Medical Officer's Review of Studies M1260/0054A and 0054 (Infections due to Vancomycin-Resistant Enterococci)

General Information

Study Title: Linezolid for the Treatment of Vancomycin-Resistant Enterococcal Infections: A Double-Blind Trial Comparing 600 mg Linezolid Every 12 Hours With 200 mg Linezolid Every 12 Hours.

Study Objective: To assess the safety, tolerance, efficacy (clinical and microbiological), and pharmacokinetics of intravenously (IV) or orally administered linezolid at a dose of 600 mg compared with linezolid 200 mg in patients with vancomycin-resistant enterococcal (VRE) infections. The study also had the objective of assessing the pharmacokinetics of linezolid in patients with VRE infection (with the results to be summarized in a separate report).

Study Design: Randomized, dose-comparison, double-blind, multi-center.

Study Period: 20 November 1998 – 4 August 1999.

Investigators: Ninety U.S. investigators participated; see Appendix 4 of applicant's study report for details.

Medical Officer's Comment

This study had a novel design for a trial of an anti-infective agent. The vast majority of antibiotic trials employ an equivalence design. However, because of the lack of an approved or accepted comparator agent for vancomycin-resistant enterococcal (VRE) infections at the time this trial was designed and conducted, the applicant chose to compare two different doses of linezolid in the treatment of such infections. Thus, the study had a superiority design, with the study hypothesis being that the higher dose of linezolid was clinically superior to the lower dose. The scientific basis for this design was that both proposed doses had pharmacodynamic properties (i.e., time above MIC) that were predictive of efficacy; however, the pharmacodynamic profiles of the different doses were felt to be distinct enough to predict a difference in clinical outcome.

Historically, such designs have been used in trials of anti-hypertensive drugs or other agents for which the immediate clinical endpoint is not directly linked to mortality or irreversible morbidity. Use of this design is problematic in the study of VRE infection, given the possibility that use of an ineffective dose might be associated with an increased risk of mortality. The design of the current trial was felt to be acceptable from an ethical standpoint because of pharmacodynamic data suggesting that the low dose met the pharmacodynamic criteria predicting efficacy, and the use of a Data Safety Monitoring Board to monitor safety and efficacy data.

From a regulatory standpoint, this design was acceptable, given the definition of a well-controlled clinical trial in 21 CFR 314, which explicitly discusses dose-comparison trials. However, in discussions with the applicant, the Agency pointed out the risk that the two doses might not be pharmacodynamically distinct enough to result in a clinical difference. In essence, both doses might be on the plateau of the dose-response curve for the drug, making it difficult to conclude that the high dose was effective. In addition, the higher dose might be associated with an higher incidence of adverse events that would cancel out its therapeutic advantage. The Agency suggested adding a third, intermediate dose arm to better define the dose-response curve and address the issue of achieving an optimal risk-benefit

ratio. The applicant chose to use only two doses because of the added complexity of conducting the trial with three arms.

The use of a single study to support approval for this indication represents another regulatory issue. A single study could support approval for VRE infection, if the drug development package as a whole showed efficacy at a variety of body sites for different organisms. Please see the Integrated Summary of Efficacy for further details.

Study populations

Inclusion criteria

Male or female patients who were at least 13 years of age and weighed at least 40 kg with known VRE infections (e.g., infections of the respiratory tract, urinary tract, peritoneum, or wounds, or VRE bacteremia of unknown source) were eligible for enrollment in the study. They were to have had a VRE-positive culture of blood, urine, wound, abscess, respiratory secretions, or peritoneal or pleural fluid; an accessible site for Gram's stain and culture; signs and symptoms of an active infection, such as chills, malaise, localized pain, heat/localized warmth, or mental status changes; or signs and symptoms that were present for the following clinical syndromes:

- Skin and soft tissue infection with at least two of the following symptoms: drainage/discharge, erythema, fluctuance, heat/localized warmth, pain/tenderness to palpation, chills, or swelling/induration.
- Urinary tract infection with at least one of the following symptoms (not required for patients unable to provide a history): dysuria, frequency, urgency, chills, costovertebral angle tenderness, or suprapubic pain, in addition, a positive urine culture defined as $\geq 10^5$ colony-forming units (CFU)/mL for asymptomatic patients or $\geq 10^3$ CFU/mL for symptomatic patients; urinalysis documenting ≥10 WBCs per high powered field.
- Patient expected to survive 60 days with effective therapy and appropriate care.

Medical Officer's Comment

The true pathogenic significance of the presence of enterococci can be difficult to determine, particularly in a critically ill patient with multiple co-morbidities who may have signs and symptoms that mimic infection. This organism is a frequent colonizer as well as pathogen. Given this, it is important in trials studying patients with VRE infection to be as clear as possible in distinguishing between colonization and infection. The inclusion criteria given above are relatively nonspecific; it would have been preferable if infection-specific criteria had been provided to investigators, particularly for bacteremia of unknown origin. The clinical basis for enrolling a given patient in the trial was often not documented on review of the patient's case report form, and a significant number of enrolled patients may have been colonized by VRE rather than infected.

