### 6.7.1 Clinical outcome in the MITTVRE population

The results were generally the same regardless of whether Mantel-Haenszel or logistic regression was used and regardless of how missing values were handled. The p-values from these analyses ranged from about .05 to .15. For example, when a logistic regression was used to predict FDA clinical outcome with missing values excluded, using all covariates listed above, the p-value was .12. However, when weight was deleted from this covariate list, the p-value dropped to .051. These regression analyses should be interpreted somewhat cautiously because they are not pre-specified, require model assumptions that are not able to be verified, p-values are somewhat anti-conservative for this small sample size, and finally, a large number of covariates, with a small sample size may lead to unstable results. Nonetheless there is some evidence that when covariates are taken into account, the treatment difference may be more demonstrable.

### 6.7.2 Mortality outcome in the Bacteremic MITTVRE population

Previous results suggest a difference in mortality for the bacteremia population. This was further explored by covariate analysis; note only a small number of covariates could be considered because of the very small sample size. With death by the end of TOC window as the dependent endpoint, and mortal score, age, and sex as covariates, the p-value associated with treatment effect was .026. This should be viewed cautiously, for reasons described in the previous section. Nonetheless, this result certainly is not inconsistent with the suggested mortality effect seen in the unadjusted analysis.

### 6.7.3 Investigative site adjustment

A Mantel-Haenszel analysis using investigative center as the stratification factor yielded a treatment p-value of .388. The larger p-value than the unadjusted analysis presumably reflects the large number of centers with very few patients; some of these small centers were unable to contribute to the analysis, so there was a loss of power. From a strict statistical perspective, this is probably the most appropriate analysis. However, given that it was not addressed at the time of the protocol, and no a priori decision was made regarding the handling of small centers, this analysis has not accorded much consideration.

## 6.8 Results for subgroups

Clinical cure rates are presented in Table 35 for a set of important subgroups. While differences are not statistically significant, the high dose observed cure rates are consistently higher than those observed for the low dose group. Groups with particularly large differences in observed cure rates were males, mortal score >15, bacteremia, and weight less than 70. Subgroup sample sizes are too small to be conclusive.

## Table 35. Clinical outcome by subgroup

| | FDA clinical | | | | FDA clinical - MF | | | |
|---|---|---|---|---|---|---|---|---|
| | Treatment Decode | | | | Treatment Decode | | | |
| | Linezolid 200 mg BID | | Linezolid 600 mg BID | | Linezolid 200 mg BID | | Linezolid 600 mg BID | |
| | N | MEAN | N | MEAN | N | MEAN | N | MEAN |
| Age Group (years) - Efficacy | | | | | | | | |
| < 65 | 18.00 | 0.56 | 23.00 | 0.74 | 21.00 | 0.48 | 25.00 | 0.68 |
| >=65 | 28.00 | 0.50 | 35.00 | 0.63 | 31.00 | 0.45 | 40.00 | 0.55 |
| Sex | | | | | | | | |
| Male | 18.00 | 0.33 | 27.00 | 0.63 | 22.00 | 0.27 | 30.00 | 0.57 |
| Female | 28.00 | 0.64 | 31.00 | 0.71 | 30.00 | 0.60 | 35.00 | 0.63 |
| Mortal >= 15 | | | | | | | | |
| No | 22.00 | 0.73 | 28.00 | 0.82 | 25.00 | 0.64 | 32.00 | 0.72 |
| Yes | 24.00 | 0.33 | 30.00 | 0.53 | 27.00 | 0.30 | 33.00 | 0.48 |
| Creatinine>2 | | | | | | | | |
| . | 8.00 | 0.38 | 14.00 | 0.79 | 10.00 | 0.30 | 15.00 | 0.73 |
| No | 26.00 | 0.58 | 30.00 | 0.70 | 29.00 | 0.52 | 34.00 | 0.62 |
| Yes | 12.00 | 0.50 | 14.00 | 0.50 | 13.00 | 0.46 | 16.00 | 0.44 |
| Patient had Bacteremia (Yes/No) | | | | | | | | |
| No | 32.00 | 0.63 | 41.00 | 0.71 | 36.00 | 0.56 | 47.00 | 0.62 |
| Yes | 14.00 | 0.29 | 17.00 | 0.59 | 16.00 | 0.25 | 18.00 | 0.56 |
| Weight > 70 kg | | | | | | | | |
| . | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 2.00 | 0.50 |
| NO | 25.00 | 0.48 | 26.00 | 0.65 | 28.00 | 0.43 | 31.00 | 0.55 |
| Yes | 20.00 | 0.55 | 31.00 | 0.68 | 23.00 | 0.48 | 32.00 | 0.66 |

