322	-.034	.082
ITT	0	.767	382	0	.725	371	-.023	.107
ITT	0	.767	382	1	.857	371	-.148	-.032
ITT	.333	.803	382	.666	.813	371	-.069	.049

3.7 Safety

The sponsor tabulated basic adverse events comparisons in the following tables. There was a statistically significant larger rate of adverse events and drug related adverse events in Linezolid than the comparator. All other comparisons were non-significant but numerically greater in the Linezolid group. Nervous system differences were also nominally statistically significant.

Table 10. Comparison of adverse event rates (Sponsor table)

Parameter	Linezolid N=382		Clarithromycin N=371		Statistical Test P-value†
	n	%‡	n	%‡	
Total Number of Patients Reporting	382	100.0	371	100.0	
Patients with ≥1 AE Reported	206	53.9	170	45.8	0.0262*
Patients with ≥1 Drug-related AE Reported	113	29.6	80	21.6	0.0118*
Patients with ≥1 AE Resulting in D/C of Study Medication	28	7.3	18	4.9	0.1557
Patients with ≥1 Drug-related AEs Resulting in D/C of Study Medication	17	4.5	11	3.0	0.2815
Patients with ≥1 Serious AE Reported	9	2.4	5	1.3	0.3058
Patients Who Died§	2	0.5	0	0.0	0.1628

* P-value ≤ 0.05 for the test of treatment indicates statistical significance.
 † Chi-square test is based on the number of patients reporting.
 ‡ Percentages are based on the number of patients reporting.
 § Deaths were not related to study medication.
 Abbreviations: D/C = Discontinued; AE = Adverse Event
 Note: Drug-related is defined as events specified as related or with relatedness not reported.
 Reference: Section 14, Table 7.1; Appendix 15, Table S-4

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Table 11. Adverse event rates by body system (Sponsor table)

	Frequencies of Study-Emergent Aes by Body System:				ITT
	Linezolid		Clarithromycin		
	N=382		N=371		Statistical Test†
COSTART Body System	n	%‡	n	%‡	P-value
Total Number of Patients Reporting	382	100.0	371	100.0	
Patients With None	176	46.1	201	54.2	
Patients With at Least One	206	53.9	170	45.8	0.0262*
Body	98	25.7	78	21.0	0.1334
Cardiovascular	7	1.8	6	1.6	0.8207
Digestive	87	22.8	71	19.1	0.2204
Endocrine	1	0.3	-	-	0.3241
Hemic and Lymphatic	9	2.4	4	1.1	0.1783
Metabolic and Nutritional	15	3.9	13	3.5	0.7593
Musculo-Skeletal	8	2.1	5	1.3	0.4317
Nervous	35	9.2	20	5.4	0.0468*
Respiratory	10	2.6	14	3.8	0.3667
Skin	31	8.1	22	5.9	0.2412
Special Senses	18	4.7	12	3.2	0.3000
Urogenital	22	5.8	17	4.6	0.4662
* P-value <0.05 for the test of treatment indicates statistical significance.					
† Chi-square test is based on the number of patients reporting.					
‡ Percentages are based on the number of patients reporting.					
Note: Patients are only counted once for each body system.					
Reference: Section 14, Table 7.2; Appendix 15,		Table	S-4		

3.8 Summary

The following summarize the results of this study:

- Baseline profiles were similar across treatment groups
- Discontinuation reasons were similar across treatment groups
- Cure rates for Linezolid were generally about .02 higher than Clarithromycin despite analysis or population
- Lower bounds of 95% confidence intervals ranged from -.01 to -.07, across analysis population and clinical endpoint algorithms
- Estimated cure rates for Linezolid were generally between .85 and .90 when missing values were excluded
- For almost every subgroup considered, the Linezolid cure rates were numerically higher than the control rates, with the exception of the low weight group
- When selected, important pathogens were considered, the lower bound of the confidence interval approached zero, suggesting a potential advantage over the control regimen

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- A large number of staphylococcus aureus pathogens were isolated, the respective cure rates were .85 and .80 for the ITT population.
- Under the assumption that missing data are truly failures, cure rates drop to .77 for Linezolid and .73 for the control
- Under the worst case scenario, where all missing outcomes are failures in the Linezolid group, and vice versa, the lower bound of the confidence interval is -.15.
- There was a greater rate of adverse events in the Linezolid group.

Other summary information about this trial and the other skin trials can be found in the Executive Summary.

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4 Supportive trial of uncomplicated skin/skin structure infection: Study 39

This trial is comprised of the non-North American sites of the original Study 39 (Study 39a is composed of the North American sites). Thus, the design is identical to that described in Section 3. Since this is only a supportive trial, only limited information is presented below. These data did not receive as much scrutiny by the FDA Medical Officer as those of Study 39a did.

4.1 Results for major populations

The estimated cure rates for Clarithromycin were generally somewhat higher in the control group than in Linezolid arm. All confidence intervals include zero and the lower bounds are generally in the -.10 range. Rates in both treatment regimens are higher than those seen in Study 39a.