The lack of specificity was most problematic for diagnosing bacteremia and urinary tract infection. A diagnosis of bacteremia of unknown origin only required one positive culture. Without a second, confirmatory culture, it is not possible to be confident that the positive culture represents growth of a true pathogen rather a contaminant. Although the protocol required that patients with BUO had to have two positive cultures to be clinically evaluable, it would be preferable to have made this a baseline requirement for entry, since superiority trials should be analyzed by the intent-to-treat principle. Only six of the BUO

patients enrolled had at least two positive cultures; it is unclear whether the others truly had VRE as a pathogen.

With respect to urinary tract infection, the original protocol contained a widely accepted definition of UTI that incorporated signs and symptoms of UTI, pyuria, and the growth from a urine culture of at least 10^5 cfu/mL. In July 1999, the protocol was amended to allow enrollment of patients with asymptomatic bacteriuria (i.e., growth of 10^5 cfu/mL), as well as symptomatic patients with as few as 10^3 cfu/mL. The applicant did not provide any scientific rationale for these changes. These criteria are problematic, since there are few or no data to support treatment of asymptomatic bacteriuria, except in special circumstances. The majority of individuals with indwelling urinary catheters will show asymptomatic bacteriuria (and pyuria), but not have a urinary tract infection that requires treatment. The criterion of 10^3 cfu/mL for symptomatic patients is not consistent with general principles for study of UTI in clinical trials, since this low of a cut-off leads to over-diagnosis and inclusion of patients who are not truly infected.

Exclusion criteria

Patients were to be excluded from the study if they met any of the following criteria: females of child-bearing potential who were unable to take adequate contraceptive precautions, had a positive pregnancy test result within 24 hours prior to study entry, were otherwise known to be pregnant, or were currently breastfeeding an infant; had endocarditis, osteomyelitis, or central nervous system (CNS) infections; had infected devices that were not to be removed; had gas gangrene or necrotizing fasciitis; had known pheochromocytoma, carcinoid syndrome, untreated hyperthyroidism, or uncontrolled or untreated hypertension; had previously enrolled in this or another linezolid study; were hypersensitive to linezolid or one of its excipients; were currently using another investigational medication; had received more than 24 hours of a potentially effective antibiotic in the last 7 days prior to entry or since the last positive blood culture.

Study methods

Treatment assignment

Patients were randomized in a 1:1 ratio to receive one of the following two treatments, administered either orally or IV based on the patient's condition and ability to swallow and absorb oral medication:

- 600 mg linezolid every 12 hours for 7 to 28 consecutive days
- 200 mg linezolid every 12 hours for 7 to 28 consecutive days

Those patients who required initial Gram-negative coverage may have received intravenous aztreonam or an aminoglycoside, as appropriate, regardless of treatment group.

Patients were not allowed to receive a nonstudy antimicrobial agent if that agent had activity against VRE. Acceptable nonstudy antimicrobial agents included those for which VRE has intrinsic resistance (eg, aztreonam, aminoglycosides, cephalosporins, anti-staphylococcal β-lactams, and clindamycin); and those for which the patient's VRE isolate had demonstrated acquired resistance based on susceptibility testing (i.e., chloramphenicol, fluroquinolines, penicillins, tetracycline, or vancomycin).

Medical Officer's Comment

Aztreonam is not active against Gram-positive pathogens, and thus its use should not confound the treatment effect of linezolid in patients with VRE infection. While amino-

glycosides may have activity against VRE, in this study all VRE isolates had high-level resistance to both streptomycin and gentamicin.

Assessments

Baseline assessments were similar to those in the other phase 3 studies. In addition, clinical observations related to VRE infection were performed. A chest radiograph was performed if clinically indicated and a cardiac ultrasound was performed on patients with bacteremia of unknown origin to rule out endocarditis. Blood cultures were obtained to qualify patients for enrollment, regardless of the source of infection. Culture samples (i.e., blood, urine, wound infection, pleural or peritoneal samples) must have been obtained 96 hours before the administration of study medication. A Mortality Probability Model-II (MPM-II) assessment was done at baseline.

Vital signs and clinical observations were recorded on Days 3, 6, 9, 15, and 21 for in-patients, and on Days 3, 9, 15, and 21 for outpatients, and (if applicable) at switch from IV to oral treatment. Laboratory assessments were performed on Days 3, 9, 15, and 21 (±1 day). Adverse event monitoring was recorded throughout the study. If applicable, a culture of the source of infection was to be obtained when the patient switched from IV to oral study medication. Positive baseline blood cultures were to be repeated at 48 to 72 hours and again 48 hours later if still positive. Within 72 hours of treatment completion (End of Treatment, EOT), patients had an evaluation that included clinical observations, vital sign assessments, laboratory assays, and completion of the Clinical Response Evaluation and a Treatment Completion Report (except for patients with urinary tract infection [UTI]). The Follow-Up (F-U) evaluation (15 to21 days post-therapy or 7 to 10 days for UTI) was considered the Test-of-Cure (TOC) evaluation. A ß-HCG pregnancy test was to be performed at the F-U visit. Those patients who had a UTI caused by VRE were to have a F-U visit 7 to 10 days after EOT, and a Long-Term Follow-up (LTFU) visit from 4 to 6 weeks after the discontinuation of linezolid in order to repeat the urine culture, safety laboratory assays, vital signs, and clinical assessments.