## 6.9 Sensitivity Analyses

Two important deviations from the protocol were considered in sensitivity analyses. First, the protocol specified that patients who were discontinued due to adverse events should be counted as failures. This was not done in either the sponsor's or the FDA analysis. As illustrated in Table 36, the cure rate for the high dose group dropped with this approach, but the low dose rate remained the same, diminishing the apparent treatment difference seen earlier. Thus, the primary results are not very robust with respect to this issue.

Second, the protocol amendment that separated Study 54a from Study 54 had specified that patients enrolled by June 20, 1999 would comprise Study 54a. However, late in the review process, the FDA discovered that 25 patients who were enrolled by this date were included in Study 54 instead of Study 54a. This was potentially a serious protocol deviation. However, as seen below, the primary analysis was largely unaffected by this omission. Had this deviation been discovered earlier in the review process, the analysis probably would have been conducted on this correct population. However, given the time constraints this was not possible; furthermore, the apparently small impact on study results provides some assurance that this re-analysis would provide little additional information. (Note: in March 2000, the sponsor stated that inclusion in Study 54a was based on completion of treatment and availability of required follow-up documentation by the cutoff data. However, this is not the definition provided in the protocol amendment, and such an approach does not preserve the original randomization.)

## Table 36. Clinical outcome in primary and two sensitivity analyses

| | | Linezolid 200 mg | | Linezolid 600 mg | | P-value from Fishers Exact Test |
|---|---|---|---|---|---|---|
| Population | Endpoint | Cure rate | n | Cure rate | n | |
| MITTVRE | FDA | .52 | 46 | .67 | 58 | .158 |
| MITTVRE | FDA- AE | .52 | 46 | .61 | 59 | .428 |
| MITTVRE plus Study 54 patients starting medication by 6/20/99 | FDA | .53 | 57 | .66 | 65 | .142 |

## 6.10 Results by pathogen

The results presented in Table 37 indicate that almost all the results apply to enterococcus faecium, and only a few to resistant or susceptible enterococcus faecalis.