Table 12. Comparison of clinical outcome between treatment groups in major analysis populations

		Linezolid		Clarithromycin		95% confidence interval of difference in cure rates with continuity correction		
Population	Endpoint	Cure rate	n	Cure rate	n	Diff	Lower bound	Upper bound
ITT	FDA	0.878	148	0.913	149	-.034	-.111	0.042
ITT	Sponsor	0.872	149	0.906	149	-.034	-.111	0.044
ITT	FDA-MF	0.783	166	0.819	166	-.036	-.128	0.056
Sponsor CE	FDA	0.911	124	0.927	123	-.016	-.092	0.061
Sponsor CE	Sponsor	0.911	124	0.927	123	-.016	-.092	0.061
FDA CE	FDA	0.890	127	0.898	127	-.008	-.092	0.076
FDA CE	Sponsor	0.890	127	0.905	126	-.015	-.098	0.068
Sponsor ME	FDA	0.981	54	0.985	68	-.004	-.066	0.059
Sponsor ME	Sponsor	0.981	54	0.985	68	-.004	-.066	0.059
FDA ME	FDA	0.953	43	0.967	60	-.013	-.111	0.084
FDA ME	Sponsor	0.953	43	0.967	60	-.013	-.111	0.084
FDA ME2	FDA	0.953	41	0.966	58	-.012	-.111	0.087

* FDA-MF is the FDA clinical outcome where missing values are analyzed as failures

4.2 Results by pathogen

Pathogen specific results followed the pattern seen above, with generally higher control rates. However, even Linezolid rates are higher in this foreign trial than those seen in domestic Study 39a. The most common pathogen was Staphylococcus aureus.

Table 13. Clinical outcome by pathogen subgroup for various populations

		ITT FDA		ITT Spon		ITT FDA_MF		FDA ME		Spon ME	
		Treatment Code		Treatment Code		Treatment Code		Treatment Code		Treatment Code	
		L	C	L	C	L	C	L	C	L	C
Pathogen											
ENTEROCOCCUS FAECALIS	N	2.000	1.000	2.000	1.000	2.000	1.000	1.000	1.000	1.000	1.000
	MEAN	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
ENTEROCOCCUS FAECIUM	N	.	1.000	.	1.000	.	1.000	.	1.000	.	1.000
	MEAN	.	1.000	.	1.000	.	1.000	.	1.000	.	1.000
STAPHYLOCOCCUS AUREUS	N	55.00	67.00	55.00	67.00	59.00	70.00	39.00	54.00	39.00	53.00
	MEAN	0.855	0.925	0.855	0.910	0.797	0.886	0.974	0.963	0.974	0.981
STAPHYLOCOCCUS EPIDERMIDIS	N	9.000	12.00	10.00	11.00	11.00	12.00	2.000	0.000	8.000	7.000
	MEAN	1.000	0.750	0.900	0.818	0.818	0.750	1.000	.	1.000	1.000
STAPHYLOCOCCUS LUGDUNENSIS	N	3.000	1.000	3.000	1.000	3.000	1.000	0.000	0.000	3.000	1.000
	MEAN	1.000	1.000	1.000	1.000	1.000	1.000	.	.	1.000	1.000
STREPTOCOCCUS AGALACTIAE	N	1.000	.	1.000	.	1.000	.	1.000	.	1.000	.
	MEAN	1.000	.	1.000	.	1.000	.	1.000	.	1.000	.
STREPTOCOCCUS PYOGENES	N	9.000	11.00	10.00	13.00	13.00	15.00	7.000	7.000	6.000	7.000
	MEAN	0.889	0.909	0.800	0.769	0.615	0.667	0.857	1.000	1.000	1.000
MRSA	N	1.000	5.000	2.000	5.000	2.000	5.000	1.000	4.000	1.000	4.000
	MEAN	1.000	1.000	0.500	1.000	0.500	1.000	1.000	1.000	1.000	1.000

* L denotes Linezolid and C denotes control group

4.3 Summary

The results can be summarized as follows:

- Clarithromycin cure rates were generally higher than those seen for Linezolid, but these differences did not approach statistical significance. Furthermore, the lower bounds of the confidence intervals were approximately in the -.10 range.
- Approximately one third of these patients had staphylococcus aureus pathogens identified. The cure rates in this pathogen category was .86 for Linezolid and .93 for control in the ITT population. The ME population yielded very high cure rates (.97 and .96).

More summary information about the skin trials can be found in the Executive Summary.

5 Trial of complicated skin/skin structure infection: Study 55

This was a multi-center double blind equivalence trial comparing Linezolid 600 mg bid versus Oxacillin sodium 2 g every six hours in the treatment of complicated skin and skin structure infection. The primary distinguishing factor between the complicated skin and uncomplicated skin infection study populations was the requirement that complicated skin patients have at least one of the following: fever, white blood cells >10,000, or neutrophil bands >15. In contrast to the sponsor's analysis, the FDA analysis did explicitly require documentation that patients met this requirement at baseline. The intent-to-treat population, ITTPRIME, was based on this requirement. In addition, patients who were not clinically evaluable for baseline reasons only (such as prior antibiotic use) were excluded from this population. The FDA CE and FDA ME populations also employed this requirement. Furthermore, the FDA ME population only included patients with one of these five pathogens: *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Enterococcus faecium*, and *Enterococcus faecalis*.