Clinical Observations

The clinical evaluation of infection was based on clinical and laboratory signs and symptoms of infection, such as fever and leukocytosis. Objective and subjective clinical observations were made by the investigator and recorded on the CRF; these assessments included:

- lesion size (length, width)
- degree of involvement for SST infections (ie, superficial versus deep)
- diagnosis for SST and UTI infections
- cardiac ultrasound for patients with bacteremia of unknown source
- radiography

Medical Officer's Comment

Although echocardiography was required by the protocol for patients with bacteremia of unknown origin in order to evaluate such patients for possible endocarditis, 7/18 of such patients did not have a cardiac ultrasound performed. However, these patients did not appear to have clinical evidence of endocarditis.

Microbiology

Microbiologic procedures were similar to those in other phase 3 studies, with the central laboratory performing microbiological isolate evaluations. Patients with UTI as the source of VRE infection were also to have urine cultures performed at the LTFU visit. All urine cultures were to be quantitative with results recorded on the appropriate central laboratory requisition form.

Bacterial Isolate Susceptibility Testing

Susceptibility tests were conducted by the central laboratory to determine if pathogens were susceptible to linezolid and vancomycin. Patients included in the study must have an organism resistant to vancomycin and sensitive to linezolid. MICs were determined from a panel of antibiotics.

Collection of Specimens for Central Laboratory

Laboratory and microbiological culture evaluations, including those at Baseline, were performed by a central laboratory so that assay results were consistent and suitable for group analysis. In some cases, Baseline safety laboratory assays were performed by a local laboratory. Each patient was to have a blood culture done at Baseline. In the absence of another source of infection, a VRE-positive baseline blood culture was required within 96 hours before enrollment. To be evaluable for efficacy, a patient with bacteremia of unknown source was to be culture-positive twice for VRE in cultures taken at least 1 hour apart or from 2 different sites. If positive at baseline, blood cultures were to be repeated 48 to 72 hours after the initiation of treatment, and if still positive, repeated at 96 to 120 hours after the initiation of treatment. Bacteremic patients were also to have a blood culture at the time the route of administration was switched from IV to oral (if applicable), at the end of treatment, and at the F-U visit(s).

Safety was evaluated throughout the study by clinical observations, vital sign assessments, laboratory evaluations, and assessment of adverse events.

Medical Officer's Comment

The medical reviewer examined clinical, microbiologic, and laboratory data for all patients in this study. The reviewer's assessment of outcome was then compared to the investigator's and discrepancies examined. Because investigators had direct contact with patients, their assessments were taken as accurate unless there was clearly documented clinical evidence to the contrary. The algorithm used for assigning outcomes was that used for other studies and is described in Dr. Brittain's review. The most important difference between the FDA's approach and the applicant's with respect to Study 54A was that patients who died before follow-up were considered failures in the FDA analysis, but usually had an outcome of missing in the applicant's analysis.

Statistical considerations

Patients were randomized in blocks of 4 at a 1:1 ratio to one of the two treatment groups. As patients entered the study, they were assigned the next available number according to a randomization scheme provided by P&U. Each site received a unique set of patient numbers that were used sequentially to identify study medication containers, CRFs, and all specimens for each given patient. The label on oral study medication included the randomization number.

This study was conducted in a double-blind fashion. The sponsor, investigators, study personnel, and patients remained blinded to the identity of the study medication during the

study. Gray blinding overbags were used for IV study medication, and capsule dosage forms appeared identical. A Data Safety Monitoring Board (DSMB) was established for this study and was independent of P&U to protect the integrity of the trial. The DSMB had access to unblinded safety and efficacy data. Confidential reports were produced by a separate biostatistics group at [redacted] These reports went directly to the DSMB and were not made available to P&U. Additionally, the DSMB minutes were not made available to P&U.

Clinical response to treatment was the primary endpoint, and microbiological response to treatment was the secondary endpoint. A combination of clinical and microbiological criteria determined the overall/global response to treatment.

The applicant defined ITT, MITT, CE, and ME populations in a manner similar to the other phase 3 trials. The applicant's analysis primarily focused on the CE and ME populations.