## Table 37. Clinical outcome by pathogen subgroups (ITT)

| | | | FDA | | Sponsor | | FDA-MF | |
|---|---|---|---|---|---|---|---|---|
| | | | Treatment Code | | Treatment Code | | Treatment Code | |
| | | | 600 | 200 | 600 | 200 | 600 | 200 |
| Vancomycin resistance status | Pathogen | | | | | | | |
| | ENTEROCOCCUS FAECALIS | N | 1.000 | . | 0.000 | . | 1.000 | . |
| | | MEAN | 1.000 | . | . | . | 1.000 | . |
| | ENTEROCOCCUS FAECIUM | N | . | 1.000 | . | 1.000 | . | 1.000 |
| | | MEAN | . | 1.000 | . | 1.000 | . | 1.000 |
| I | ENTEROCOCCUS FAECALIS | N | . | 1.000 | . | 1.000 | . | 1.000 |
| | | MEAN | . | 1.000 | . | 1.000 | . | 1.000 |
| R | ENTEROCOCCUS AVIUM | N | . | 1.000 | . | 1.000 | . | 1.000 |
| | | MEAN | . | 1.000 | . | 1.000 | . | 1.000 |
| | ENTEROCOCCUS FAECALIS | N | 4.000 | 2.000 | 5.000 | 1.000 | 5.000 | 2.000 |
| | | MEAN | 0.750 | 0.000 | 0.800 | 0.000 | 0.600 | 0.000 |
| | ENTEROCOCCUS FAECIUM | N | 57.00 | 45.00 | 50.00 | 40.00 | 64.00 | 51.00 |
| | | MEAN | 0.667 | 0.533 | 0.740 | 0.600 | 0.594 | 0.471 |
| S | ENTEROCOCCUS FAECALIS | N | 3.000 | 5.000 | 3.000 | 6.000 | 3.000 | 6.000 |
| | | MEAN | 0.333 | 0.600 | 0.333 | 0.500 | 0.333 | 0.500 |
| | ENTEROCOCCUS FAECIUM | N | 1.000 | . | 1.000 | . | 1.000 | . |
| | | MEAN | 1.000 | . | 1.000 | . | 1.000 | . |

(Technical note: there were a very small number of discrepancies between the "VREFLAG" variable used to determine MITTVRE and the "INTVAN" variable on the sponsor's "pout" data set that was used to designate vancomycin resistance status in this table. The differences are of little consequence.)

## 6.11 Missing data

As shown in Table 38 a worst case scenario approach to missing data suggests that the results are not very robust to varying assumptions about missing data.

## Table 38. Sensitivity analysis of missing data: treatment comparisons of FDA clinical endpoint under various imputation assumptions for missing data

| | Linezolid 200 mg | | | Linezolid 600 mg | | | P-value (Fishers Exact Test) |
|---|---|---|---|---|---|---|---|
| Population | Imputed cure rate | Cure rate | n | Imputed cure rate | Cure rate | n | |
| MITTVRE | none | .522 | 46 | none | .672 | 58 | .158 |
| MITTVRE | 0 | .462 | 52 | 0 | .600 | 65 | .142 |
| MITTVRE | 1 | .577 | 52 | 0 | .600 | 65 | .851 |
| MITTVRE | .666 | .538 | 52 | .333 | .631 | 65 | .348 |

## 6.12 Compliance

The following tables consider post-baseline variables; these are stratified by mortality status, so that compliance rates, for example, are considered in individuals with and without complete opportunity for full compliance. Under this stratification, number of doses are very similar across the arms. Aminoglycoside use however was quite different between the groups, with greater use in the high dose arm. The issue of aminoglycoside use is further considered in Table 41, although these data are very difficult to interpret.

## Table 39. Comparison of post-baseline events in patients who did not die by end TOC window: MITTVRE

| | | Treatment Decode | |
|---|---|---|---|
| | | Linez-olid 200 mg BID | Linez-olid 600 mg BID |
| Number of Doses of Medication Taken | N | 34.00 | 49.00 |
| | MEAN | 29.59 | 28.01 |
| Any serious adverse events? | N | 34.00 | 49.00 |
| | MEAN | 0.35 | 0.37 |
| Patient Completed Treatment (Yes/No) | N | 34.00 | 49.00 |
| | MEAN | 0.97 | 0.86 |
| Patient Completed STFU (Yes/No) | N | 34.00 | 49.00 |
| | MEAN | 0.82 | 0.86 |
| Concomita-nt Use of Aminoglyc-osides (yes/ | N | 34.00 | 49.00 |
| | MEAN | 0.09 | 0.14 |