5.1 Baseline Comparisons

Baseline comparisons presented in Table 14 and Table 15 suggest the treatment groups were quite comparable at baseline. Comparisons of the treatment group in the FDA CE groups are not presented, but they show a similar pattern.

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Table 14. Baseline comparison between two treatment groups: ITTPRIME Population

	Treatment Decode			
	Linezolid		Oxacillin/Di-cloxacil	
	N	MEAN	N	MEAN
Selected 5 Pathogens	316.00	0.45	313.00	0.46
Male sex	316.00	0.64	313.00	0.64
Age >=65	316.00	0.16	313.00	0.24
White race	316.00	0.57	313.00	0.55
DEEP	314.00	0.82	311.00	0.78
Weight (kg)	313.00	79.46	311.00	78.92

	Treatment Decode					
	Linezolid			Oxacillin/Dicloxacil		
	N	MEAN	STD	N	MEAN	STD
Age (years)	316.00	47.16	16.56	313.00	48.16	18.43
Sum sign/symptom score	313.00	12.54	3.19	308.00	12.50	3.24
LESAREA at baseline	307.00	449.91	1480.0	301.00	424.02	597.43
LOG (lesarea)	307.00	4.78	1.89	301.00	4.90	1.97
INFECOUR at baseline	314.00	4.92	4.85	311.00	6.19	16.11

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Table 15. Distribution of clinical diagnosis for two treatment groups: ITT/PRIME Population

Col Pct	TRTMNT(Treatment Decode)		Total
	Linezolid	Oxacillin/Dicloxacil	
Infected Wound	6.96	9.58	
Cellulitis	40.51	41.21	
Erysipelas	10.76	9.27	
Skin Ulcer	3.48	3.19	
Skin Abscesses	15.19	17.89	
Infected bite	1.58	0.96	
Infected Surgical Incision	7.28	5.43	
Other	14.24	12.46	
Total	316	313	629

5.2 Disposition of patients

The following table presents investigator stated reasons for treatment and study follow-up discontinuations. Discontinuations were somewhat more frequent in the control group; with slightly greater discontinuation rates across almost all reasons. A small number of deaths occurred in the Linezolid group.

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Table 16. Reason discontinued from treatment according to study investigator

Reasons for Discontinuations	Linezolid N = 400		Oxacillin/Dicloxacillin N = 419	
	n	%†	n	%†
Discontinued Patients	43	10.8	70	16.7
Lack of Efficacy	9	2.3	15	3.6
Death	1	0.3	0	-
AE (Serious)	2	0.5	7	1.7
AE (Non-serious)	8	2.0	13	3.1
Ineligible, but Started Study Medication	4	1.0	3	0.7
Protocol Noncompliance	3	0.8	5	1.2
Subject's Personal Request	2	0.5	6	1.4
Lost to F-U	8	2.0	10	2.4
Other	6	1.5	11	2.6
† Percentages are based on the total number of patients in each treatment group.				
AE = Adverse event; F-U = Follow-up				
<i>(Sponsor table) Reference: Section 14, Table 1.2; Appendix 14, Table E-1</i>				

Table 17. Reason discontinued from study follow-up according to study investigator

Reasons for Discontinuations	Linezolid N = 400		Oxacillin/Dicloxacillin N = 419	
	n	%†	n	%†
Discontinued Patients	54	13.5	73	17.4
Lack of Efficacy	8	2.0	10	2.4
Death	2	0.5	0	-
AE (Serious)	1	0.3	3	0.7
AE (Non-serious)	5	1.3	6	1.4
Ineligible, but Started Study Medication	2	0.5	4	1.0
Protocol Noncompliance	3	0.8	3	0.7
Subject's Personal Request	3	0.8	5	1.2
Lost to F-U	27	6.8	32	7.6
Other	3	0.8	10	2.4
† Percentages are based on the total number of patients in each treatment group.				
AE = Adverse event; F-U = Follow-up				
<i>(Sponsor's table) Reference: Section 14, Table 1.6; Appendix 14, Table E-1</i>				

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5.3 Results for major populations

The results indicate that the Linezolid cure rates were numerically higher than the Oxacillin rates, and in fact, this difference was sometimes statistically significant. Except the for ME populations which were quite small, the lower bounds of confidence intervals were generally in -.02 range..