To establish sample size, the binomial test of proportions was used. Using a 2-sided test level of 5% and a desired statistical power of 80% under the assumption that the 200 mg treatment group would yield a 40% success rate in patients with a diagnosis of bacteremia, and the 600 mg group would yield at least a 60% success rate in patients with a diagnosis of bacteremia, a sample size of 97 evaluable patients per group was required. Assuming an evaluability rate of 80% with a diagnosis of bacteremia, this translated to a requirement of 122 enrolled patients with a diagnosis of bacteremia per treatment group. To achieve this number of bacteremia patients, each treatment group required a total of 250 patients with VRE infections.

Medical Officer's Comment

For purposes of the FDA review, the primary analysis was conducted on the modified intent-to-treat population that had a positive culture at baseline (designated MITT-VRE). Please see the discussion of this issue by the statistical reviewer (Dr. Erica Brittain). The medical officer strongly concurs with her statement that superiority trials should be analyzed using the intent-to-treat principle. Failure to do so can easily lead to dramatically incorrect conclusions. The applicant did not provide a rationale for not using an intent-to-treat population for the primary analysis.

Changes in study conduct

Amendment 1 - 06 October 1998

This amendment was issued in response to regulatory agency recommendations, and also to clarify or refine some sections of the original protocol. This amendment was approved before the start of patient enrollment. The following changes were made:

- Pharmacokinetic testing, included in the original protocol as a required laboratory evaluation, was designated as a primary study objective.

Medical Officer's Comment

Correlation of pharmacokinetic data with clinical results could provide substantial corroboration of the results of this trial. Unfortunately, these were not submitted with the clinical study report.

- A positive blood culture was added to the inclusion criteria (positive culture of urine, wound, abscess, respiratory secretions, or peritoneal or pleural fluid) satisfying the requirement for a VRE-positive culture within 72 hours before enrollment. The alternative

entry requirement for 2 VRE-positive blood cultures taken at least 8 hours apart was dropped.

• For patients with bacteremia of unknown source, the presence of two VRE-positive blood cultures taken at least 8 hours apart was designated as an evaluability criterion for efficacy. The list of screening activities was revised to require a baseline blood culture for all patients, along with cultures from other evident sources as clinically indicated. The original description of screening activities required culture from blood or another source as clinically indicated.

• For UTI, the inclusion criterion for characteristic symptoms was made conditional on the patient's ability to provide history.

• Gas gangrene and necrotizing fasciitis were added as exclusion criteria.

• MPM II was added to the study procedures pursuant to the request of regulatory authorities for an index of illness severity.

• A requirement was added for recording of clinical observations and vital signs and (for bacteremic patients) blood culture when a patient was switched from IV to PO dosing.

• A requirement was added for a second baseline culture (subsequent to the culture qualifying the patient for enrollment) in cases where a potentially effective antibiotic was administered.

• The amendment deleted a requirement for quantitation of WBCs and bacteria in the analysis of Gram's stains.

• Reference to the LTFU as the TOC for UTI patients was deleted.

• The primary efficacy variable was changed from microbiological outcome to clinical outcome.

Some revisions were made to the following for explanatory or procedural clarification or administrative purposes (with no substantive effect on study conditions): study personnel, rationale for dose and regimen, entry criteria, study procedures, and study activities schedule.

Amendment 2 - 07 July 1999

Changes were made regarding the sponsor's medical monitor and in the address and telephone numbers of the contract research organization monitoring the sites. The study objective was changed from a microbiological endpoint to a clinical endpoint. Changes in microbiological entry criteria were made regarding blood cultures, urine cultures, and the time before enrollment that culture samples were collected. Patient evaluability status was clarified. Test-of-Cure according to source of the infection was defined.

Medical Officer's Comment

As discussed above, the change in microbiologic criteria for diagnosis for urinary tract infection had the effect of allowing inclusion of patients with asymptomatic bacteriuria, a condition for which treatment is of undefined benefit. In addition, the mid-study change in primary endpoint from microbiologic outcome to clinical outcome greatly confused assessment of outcomes, since several investigators appear to have based their test-of-cure clinical assessment on the presence or absence of VRE in follow-up cultures (i.e., microbiologic outcome), rather than the patients' clinical status. This was an issue in patients enrolled without signs or symptoms of infection at baseline.

Amendment 3 - 13 July 1999

Changes were made to define two data sets for analysis purposes. Patients enrolled on or prior to 20 June 1999 were to be analyzed separately. A second analysis was to be done for all patients enrolled after 20 June 1999. Patients in the first data set were to be included in the NDA submission. The second data set was utilized as supportive microbiological data if necessary.