## Table 40. Comparison of post-baseline events in patients who died by end TOC window: MITTVRE

| | | Treatment Decode | |
|---|---|---|---|
| | | Linez-olid 200 mg BID | Linez-olid 600 mg BID |
| Number of Doses of Medication Taken | N | 18.00 | 16.00 |
| | MEAN | 18.61 | 19.88 |
| Any serious adverse events? | N | 18.00 | 16.00 |
| | MEAN | 1.00 | 1.00 |
| Patient Completed Treatment (Yes/No) | N | 18.00 | 16.00 |
| | MEAN | 0.61 | 0.56 |
| Patient Completed STFU (Yes/No) | N | 18.00 | 16.00 |
| | MEAN | 0.00 | 0.06 |
| Concomita-nt Use of Aminoglyc-osides (yes/ | N | 18.00 | 16.00 |
| | MEAN | 0.17 | 0.50 |

## Table 41. Clinical outcome as a function of treatment, concomitant use of aminoglycosides, and mortality status: MITTVRE

| | | Treatment Decode | | | |
|---|---|---|---|---|---|
| | | Linezolid 200 mg BID | | Linezolid 600 mg BID | |
| | | C_M | | C_M | |
| | | N | MEAN | N | MEAN |
| Concomitant Use of Aminoglycosides (yes/ | Did patient die by end of TOC window? | | | | |
| 0 | No | 25.00 | 0.84 | 35.00 | 0.86 |
| | Yes | 15.00 | 0.13 | 8.00 | 0.00 |
| | ALL | 40.00 | 0.58 | 43.00 | 0.70 |
| 1 | Did patient die by end of TOC window? | | | | |
| | No | 3.00 | 0.33 | 7.00 | 1.00 |
| | Yes | 3.00 | 0.00 | 8.00 | 0.25 |
| | ALL | 6.00 | 0.17 | 15.00 | 0.60 |
| ALL | | 46.00 | 0.52 | 58.00 | 0.67 |

## 6.13 Safety

The sponsor extensively considered adverse event profiles and changes in certain key hematologic variables. The lower dose has a larger proportion of patients with adverse events reported than the high dose (p=.03). However, this is probably due, at least in part, to the higher mortality rate in the low dose arm. Thus, this adverse event table probably reflect differences in efficacy as well. The sponsor also reported thrombocytopenia in 10% of the high dose treatment group versus 1.5% in the low dose group. Other sponsor investigations suggest that these effects are temporary.

## Table 42. Comparison of adverse event rates (Sponsor table)

| Parameter | 600 mg BID N = 79 | | 200 mg BID N = 66 | | P-Value† |
|---|---|---|---|---|---|
| | n | %‡ | n | %‡ | |
| Patients with ≥1 AE Reported | 71 | 89.9 | 65 | 98.5 | 0.0323* |
| Patients with ≥1 Drug-Related AE Reported | 20 | 25.3 | 14 | 21.2 | 0.5613 |
| Patients with ≥1 AE Resulting in Discontinuation of Study Medication | 7 | 8.9 | 4 | 6.1 | 0.5260 |
| Patients with ≥1 Drug-Related AE Resulting in Discontinuation of Study Medication | 5 | 6.3 | 2 | 3.0 | 0.3561 |
| Patients with ≥1 Serious AE Reported | 40 | 50.6 | 37 | 56.1 | 0.5143 |
| Patients Who Died | 19 | 24.1 | 23 | 34.8 | 0.1534 |

† Chi-square test is based on the number of patients reporting.

* P-value ≤0.05 indicates statistical significance.

‡ Percentages are based on the number of patients reporting.

Drug-related is defined as events specified as related or with relatedness not reported.