Table 18. Comparison of clinical outcome between treatment groups in major analysis populations

		Linezolid		Oxacillin		95% confidence interval of difference in cure rates with continuity correction		
Population	Endpoint	Cure rate	n	Cure rate	n	Diff	Lower bound	Upper bound
ITT	FDA	0.850	327	0.787	348	0.063	0.002	0.124
ITT	Sponsor	0.851	328	0.768	354	0.082	0.021	0.144
ITT	FDA-MF	0.695	400	0.654	419	0.041	-.025	0.108
ITTPRIME	FDA	0.862	269	0.820	267	0.042	-.023	0.108
ITTPRIME	Sponsor	0.863	270	0.807	270	0.056	-.011	0.122
ITTPRIME	FDA-MF	0.734	316	0.700	313	0.034	-.039	0.108
Sponsor CE	FDA	0.907	290	0.866	299	0.041	-.014	0.095
Sponsor CE	Sponsor	0.907	291	0.863	300	0.044	-.011	0.098
FDA CE	FDA	0.898	245	0.851	242	0.047	-.016	0.110
FDA CE	Sponsor	0.902	245	0.851	242	0.051	-.012	0.113
Sponsor ME	FDA	0.893	140	0.867	150	0.026	-.055	0.108
Sponsor ME	Sponsor	0.900	140	0.861	151	0.039	-.042	0.120
FDA ME	FDA	0.851	101	0.824	108	0.027	-.082	0.137
FDA ME	Sponsor	0.861	101	0.824	108	0.037	-.071	0.145

5.4 Results for subgroups

The observed cure rates were almost always higher for the Linezolid arm than the control arm. One important exception was consideration of the important pathogen subset, which yielded very similar rates for the two arms, but, of course, these sample sizes were smaller than the overall study. Even subgroup confidence interval lower bounds were generally in the -.05 range. It is noted that these analyses are exploratory in nature and the study was not powered to produce precise estimates of treatment difference in subgroups.

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Table 19. Comparison of FDA clinical outcome between treatment groups in important subgroups

		Linezolid		Oxacillin		95% confidence interval of difference in cure rates with continuity correction		
Population	Subgroup	Cure rate	n	Cure rate	n	Diff	Lower	Upper
ITTPRIME	Important pathogen *	0.789	123	0.800	120	-.011	-.121	0.098
ITTPRIME	Age < 65	0.861	231	0.820	205	0.042	-.032	0.116
ITTPRIME	Age >= 65	0.868	38	0.823	62	0.046	-.119	0.211
ITTPRIME	Female	0.878	98	0.817	93	0.060	-.052	0.173
ITTPRIME	Male	0.854	171	0.822	174	0.032	-.052	0.115
ITTPRIME	Cellulitis	0.874	111	0.829	111	0.045	-.057	0.147
ITTPRIME	Weight<=75	0.883	137	0.820	133	0.064	-.028	0.156
ITTPRIME	Weight>75	0.846	130	0.820	133	0.027	-.071	0.124
FDA CE	Important pathogen*	0.833	108	0.809	110	0.024	-.087	0.135
FDA CE	Age < 65	0.900	210	0.849	186	0.051	-.020	0.121
FDA CE	Age >= 65	0.886	35	0.857	56	0.029	-.134	0.191
FDA CE	Female	0.907	86	0.861	79	0.046	-.064	0.156
FDA CE	Male	0.893	159	0.847	163	0.046	-.033	0.126
FDA CE	Cellulitis	0.938	97	0.870	100	0.068	-.024	0.160
FDA CE	Weight<=75	0.913	127	0.857	119	0.056	-.032	0.144
FDA CE	Weight>75	0.888	116	0.844	122	0.044	-.051	0.138

* Important pathogen denotes the following pathogens: *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Enterococcus faecium*, and *Enterococcus faecalis*.

5.5 Results by pathogen

The most prevalent pathogen was *staphylococcus aureus*. The cure rates were very similar for the two groups in this pathogen, with cure rates of .81 and .83 respectively for the ITT population, with missing values excluded.

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Table 20. Clinical outcome by pathogen subgroup for various populations

		ITT' FDA		ITT' Spon		ITT' FDA_MF		FDA ME		Spon ME	
		Treatment Code		Treatment Code		Treatment Code		Treatment Code		Treatment Code	
		L	C	L	C	L	C	L	C	L	C
Pathogen											
ENTEROCOCCUS FAECALIS	N	5.000	7.000	5.000	6.000	9.000	9.000	2.000	5.000	4.000	7.000
	MEAN	0.000	0.714	0.000	0.667	0.000	0.556	0.000	0.800	0.500	0.714
ENTEROCOCCUS FAECIUM	N	3.000	0.000	3.000	0.000	3.000	0.000	2.000	0.000	3.000	1.000
	MEAN	0.333		0.333		0.333		0.500		0.667	1.000
STAPHYLOCOCCUS AUREUS	N	102.0	94.00	102.0	96.00	113.0	110.0	83.00	84.00	93.00	103.0
	MEAN	0.814	0.830	0.814	0.813	0.735	0.709	0.880	0.857	0.892	0.854
STAPHYLOCOCCUS EPIDERMIDIS	N	16.00	11.00	17.00	12.00	19.00	16.00	5.000	2.000	19.00	12.00
	MEAN	1.000	0.636	0.941	0.583	0.842	0.438	1.000	0.000	1.000	0.833
STAPHYLOCOCCUS LUGDUNENSIS	N	1.000	3.000	1.000	3.000	1.000	3.000	1.000	1.000	1.000	3.000
	MEAN	1.000	0.333	1.000	0.333	1.000	0.333	1.000	1.000	1.000	1.000
STREPTOCOCCUS AGALACTIAE	N	7.000	6.000	7.000	7.000	7.000	10.00	6.000	6.000	7.000	6.000
	MEAN	1.000	0.500	1.000	0.429	1.000	0.300	1.000	0.500	1.000	0.667
STREPTOCOCCUS PYOGENES	N	30.00	29.00	29.00	30.00	35.00	36.00	26.00	28.00	29.00	32.00
	MEAN	0.667	0.759	0.724	0.733	0.571	0.611	0.692	0.750	0.793	0.844
MRSA	N	9.000	5.000	9.000	5.000	9.000	6.000	3.000	0.000	4.000	2.000
MRSA	MEAN	0.667	0.400	0.667	0.400	0.667	0.333	0.667		0.750	0.500