Medical Officer's Comment

This one change in the conduct and analysis of the study complicated the interpretation of the trial results more than any other event. In essence, this amendment represents an unscheduled interim analysis of the trial after reaching less than one-third of the planned enrollment, without any prespecified statistical adjustment. Dr. Brittain's review discusses this issue in greater detail, but salient points are as follows:

- *The amendment does not discuss any statistical implications of this change with respect to adjustments to avoid underestimation of type I error; in fact, the amendment states that "there are no changes to the design or scope of the study."*
- *The Agency advised the applicant not to submit data from the trial in this fashion, but rather to continue the trial in a blinded fashion.*
- *The Data Safety Monitoring Board for the trial did not appear to be involved with this decision.*
- *The amendment stated that patients enrolled prior to 20 June 1999 were to be analyzed separately. In fact, not all patients enrolled prior to this date were made part of the dataset, apparently because of logistic issues involved in processing case report forms. This had the effect of excluding some sequentially enrolled patients, thus distorting the randomization scheme and potentially introducing bias.*
- *The pre-June 20 dataset (designated 'Study 54A') comprised data from 145 patients. Discussions with the applicant in the fall of 1999 revealed that some data from the post-June 20 dataset (designated 'Study 54') could be provided to the Agency, in essence representing a second unplanned interim analysis. After internal discussions, the Agency requested that data from as many patients as possible from Study 54 be submitted. The sponsor subsequently submitted data from 82 patients. The entire study was closed at the end of 1999; the basis for study closure is not clear. Data from an additional 104 patients is being processed by the applicant. Thus, the entire study comprises data from 331 patients.*
- *The issue of how to interpret differences between treatment arms in Study 54A has been discussed extensively within the Division of Anti-Infective Drug Products and Division of Biometrics. The initial decision has been to treat this as a stand-alone study with 'all alpha spent'; in other words, to require a p value of <0.05 for a finding of statistical significance. Another possibility would be to analyze data from the entire populations of 331 patients. Please see Dr. Brittain's review for discussion of this issue.*

In addition to the Investigator's Assessment of Patient Clinical Outcome, a Sponsor's Clinical Outcome assessment was generated. In addition to the Investigator-Defined Patient Clinical Outcome, a primary efficacy endpoint was the Sponsor-Defined Patient Clinical Outcome. Additional secondary efficacy endpoints were Sponsor-Defined Patient Microbiological Outcome and Sponsor-Defined Patient Overall Outcome. Also, results for

patient clinical, microbiological, and overall outcomes were presented considering indeterminate outcomes as failures. In addition to the overall frequency tables and analyses generated for Sponsor-Defined Patient Clinical Outcome, Sponsor-Defined Patient Microbiological Outcome, and Sponsor-Defined Patient Overall Outcome, corresponding frequency tables and analyses were produced for these variables by primary source of VRE infection, by pathogen, and for patients with bacteremia (if there are at least 10 patients in each treatment group who were bacteremic).

Results

Medical Officer's Comment

Unless otherwise indicated, all results presented involve only data from the 145 patients submitted as Study 54A.

Demographics and disposition

One hundred and forty-five patients were enrolled and treated; of these, all received study medication. There were 79 treated patients in the high-dose arm and 66 in the low-dose arm. Table 54A.1 shows the demographics of the ITT patient populations, as determined by the applicant.

Medical Officer's Comment

The site with the highest number of patients enrolled was located in St. Petersburg, Florida; the principal investigator was Dr. Jeffrey Levenson. An inspection at this site by the Division of Scientific Investigations (DSI) found numerous protocol violations, including enrollment of patients who did not appear to meet inclusion criteria. DSI recommended exclusion of data from this site.

This issue was discussed extensively by the clinical and statistical reviewers. The medical reviewer examined the cited protocol violations at this site, and determined that these generally did not affect the appropriateness of patient enrollment or data integrity. It was possible to conclude that patients enrolled at this site who met appropriate criteria did in fact have VRE infection. Furthermore, because the blinded design of the trial offered substantial protection against introduction of bias. In addition, the superiority design meant that inclusion of patients without the disease in question would decrease the likelihood of finding a difference, acting to control type I error.

Because of these considerations, and the risk of reaching an erroneous conclusion because of exclusion of otherwise valid data, the Division chose to retain data from this site, and all analyses shown in this review include data from this site. Sensitivity analyses by the statistical reviewer that excluded data from this site gave similar results to analyses including data from this site, supporting this approach.

Table 54A.1. Applicant's analysis of demographics of ITT patients – Study 54A					
	600 mg BID		200 mg BID		
		N = 79		N = 66	
Parameters	**n**	**%**	**n**	**%**	**P-Value**
Age (years)					
Total Reporting	79	100.0	66	100.0	
18-44	12	15.2	10	15.2	
45-64	21	26.6	20	30.3	
≥ 65	46	58.2	36	54.5	
Mean ± SD	63.8 ± 16.6		63.6 ± 18.2		0.9252
Weight (kg)					
Total Reporting	75	100.0	65	100.0	
Mean ± SD	76.72 ± 21.54		71.67 ± 19.70		0.1518
Race					
Total Reporting	79	100.0	66	100.0	0.7465
White	60	75.9	49	74.2	
Black	18	22.8	15	22.7	
Asian or Pacific Islander	0	-	1	1.5	
Mixed	1	1.3	1	1.5	
Sex					
Total Reporting	79	100.0	66	100.0	0.9889
Male	36	45.6	30	45.5	
Female	43	54.4	36	54.5	
Diagnosis					
Total Number of Patients	79	100.0	66	100.0	
Pneumonia	5	6.3	1	1.5	0.1472
SST	18	22.8	9	13.6	0.1588
SST with Bacteremia	3	3.8	0	-	0.1096
UTI	29	36.7	25	37.9	0.8846
UTI with Bacteremia	2	2.5	3	4.5	0.5081
Other	14	17.7	20	30.3	0.0750
Other with Bacteremia	4	5.1	6	9.1	0.3405
Bacteremia of Unknown Source	13	16.5	11	16.7	0.9728