AE = adverse event; BID = Twice daily

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

## Table 43. Adverse event rates by body system (Sponsor table)

| Table 71. Study-Emergent Adverse Events by Body System: ITT | | | | | |
|---|---|---|---|---|---|
| | | | | | |
| | 600 mg BID | | 200 mg BID | | |
| | | N = 79 | | N = 66 | |
| COSTART Body System¶ | n | %‡ | n | %‡ | P-Value† |
| Patients With None | 8 | 10.1 | 1 | 1.5 | |
| Patients With at Least One | 71 | 89.9 | 65 | 98.5 | 0.0323* |
| Body | 50 | 63.3 | 45 | 68.2 | 0.5372 |
| Cardiovascular | 28 | 35.4 | 30 | 45.5 | 0.2204 |
| Digestive | 43 | 54.4 | 39 | 59.1 | 0.5729 |
| Endocrine | 1 | 1.3 | 1 | 1.5 | 0.8980 |
| Hemic and Lymphatic | 19 | 24.1 | 13 | 19.7 | 0.5290 |
| Metabolic and Nutritional | 28 | 35.4 | 19 | 28.8 | 0.3939 |
| Musculo-Skeletal | 2 | 2.5 | 2 | 3.0 | 0.8551 |
| Nervous | 19 | 24.1 | 26 | 39.4 | 0.0467* |
| Respiratory | 33 | 41.8 | 23 | 34.8 | 0.3938 |
| Skin | 24 | 30.4 | 24 | 36.4 | 0.4458 |
| Special Senses | 12 | 15.2 | 2 | 3.0 | 0.0136* |
| Urogenital | 23 | 29.1 | 18 | 27.3 | 0.8063 |
| † Chi-square test is based on the number of patients reporting. | | | | | |
| * P-value ≤0.05 indicates statistical significance. | | | | | |
| ‡ Percentages are based on the number of patients reporting. | | | | | |
| ¶ Patients are only counted once for each body system. | | | | | |
| COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms; BID = Twice daily | | | | | |
| *Reference: Section 14, Table 7.2; Appendix 15, Table S-4* | | | | | |

## 6.14 Summary

The results from Study 54a suggest potentially substantial treatment benefits of 600 mg over 200 mg; however, the study is too small to yield firmly conclusive results. See Section 8 for a detailed, integrated summary for Study 54a and 54.



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# 7 Supportive Trial of Vancomycin-resistant enterococcal infections: Study 54

Prior to reviewing the results fully, various options were considered for interpreting the results of the trial given the difficult circumstance that had arisen: that the truncation of the trial was not pre-planned and the trial, in some sense remained ongoing. These options included: a) considering the first 145 as the trial of interest, b) viewing the 145+82 patients as a single trial, or c) imposing a stringent post-hoc monitoring boundary rule and letting the trial run to completion. It was agreed that all approaches were problematic, however; the final decision was to consent to the sponsor's interpretation. That is, that the first submitted trial was a stand-alone trial and that all $\alpha$ has been spent on this sub-trial, as implied by the July 1999 protocol amendment and the October 1999 study report. Unfortunately, this decision left FDA with an awkward situation regarding the interpretation of the second set of data (Study 54). The pooled p-value has no straightforward interpretation, but how can the Study 54 data be incorporated into the overall interpretation, given that all $\alpha$ has been spent on 54a? It was agreed that it is statistically inappropriate that the sponsor "wins" with a good result on **either** 54a or (54a+54) without a pre-specified adjustment. In addition, supporting a borderline p-value for 54a coupled with consistent results for 54 is loosely equivalent to consideration of the pooled p-value, or a second opportunity to demonstrate significance for free. Conversely, there was apparent consensus that if the results for 54 were less favorable than 54a, then the results of 54a might be somewhat discredited, especially given the unusual history of the 54a study. Thus, the results for Study 54 are presented below, but any conclusions must be made cautiously.

## 7.1 Results for important populations

The results for overall populations are presented in Table 44 and Table 46. The results are highly consistent with those observed for Study 54a. It is noted that, unlike Study 54a where the FDA and sponsor results were quite similar, the FDA results provide more evidence of a treatment effect than the sponsor endpoint.