* L denotes Linezolid and C denotes control group

5.6 Missing Data

There were enough missing outcomes so that a "worst case scenario" analysis indicated that the lower bound of the confidence interval could be as large as -.18, under the most extreme assumptions. Thus, this does introduce some uncertainty into the results.

Table 21. Sensitivity analysis of missing data: treatment comparisons of FDA clinical endpoint under various imputation assumptions for missing data

Pop	Linezolid			Oxacillin			95% confidence interval of difference in cure rates with continuity correction	
	Imputed cure rate	Cure rate	n	Imputed cure rate	Cure rate	n	Lower bound	Upper bound
ITTPRIME	none	0.862	269	none	0.820	267	-.023	0.108
ITTPRIME	0	0.734	316	0	0.700	313	-.039	0.108
ITTPRIME	0	0.734	316	1	0.847	313	-.179	-.046
ITTPRIME	.333	0.784	316	.666	0.798	313	-.081	0.053

5.7 Safety

The overall adverse event rate was higher in the Linezolid group than the comparator arm. However, drug related adverse events resulting in discontinuation of study drug was more common in the comparator group. There appeared to be a somewhat increased rate of adverse events for both the cardiovascular and nervous system categories as seen in Table 23

Table 22. Comparison of adverse event rates (Sponsor table)

Parameter	Linezolid N = 400		Oxacillin/ Dicloxacillin N = 419		P-Value†
	n	%†	n	%†	
Patients with ≥1 AE Reported	189	47.3	173	41.3	0.0860
Patients with ≥1 Drug-Related AE Reported	67	16.8	72	17.2	0.8687
Patients with ≥1 AE Resulting in Discontinuation of Study Medication	12	3.0	23	5.5	0.0783
Patients with ≥1 Drug-Related AE Resulting in Discontinuation of Study Medication	4	1.0	15	3.6	0.0142*
Patients with ≥1 Serious AE Reported	22	5.5	19	4.5	0.5265
Patients Who Died	3	0.8	1	0.2	0.2941

† Percentages are based on the number of patients reporting.
 ‡ Chi-square test is based on the number of patients reporting.
 * P-value ≤0.05 indicates statistical significance.

Reference: Section 14, Table 7.1, Appendix 15, Table S-4

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6 Trial of Vancomycin-resistant enterococcal infections: Study 54a

In consultation with the FDA, the sponsor designed this trial as dose-comparative study. This novel approach was used because there was no documented drug for use as a comparator at the time the trial was designed. This method has the additional advantage of utilizing a superiority design, so that it does not suffer from the interpretational difficulties inherent to equivalence designs.

The sponsor initiated a low-dose versus high-dose trial of Linezolid for the treatment of Vancomycin Resistant Enterococcus (VRE), a serious life-threatening illness. The initial sample size for the trial was approximately 500 overall, with a planned interim analysis after 50% and 75% of the trial had been completed. However, according to a statement made by the sponsor in November 1999, the sponsor decided in June 1999, after the trial was less than one third completed, to close the completed portion of the trial into a stand alone trial (denoted 54a). The continuing trial would be used for supportive purposes only. The November statement asserted that this June decision was made blinded to study results and before the DSMB saw any unblinded data, and that corporate considerations were paramount. The sponsor planned to submit the VRE trial at the same time as trials for related indications. This decision was not directly communicated to FDA; however, a protocol amendment dated 7/14/99 briefly outlined this trial truncation. In an August telecon, the FDA, still unaware of this formal amendment, strongly urged the sponsor not to submit the VRE trial until the study was completed as planned. The sponsor said it would reconsider its decision not to submit, but the October submission did, in fact, include the truncated 145 patient VRE trial. This submission stated that any p-value less than .05 should be considered statistically significant. Furthermore, by December completed data were available for an additional 82 patients from the second phase of the trial, Study 54. (Note: a further complication was discovered late in the review period; that 25 of the patients included in Study 54 were enrolled prior to June 20 and should have been included in Study 54a. This potentially serious protocol deviation is addressed in Section 6.9. Similarly, based on communication from the sponsor at the 3/24/2000 Advisory Committee Meeting, it is highly probable that the patients in 54a/54 submitted thus far do not represent the first 145+82 patients randomized. Thus, Study 54a sample, Study 54 sample, and the combined 54a/54 sample are all subject to ascertainment bias.)