Medical Officer's Comment

The treatment arms appear roughly balanced with respect to demographic factors. The sources of infection varied between treatment arms, but this is to be expected given the small sample size. Mean MPM-II scores were similar between treatment arms; the mean risk of mortality was 25.7 in the high-dose arm and 25.3 in the low-dose arm.

Table 54A.2 shows the numbers of patients in each treatment arm completing treatment and completing follow-up, as determined by the applicant.

Table 54A.2. Applicant's analysis of patient disposition – Study 54A				
	600 mg BID		200 mg BID	
Population	**n**	**%**	**n**	**%**
All Randomized Patients	79	-	66	-
Intent-To-Treat Patients (ITT)	79	100.0	66	100.0
Discontinued During Treatment	19	24.1	16	24.2
Completed Treatment	60	75.9	50	75.8
Discontinued During Follow-up	28	35.4	32	48.5
Completed Follow-up	51	64.6	34	51.5
Discontinued During Treatment and/or Follow-up	33	41.8	33	50.0
Completed Treatment and Follow-up	46	58.2	33	50.0

Medical Officer's Comment

Somewhat fewer patients completed follow-up in the low-dose arm; this may be partially due to an increased mortality rate in that arm (see below).

The frequencies of reasons for the discontinuation of treatment for the ITT population, as determined by the applicant, are provided in Table 54A.3.

Table 54A.3. Applicant's analysis of reasons for discontinuation – Study 54A				
	600 mg BID		200 mg BID	
Discontinuations during follow-up	N = 79		N = 66	
Reasons for Discontinuation	**n**	**%**	**n**	**%**
Discontinued Patients	19	24.1	16	24.2
Lack of Efficacy	0	-	2	3.0
Death	6	7.6	5	7.6
Adverse Event (Serious)	3	3.8	3	4.5
Adverse Event (Nonserious)	3	3.8	0	-
Ineligible, but Started Study Medication	6	7.6	4	6.1
Lost to Follow-up	1	1.3	0	-
Other‡	0	-	2	3.0
Discontinuations during follow-up				
Discontinued Patients	28	35.4	32	48.5
Lack of Efficacy	1	1.3	2	3.0
Death	18	22.8	21	31.8
Adverse Event (Serious)	0	-	1	1.5
Ineligible, but Started Study Medication	5	6.3	3	4.5
Lost to F-U	4	5.1	4	6.1
Other	0	-	1	1.5

Populations analyzed

Table 54A.4 shows the FDA MITT-VRE populations that were analyzed.

Table 54A.4. FDA evaluable populations – Study 54A		
Evaluation Group	**600 mg Linezolid**	**200 mg Linezolid**
All randomized subjects	79	66
ITT subjects	79 (100%)	66 (100%)
MITT-VRE subjects	65 (82.3%)	58 (87.9%)
MITT-VRE (non-missing outcomes)	58 (73.4%)	46 (69.7%)
MITT-VRE bacteremia	18 (22.8%)	16 (24.2%)
MITT-VRE bacteremia (non-missing outcomes)	17 (21.5%)	14 (21.2%)

Medical Officer's Comment

The majority of the MITT-VRE population was infected with E. faecium, *as would be expected from the epidemiology of VRE infection. There were five patients who also had infection with* E. faecalis, *but almost all of these also had infection with* E. faecium. *One patient in the low-dose arm had* E. avium *infection*

Efficacy

Table 54A.5 shows clinical outcomes in the MITT-VRE and MITT-VRE bacteremic populations. The numbers of subjects listed in Table 54A.5 exclude patients with missing or indeterminate outcomes, except for analyses where missing outcomes were changed to failures.