**Table 44. Clinical outcome in various populations in MITTVRE:**

| | | **Linezolid 200 mg** | | **Linezolid 600 mg** | | **P-value from Fishers Exact Test** |
|---|---|---|---|---|---|---|
| Population | Endpoint | Cure rate | n | Cure rate | n | |
| MITTVRE | FDA | 0.486 | 35 | 0.643 | 28 | 0.308 |
| MITTVRE | Sponsor | 0.548 | 31 | 0.680 | 25 | 0.412 |
| MITTVRE | FDA-MF | 0.415 | 41 | 0.600 | 30 | 0.153 |
| bacteremia | FDA | 0.273 | 11 | 0.700 | 10 | 0.086 |
| bacteremia | Sponsor | 0.500 | 8 | 0.889 | 9 | 0.131 |
| bacteremia | FDA-MF | 0.273 | 11 | 0.636 | 11 | 0.198 |
| pneumonia | FDA | 0.000 | 2 | 0.000 | 1 | |
| pneumonia | FDA-MF | 0.000 | 3 | 0.000 | 1 | |
| skin | FDA | 0.600 | 5 | 0.333 | 3 | 1.000 |
| skin | FDA-MF | 0.500 | 6 | 0.333 | 3 | 1.000 |
| BUO | FDA | 0.300 | 10 | 0.571 | 7 | 0.350 |
| BUO | FDA-MF | 0.300 | 10 | 0.500 | 8 | 0.630 |
| UTI | FDA | 0.636 | 11 | 0.692 | 13 | 1.000 |
| UTI | FDA-MF | 0.467 | 15 | 0.643 | 14 | 0.462 |
| other | FDA | 0.571 | 7 | 1.000 | 4 | 0.236 |
| other | FDA-MF | 0.571 | 7 | 1.000 | 4 | 0.236 |

**Table 45. Clinical outcome for ITT population:**

| | | Linezolid 200 mg | | Linezolid 600 mg | | P-value from Fishers Exact Test |
|---|---|---|---|---|---|---|
| Population | Endpoint | Cure rate | n | Cure rate | n | |
| ITT | FDA | 0.463 | 41 | 0.633 | 30 | 0.228 |
| ITT | Sponsor | 0.500 | 36 | 0.621 | 29 | 0.452 |
| ITT | FDA-MF | 0.396 | 48 | 0.559 | 34 | 0.180 |

**Table 46. 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 | 0.366 | 41 | 0.333 | 30 | 0.807 |
| ITT | Death | 0.396 | 48 | 0.324 | 34 | 0.642 |
| MITTVRE bacteremia | Death | 0.545 | 11 | 0.273 | 11 | 0.387 |



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## 7.2 Results by pathogen

### Table 47. Clinical outcome by pathogen subgroups (ITT)

| | | | C_M | | SC_M | | C_MF | |
|---|---|---|---|---|---|---|---|---|
| | | | Treatment Code | | Treatment Code | | Treatment Code | |
| | | | 6 | 2 | 6 | 2 | 6 | 2 |
| Vancomycin resistance status | SPECIAL | | | | | | | |
| I | ENTEROCOCCUS CASSELIFLAVUS | N | . | 1.000 | . | 1.000 | . | 1.000 |
| | | MEAN | . | 0.000 | . | 0.000 | . | 0.000 |
| | ENTEROCOCCUS GALLINARUM | N | . | 1.000 | . | 1.000 | . | 1.000 |
| | | MEAN | . | 0.000 | . | 0.000 | . | 0.000 |
| R | ENTEROCOCCUS FAECIUM | N | 28.00 | 35.00 | 25.00 | 31.00 | 30.00 | 41.00 |
| | | MEAN | 0.643 | 0.486 | 0.680 | 0.548 | 0.600 | 0.415 |
| S | ENTEROCOCCUS FAECALIS | N | 3.000 | 0.000 | 3.000 | 1.000 | 3.000 | 1.000 |
| | | MEAN | 0.667 | . | 0.667 | 1.000 | 0.667 | 0.000 |

## 7.3 Study 54a & Study 54 data collapsed

When data from 54a and 54 are collapsed into a single data set, the test of the primary endpoint is statistically significant. Of course, if one views Study 54a as the stand-alone pivotal study, then these p-values have no interpretation. **Thus, these data need to be considered very cautiously.** In addition, these patients do not necessarily represent the first 145+82 patients randomized, so there may be ascertainment bias. **However, had no decision been made to submit 54a subjects as the pivotal study,** then the following would represent the evidence available to date.