It is noted that the sponsor was not subject to an investigation to ensure that no unblinding occurred before the June 1999 decision to submit 54a as a stand-alone trial. While some FDA staff recommended such an investigation, it ultimately was not conducted. (Note: It is also recognized that the period from August to October might also have been subject to scrutiny, in addition to the June time frame, since the sponsor theoretically could have decided not to submit, following advice given by the FDA in August. It is not known at what point the sponsor was unblinded to the results.)

Prior to reviewing the results fully, various options were considered by the FDA for interpreting the results of the trial given that the truncation of the trial was not pre-planned and the trial, in some sense remained ongoing. While recognizing that all options were problematic, the FDA decided to accept the sponsor's approach to view the first 145 trial as the trial of interest, since this was specified in the protocol amendment prior to unblinding. Under this scenario, all α was spent on 54a, and the interpretation of the results of this trial is straightforward. Issues in the interpretation of p-values are addressed more fully in Section 7.

6.1 Major population of interest

Since the goal of this trial was to establish a statistically significantly superior outcome in the high dose arm than the low-dose arm, the main population of interest should be based on the intent-to-treat principle. Furthermore, since this indication is based on the VRE pathogen, the main ITT analysis population considered was only those patients with documented VRE infections at baseline; namely, the MITTVRE population. If patients without VRE infections are included in the analysis, it is possible that high dose might be better than low dose amongst these patients, and lead to a statistically significant difference even when there is no difference in the true VRE population. The sponsor, however, did not require a documented baseline VRE infection for any major analyses. The ITT and clinically evaluable populations did not consider baseline pathogen at all; even the sponsor's MITT and microbiological evaluable populations include patients with vancomycin susceptible enterococcal infections.

Also, the protocol is somewhat confusing regarding the importance of the bacteremic population. In the sample size and the interim analysis section, it was implied that the major analysis group was bacteremic patients. However, in no other part of the protocol is this stated. This review did consider the VRE bacteremic population as the most important subgroup.

6.2 Baseline Comparisons

There was reasonable comparability of the groups at baseline. However, there was some difference in the distribution of primary site of infection. The high dose arm had more skin infections and the low dose arm had more "other" infections.

Table 24. Baseline comparison between two treatment groups: MITTVRE

	Treatment Decode			
	Linezolid 200 mg BID		Linezolid 600 mg BID	
	N	MEAN	N	MEAN
Mortality %	52.00	25.67	65.00	25.34
Male sex	52.00	0.42	65.00	0.46
Age (years)	52.00	64.94	65.00	64.74
Age >=65	52.00	0.60	65.00	0.62
White race	52.00	0.73	65.00	0.77
Dx=Pneumonia	52.00	0.02	65.00	0.06
Dx=Skin	52.00	0.10	65.00	0.20
Dx=UTI	52.00	0.40	65.00	0.38
Dx=Other	52.00	0.31	65.00	0.20
Dx=BUO	52.00	0.17	65.00	0.15
Faecalis is only path	52.00	0.02	65.00	0.02
Faecium is only path	52.00	0.88	65.00	0.91
Both pathogens	52.00	0.08	65.00	0.08
Faecium is present	52.00	0.96	65.00	0.96
Creatinine>2	42.00	0.31	50.00	0.32
Patient had Bacteremia (Yes/No)	52.00	0.31	65.00	0.28

6.3 Disposition of patients

There were 66 patients randomized to 200 mg and 79 to 600. However, the respective numbers in the MITTVRE population were 52 and 65. As seen in the following tables, a somewhat greater number of patients in the high dose group did not complete treatment according to the investigator. The differential appeared to be due to a few more deaths and adverse events during the treatment period in the high dose group. However, there is a reversal for the investigator's stated reason for discontinuation of study follow-up. There was a

greater discontinuation rate in low dose group, apparently largely due to a larger number of deaths than the high dose group in the overall study period.