Table 54A.5. FDA Analysis of Clinical Outcome - Study 54A					
FDA-Defined Study Population	**Linezolid 600 mg**		**Linezolid 200 mg**		**p value (Fisher's exact test)**
	N	**Success Rates (%)**	**N**	**Success Rates (%)**	
MITT-VRE	58	67.2	46	52.2	0.158
MITT-VRE (missing as failure)	65	60.0	52	46.2	0.142
Bacteremic MITT-VRE	17	58.8	14	28.6	0.149
Bacteremic MITT-VRE (missing as failure)	18	55.6	16	25.0	0.092
MITT-VRE (excluding BUO pts with 1 BCx)	50	70.0	44	50.0	0.059
MITT-VRE (missing as failure) (excluding BUO pts with 1 BCx)	57	61.4	48	45.8	0.121
Bacteremic MITT-VRE(excluding BUO pts with 1 BCx)	9	66.7	12	16.6	0.03
Bacteremic MITT-VRE (missing as failure) (excluding BUO pts with 1 BCx)	10	60.0	14	14.3	0.032

Medical Officer's Comment

Response rates were higher in the high-dose arm, but the difference was not statistically significant. The results in the bacteremic population are interesting, but inconclusive given the small sample size, and it is important to remember that these patients were defined as bacteremic on the basis of only one positive blood culture. Thus, some of these patients may not have been truly infected. If one excludes BUO patients with only one

documented blood culture from the analysis, the response rates are markedly higher in the high-dose arm; however, given the small numbers of patients and the potential for introduction of bias, the associated p-values should be interpreted cautiously.

The impact of missing data was substantial, given the small sample size. The statistical reviewer performed a number of sensitivity analyses showing that the response rates were not particularly robust. Please see Dr. Brittain's review for more details.

Exclusion of BUO patients with only one positive blood culture has a proportionately greater impact on the analysis of bacteremic patients, as would be expected from the small sample size.

Table 54A.6. shows outcomes by site of infection; the analysis presented excludes patients with missing outcomes.

Table 54A.6. FDA Analysis of Clinical Outcome in Study 54A by site of infection

FDA-Defined Study Population	Linezolid 600 mg		Linezolid 200 mg		p value (Fisher's exact test)
	N	Success Rates (%)	N	Success Rates (%)	
MITT-VRE (all)	58	67.2	46	52.2	0.158
Bacteremia of unknown origin	10	50.0	7	28.6	0.622
Skin/skin structure	13	69.2	5	100.0	0.278
Urinary tract infection	19	63.2	20	60.0	1.000
Pneumonia	3	66.7	1	0.0	1.000
Other	13	84.6	13	38.5	0.041

Medical Officer's Comment

The most pronounced difference was in the category of 'Other', which primarily consisted of complicated intra-abdominal infections. The response rates for BUO when patients with only one positive blood culture were excluded were 1/2 (50%) for the high-dose arm and 1/4 (25%) for the low dose arm.

The statistical reviewer also analyzed response rates for a number of potentially important clinical factors, including age, sex, risk of mortality, elevated serum creatinine, and weight. In all cases the response rate was higher in the high-dose arm, but in no case was the difference statistically significant.

Table 54A.7 shows response rates by pathogen; the response rates exclude patients with missing outcomes except for analyses where missing outcomes were changed to failures.

Table 54A.7. FDA analysis of clinical outcomes by pathogen – Study 54A		
Subset	**600 mg linezolid**	**200 mg linezolid**
Vancomycin-resistant *E. faecium*	38/57 (66.7%)	24/45 (53.3%)
Vancomycin-resistant *E. faecium* (missing as failures)	38/64 (59.4%)	24/51 (47.1%)
Vancomycin-resistant *E. faecalis*	3/4 (75.0%)	0/2 (0.0%)
Vancomycin-resistant *E. faecalis* (missing as failures)	3/5 (60.0%)	0/2 (0.0%)
Vancomycin-resistant *E. avium*	0/0 (NA)	1/1 (100%)
Vancomycin-susceptible *E. faecium*	1/1 (100%)	0/0 (NA)
Vancomycin-susceptible *E. faecalis*	1/3 (33.3%)	3/6 (50.0%)

Medical Officer's Comments

The results for vancomycin-resistant E. faecium *parallel those for the trial as a whole, an expected result given the predominance of this species. There are too few isolates to evaluate the clinical effectiveness of linezolid against* E. faecalis.

With respect to microbiologic outcome rates, these were difficult to assess because of inconsistency among investigators in obtaining follow-up cultures. The statistical reviewer analyzed the available culture data from the MITT-VRE population; her analysis showed that among cured patients, there was a higher number of cases of eradication in the high-dose arm (13 vs. 7); however, among cured patients, there was also a higher number of cases of emergence of a new pathogen in the high-dose arm (4 vs. 0).

Table 54A.8. shows all-cause mortality rates for the MITT-VRE population, and for MITT-VRE patients with bacteremia at baseline.

Table 54A.8. FDA Analysis of Mortality Rates - Study 54A					
FDA-Defined Study Population	**Linezolid 600 mg**		**Linezolid 200 mg**		**p value (Fisher's exact test)**
	N	**Mortality Rate (%)**	**N**	**Mortality Rate (%)**	
MITT-VRE	65	24.6	52	34.6	0.306
Bacteremic MITT-VRE	18	22.2	16	56.3	0.076

Medical Officer's Comment

The difference in mortality rates between treatment arms is interesting and unexpected. The interpretation of this result is not straightforward, given the uncertainty over the contribution of VRE to fatal outcomes in infected patients, but is consistent with efficacy of the higher dose of linezolid in the treatment of VRE infection.