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## Table 48. Clinical outcome by MITTVRE population for 54a & 54 combined

| | | Linezolid 200 mg | | Linezolid 600 mg | | P-value from Fishers Exact Test |
|---|---|---|---|---|---|---|
| Population | Endpoint | Cure rate | n | Cure rate | n | |
| MITTVRE | FDA | 0.506 | 81 | 0.663 | 86 | 0.043 |
| MITTVRE | Sponsor | 0.569 | 72 | 0.724 | 76 | 0.059 |
| MITTVRE | FDA-MF | 0.441 | 93 | 0.600 | 95 | 0.041 |
| bacteremia | FDA | 0.280 | 25 | 0.630 | 27 | 0.014 |
| bacteremia | Sponsor | 0.471 | 17 | 0.760 | 25 | 0.100 |
| bacteremia | FDA-MF | 0.259 | 27 | 0.586 | 29 | 0.017 |
| pneumonia | FDA | 0.000 | 3 | 0.500 | 4 | 0.429 |
| pneumonia | FDA-MF | 0.000 | 4 | 0.400 | 5 | 0.444 |
| skin | FDA | 0.800 | 10 | 0.625 | 16 | 0.420 |
| skin | FDA-MF | 0.727 | 11 | 0.625 | 16 | 0.692 |
| BUO | FDA | 0.294 | 17 | 0.529 | 17 | 0.296 |
| BUO | FDA-MF | 0.263 | 19 | 0.500 | 18 | 0.184 |
| UTI | FDA | 0.613 | 31 | 0.656 | 32 | 0.797 |
| UTI | FDA-MF | 0.528 | 36 | 0.538 | 39 | 1.000 |
| other | FDA | 0.450 | 20 | 0.882 | 17 | 0.014 |
| other | FDA-MF | 0.391 | 23 | 0.882 | 17 | 0.003 |

## Table 49. Mortality outcome by population for 54a & 54 combined

| | | Linezolid 200 mg | | Linezolid 600 mg | | P-value from Fishers Exact Test |
|---|---|---|---|---|---|---|
| Population | Endpoint | Death rate | n | Death rate | n | |
| MITTVRE | Death | 0.355 | 93 | 0.274 | 95 | 0.272 |
| MITTVRE bacteremia | Death | 0.556 | 27 | 0.241 | 29 | 0.028 |

## 7.4 Summary

Sample sizes were very small, but Study 54 consistently produced better cure rates in the high dose arm than in the low dose arms; these differences were not statistically significant at .05. Results were generally very consistent with those seen in Study 54a. See Section 8 for a detailed, integrated summary for Study 54a and 54.

# 8 Summary: Vancomycin-resistant enterococcal infections

## 8.1 Study 54a summary

The findings for the primary trial, Study 54a, based on the FDA approach are summarized below (Note: results from the sponsor's approach are generally similar despite the fact that many individual patients' assessments were different):