Table 25. Percentage discontinued from treatment by reason according to study investigator: MITVRE

TABLE OF REASTRT BY TRTMNT

REASTRT(RSNDISC at treatment completion)
TRTMNT(Treatment Decode)

Col Pct	TRTMNT(Treatment Decode)		Total
	Linezolid 200 mg BID	Linezolid 600 mg BID	
	84.62	78.46	
Lack of efficacy	1.92	0.00	
Death of subject	5.77	9.23	
Adverse event(s) -- serious	1.92	4.62	
Adverse event(s) -- non-serious	0.00	4.62	
Subject ineligible but inv med s started	1.92	1.54	
Subject lost to follow-up	0.00	1.54	
Other reason(s)	3.85	0.00	
Total	52	65	117

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Table 26. Percentage discontinued from study follow-up by reason according to study investigator: MITTVRE

TABLE OF REASSTDY BY TRTMNT

REASSTDY(RSNDISC at study completion)

Col Pct	TRTMNT(Treatment Decode)		Total
	Linezolid 200 mg BID	Linezolid 600 mg BID	
	53.85	66.15	
Lack of efficacy	1.92	1.54	
Death of subject	34.62	24.62	
Subject ineligible but inv med s started	0.00	1.54	
Subject lost to follow-up	7.69	6.15	
Other reason(s)	1.92	0.00	
Total	52	65	117

6.4 Results for major populations

The following tables suggest a possible advantage of the high dose regimen over low dose, but results are generally not statistically significant at the .05 level. Table 27 shows a promising but not statistically significant for the FDA's primary analysis population and endpoint (p=.158). Despite the fact that many individual patients had different assessments under the FDA analysis than the sponsor's analysis, most of these differences cancelled out, so that the p-values were quite similar. Results when missing values were changed to failures again yielded a similar p-value, but lower cure rates. It is not surprising that a statistically significant difference was not observed, given that the trial was powered at 80% with more than three times the current sample. In fact, the magnitude of the difference in the observed cure rates is somewhat similar to what was specified in the sample size computation (.40 vs. .60 among bacteremic patients).

Table 27. Clinical outcome in primary FDA analysis population: MITTVRE

Population	Endpoint	Linezolid 200 mg		Linezolid 600 mg		P-value from Fishers Exact Test
		Cure rate	n	Cure rate	n	
MITTVRE	FDA	0.522	46	0.672	58	0.158
MITTVRE	Sponsor	0.585	41	0.745	51	0.122
MITTVRE	FDA-MF	0.462	52	0.600	65	0.142

Results were also considered within several critical subgroups: bacteremia and site of diagnosis. Bacteremia was a pre-specified subgroup of definite interest in the protocol. In fact, both the sample size section and the interim analysis section focused almost exclusively on this subgroup. Table 28 exhibits large differences in the observed cure rates, but because the sample sizes are very small, none were statistically significant.

Table 28. Clinical outcome in primary subgroup population: MITTVRE bacteremia

		Linezolid 200 mg		Linezolid 600 mg		P-value from Fishers Exact Test
Population	Endpoint	Cure rate	n	Cure rate	n	
MITTVRE bacteremia	FDA	0.286	14	0.588	17	0.149
MITTVRE bacteremia	Sponsor	0.444	9	0.688	16	0.397
MITTVRE bacteremia	FDA-MF	0.250	16	0.556	18	0.092

Results in Table 29 compare very small sample sizes at each primary site of diagnosis and thus are difficult to interpret. However, there is actually a statistically significant difference for the other category. However, given the number of multiple comparisons, any result that is nominally statistically significant needs to be viewed cautiously.

Table 29. Clinical outcome by site of diagnosis in MITTVRE population

		Linezolid 200 mg		Linezolid 600 mg		P-value from Fishers Exact Test
Diagnosis	Endpoint	Cure rate	n	Cure rate	n	
pneumonia	FDA	0.000	1	0.667	3	1.000
pneumonia	FDA-MF	0.000	1	0.500	4	1.000
skin	FDA	1.000	5	0.692	13	0.278
skin	FDA-MF	1.000	5	0.692	13	0.278
BUO	FDA	0.286	7	0.500	10	0.622
BUO	FDA-MF	0.222	9	0.500	10	0.350
UTI	FDA	0.600	20	0.632	19	1.000
UTI	FDA-MF	0.571	21	0.480	25	0.568
other	FDA	0.385	13	0.846	13	0.041
other	FDA-MF	0.313	16	0.846	13	0.008

Results in Table 30 suggest a possibly larger difference in the ITT population than in the MITTVRE population, with one result approaching statistical significance. However, this result is very difficult to interpret because it is unknown whether patients included in the ITT population but excluded from the MITTVRE population have any relevance to the assessment of efficacy in VRE.

Table 30. Clinical outcome in ITT population

		Linezolid 200 mg		Linezolid 600 mg		P-value from Fishers Exact Test
Population	Endpoint	Cure rate	n	Cure rate	n	
ITT	FDA	0.491	57	0.662	65	0.067
ITT	Sponsor	0.538	52	0.667	63	0.183
ITT	FDA-MF	0.424	66	0.544	79	0.183

6.5 Mortality

Mortality rates are presented in Table 31. Death rates were somewhat higher in the lower dose group. In the bacteremia subgroup, this difference approaches statistical significance.

Table 31. Mortality outcome in important populations: Death by end of test-of-cure window

		Linezolid 200 mg		Linezolid 600 mg		P-value from Fishers Exact Test
Population	Endpoint	Rate	n	Rate	n	
MITTVRE	Death	0.346	52	0.246	65	0.306
ITT	Death	0.333	66	0.228	79	0.192
MITTVRE bacteremia	Death	0.563	16	0.222	18	0.076

6.6 Microbiologic outcome

Microbiologic outcome uses the results at the follow-up culture to determine success. However, for the many patients without a follow-up culture, the outcome on the clinical endpoint is substituted for the microbiological outcome. Thus, many of these values are based on imputations. The results presented in Table 32 indicate statistically significant differences for this endpoint, regardless of analytic approach. The cure rate for both clinical and microbiologic outcomes are very similar in the high dose group. However, the cure rate in the low dose group is lower on the microbiologic endpoint versus the clinical endpoint (.46 vs. .52). This leads to the statistically significant difference in the microbiologic endpoint.

Table 32. Microbiologic outcome for primary FDA population: MITTVRE

		Linezolid 200 mg		Linezolid 600 mg		P-value from Fishers Exact Test
Population	Endpoint	Cure rate	n	Cure rate	n	
MITTVRE	FDA	0.457	46	0.678	59	0.029
MITTVRE	Sponsor	0.500	42	0.736	53	0.020
MITTVRE	FDA-MF	0.404	52	0.615	65	0.027

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However, the microbiologic outcome is difficult to interpret because of the mix of true and imputed follow-up culture values. A follow-up culture was required on all patients, but quite a few did not receive them. While death was often the cause of the missed culture, many other missed cultures are not explained. As seen in Table 33, only a few patients have different results for microbiologic results than the clinical outcome. There are 4 patients in the low dose group who were considered clinical cures but who still had positive cultures at follow-up. In contrast, none of the high dose clinical cure patients with culture data were found to have positive cultures, but five had a new enterococcal infection; that is, they had faecium at baseline and faecalis at follow-up. New pathogens at follow-up are viewed as microbiologic success. Again, all these data are difficult to interpret because there is so much missing data for follow-up culture.

Table 33. Follow-up culture result by clinical outcome and treatment group:
MITTVRE

	Treatment Decode								
	Linezolid 200 mg BID				Linezolid 600 mg BID				
	N				N				
	ALL	FU_CULT			ALL	FU_CULT			
		Doc Erad	Doc Pers	No Data		Doc Erad	Doc Pers	New Path	No Data
FDA clinical									
Clin Cure	24	7	4	13	39	14	.	5	20
ClinFail-Alive	6	1	1	4	5	.	1	1	3
ClinFail-Death	16	.	2	14	14	.	.	.	14
Clinical Miss	6	.	.	6	7	1	.	.	6
ALL	52	8	7	37	65	15	1	6	43

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It is informative to consider these cross-tabulations by study site, since reason for lack of follow-up culture may vary by site of infection. It is also noted in Table 34 that most of the patients of interest (3 of the 4 low dose with persistent cultures, and 4 of 5 high dose patients with new pathogens) were UTI patients.

Table 34. Clinical and culture result cross-tabulated by treatment and site of diagnosis: MITVRE

	ALL		Study Indication									
			BACT		CSST		HAP		OTH		UTI	
	Treatment Decode		Treatment Decode		Treatment Decode		Treatment Decode		Treatment Decode		Treatment Decode	
	Line-zolid 200 mg BID	Line-zolid 600 mg BID	Line-zolid 200 mg BID	Line-zolid 600 mg BID	Line-zolid 200 mg BID	Line-zolid 600 mg BID	Line-zolid 200 mg BID	Line-zolid 600 mg BID	Line-zolid 200 mg BID	Line-zolid 600 mg BID	Line-zolid 200 mg BID	Line-zolid 600 mg BID
	N	N	N	N	N	N	N	N	N	N	N	N
FDA Clinical & Culture												
a.Cure and erad	7	13	2	4	1	4	.	2	.	2	4	1
b.Cure but no Cult	11	19	.	1	4	5	.	.	4	8	3	5
c.Cure but new pat	.	5	1	.	4
d.Cure but pers	4	1	.	3	.
e.Cure but died	2	2	2	2
f.Fail but erad	1	1	.
g.Fail but new pat	.	1	1
h.Fail but no Cult	4	3	.	2	.	1	.	.	2	.	2	.
i.Fail and pers	3	1	1	1	1	1	.
k.Fail/Died/nocult	14	14	4	3	.	3	1	1	5	1	4	6
m.Missing clinical	6	7	2	1	3	.	1	6
ALL	52	65	9	10	5	13	1	4	16	13	21	25

6.7 Covariate adjusted analyses

There was no discussion of covariate adjusted analyses in the protocol. However, given the relatively small size of this data set and the somewhat marginal results in the primary analysis, it is prudent to consider such analyses. Unfortunately, there was no pre-specified set of covariates to use. Based simply on perceived clinical importance to the outcome, the following baseline variables were considered in various combinations in Mantel-Haenszel and logistic regression analyses: mortal score, primary site of diagnosis, age, sex, weight, and bacteremia. Mantel-Haenszel analyses required dichotomization of continuous variables, and often could not handle large combinations of variables. Finally, a Mantel-Haenszel analysis with center as the stratification factor was also conducted to reflect the randomization stratification.