- The clinical outcome success rate is .67 for the high dose arm in the primary analysis population, those with documented VRE at baseline, as opposed to .52 for the low dose arm; however this difference is not statistically significant at the $\alpha$=.05 level (p=.16). Similar results are seen across many subgroups and populations; that is, the point estimates are almost always better in the high dose arm, but not usually statistically significant at the .05 level. This is not surprising, given that the study was planned for 80% power, and has a sample size that is less than one third of the originally planned size.
- Particularly striking results are observed in the bacteremia population, success rates of .59 versus .29, however the sample sizes are very small, and differences are not statistically significant. Differences in mortality approach statistical significance in this group (.56 in the low dose group versus .22 in the high dose group ; p=.08). This subgroup was treated specially in the protocol in that sample size and interim testing plan were based specifically on this subgroup; however, no other part of the protocol particularly emphasized this subgroup. This subgroup presumably was highlighted, at least in part of the protocol, because bacteremic patients with isolated VRE pathogens almost surely have a true VRE infection, which is not necessarily the case for non-bacteremic patients.
- The fully randomized patient population had similar success rates as the MITTVRE population, but because of larger sample size, the corresponding p-value approach statistical significance (p=.07). However, since the ITT patients who are not part of the MITTVRE population may not truly have VRE infections, this particular result may not reliably reflect the ability of Linezolid to treat of VRE.
- Follow-up cultures were not performed consistently enough to be easily interpreted. However, it is interesting to note that amongst those patients whose cultures were performed, there were several clinical cures with persistent pathogens in the low dose groups. This is in contrast to the high dose arm, where several clinical cures in which the original pathogen was eradicated, but a new enterococcal infection appeared at follow-up.
- The results were not very robust to pessimistic assumptions about missing data (i.e., worse results in the high dose arm among missing data patients than in the low dose group). Similarly, the results were not robust to consideration of discontinuation due to adverse event as a failure, which had been specified in the protocol.
- Covariate adjusted analyses tended to provide a little additional evidence for the treatment differences, but the results varied by the covariate set considered.
- Some Study 54 patients who were enrolled prior to June 20, 1999 and should have been submitted as part of Study 54a. When these were added to the Study 54a population database, there was little impact on the results for the primary analysis.
- There was a higher proportion of use of aminoglycosides in the high dose arm than the low dose arm. It is difficult to interpret this finding; however, it does introduce some uncertainty into the final results.

## 8.2 Study 54 summary

Results for the limited data of Study 54 are highly consistent with those observed in Study 54a.

## 8.3 Integrated VRE trials summary

Study 54a produced many promising results, especially for the bacteremic population. However, the size of the study was too small to yield clear conclusions.

One might argue that since the results of Study 54 were consistent, that if the two studies were pooled together, there would be sufficient evidence of a treatment benefit. However, to pool these trials (or subtrials) together, in any fashion, having not prespecified this is in the protocol, inflates the Type I error. While p-values are not the only determining factor in whether evidence is strong enough to support approval, they should have a

straightforward interpretation. Obviously, it would be highly problematic if trials were routinely continually tested until statistical significance is obtained.

One way to look at this situation is that two small trials were conducted, both of which showed promise, but neither of which yielded a statistically significant result for the primary endpoint. Only the first trial was designated as the formal basis for demonstrating a statistically significant result. Nonetheless, the data of Study 54 certainly do not, in any way, undermine, the promising results seen in Study 54a. And, it is true and noteworthy, that had the study been planned to terminate after 145+82 patients were enrolled, then a statistically significant result would have been obtained. However, this was not the plan.

That said, one could have taken the contrary, but reasonable, view that 54a and 54 is truly all one study and that the decision to submit 54a as a stand-alone trial is essentially ignorable given that the study continued, and nothing really changed as a result of this decision (see Section 7). Under this scenario, the p-value for the 145 and 82 patients for the FDA's primary analysis is less than .05. However, this approach should really be taken further to consider all the patients randomized; an additional 104 patients were randomized before the study was terminated for reasons that have not yet been submitted. These data have not yet been submitted to the FDA. Furthermore, the current 54a/54 data base may not represent the first 145+82 patients randomized, a phenomenon observed in the 54a database alone. In any event, it is critical that the complete data set be submitted, so that the FDA can analyze the full results to determine if the final phase of the study has similar results, and potentially to form the basis for specification of delta in future equivalence trials.

Finally, if one accepts the premise that 54a forms the basis of the pivotal study, from a strict statistical point of view, the results are promising, but not conclusive.



APPEARS THIS WAY
ON ORIGINAL

Sign off sheet

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