Study 54

As discussed above, the applicant submitted data on an additional 82 patients from a continuation of the trial, designated Study 54. Table 54A.9A shows clinical outcomes for Study 54, and Table 54A.9B outcomes for all 227 patients in Studies 54A and 54.

Table 54A.9. FDA Analysis of Clinical Outcome - Study 54					
FDA-Defined Study Population	**Linezolid 600 mg**		**Linezolid 200 mg**		**p value (Fisher's exact test)**
	N	**Success Rates (%)**	**N**	**Success Rates (%)**	
MITT-VRE	28	64.3	35	48.6	0.308
MITT-VRE (missing as failure)	30	60.0	41	41.5	0.153

Table 54A.9B. FDA Analysis of Clinical Outcome - Study 54A + Study 54					
FDA-Defined Study Population	**Linezolid 600 mg**		**Linezolid 200 mg**		**p value (Fisher's exact test)**
	N	**Success Rates (%)**	**N**	**Success Rates (%)**	
MITT-VRE	86	66.3	81	50.6	0.043
MITT-VRE (missing as failure)	95	60.0	93	44.1	0.059

Medical Officer's Comment

These results are consistent with those from Study 54A in that the high-dose arm showed a higher cure rate. The interpretation of p values is complicated by the issues discussed above; please see Dr. Brittain's review for a more detailed discussion of this issue.

Safety

Medical Officer's Comment

The safety analysis focused on the 145 patients in the 54A dataset.

Deaths, serious adverse events, discontinuations and clinical adverse events

Deaths, serious adverse events, discontinuations due to adverse events, and clinical adverse events are summarized in Table 54A.10.

Table 54A.10. Summary of deaths, SAEs, discontinuations,– Study 54A					
	600 mg BID		**200 mg BID**		
		N = 79		**N = 66**	
Parameter	**n**	**%**	**n**	**%**	**P-Value**
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

Medical Officer's Comments

All case report forms for patients who died were examined by the medical reviewer. There were no deaths that were attributable to study drug. As noted above, the mortality rate was higher in the low-dose arm. Mortality rates for patients with VRE bacteremia were 4/18 (22.2%) in the high-dose arm and 9/16 (53.1%) in the low-dose arm. Of patients with VRE bacteremia who died, one patient in the high-dose arm and 3 patients in the low-dose arm had VRE infection listed as a cause of death. There was a high incidence of drug-related

adverse events in both arms, and a high incidence of drug-related discontinuations in both arms.

Drug-related adverse events that led to discontinuation of study drug in the high-dose arm included nausea, vomiting, leukopenia, thrombocytopenia, rash, and increased serum creatinine (one each). Only the thrombocytopenia was assessed as severe in intensity. Drug-related adverse events that led to discontinuation of study drug in the low dose arm included bradycardia, hypotension, and hemorrhage (one each, all severe).

Serious adverse events are summarized in Table 54A.11. SAEs that were drug-related were reported for 4 patients (6 serious adverse events) in the low dose group and in 4 of the patients (4 serious adverse events) in the high-dose group. The drug-related serious adverse events in the low dose group were anemia, hypotension, bradycardia, hemorrhage, abdominal pain, and diarrhea. The drug-related serious adverse events in the high-dose group were thrombocytopenia, pancreatitis, leukopenia, and localized abdominal pain.

Table 54A.11. Serious Adverse Events – Study 54A

	600 mg BID		200 mg BID	
		N = 79		N = 66
COSTART Body System/MET	**n**	**%**	**n**	**%**
Patients With at Least One	40	50.6	37	56.1
BODY				
Sepsis	5	6.3	4	6.1
Septic Shock	2	2.5	2	3.0
CARDIOVASCULAR				
Hemorrhage	0	-	3	4.5
Hypotension	3	3.8	2	3.0
DIGESTIVE				
Intestinal Perforation	2	2.5	0	-
Multiple Organ Failure	3	3.8	3	4.5
Vomiting	2	2.5	0	-
RESPIRATORY				
Dyspnea	0	-	3	4.5
Respiratory Failure	6	7.6	2	3.0
UROGENITAL				
Kidney Failure	3	3.8	1	1.5

Specific adverse events and drug-related adverse events are shown in Tables 54A.12 and 54A.13, respectively.

Table 54A.12. Study-Emergent Adverse Events >10% Within Body Systems: ITT				
	600 mg BID		200 mg BID	
		N = 79		N = 66
COSTART Body System /MET	**n**	**%**	**n**	**%**
Patients With at Least One	71	89.9	65	98.5
BODY				
Fever	11	13.9	11	16.7
Sepsis	9	11.4	9	13.6
Localized Pain	3	3.8	8	12.1
CARDIOVASCULAR				
Hypertension	5	6.3	7	10.6
Hypotension	7	8.9	13	19.7
DIGESTIVE				
Diarrhea	9	11.4	13	19.7
Nausea	7	8.9	12	18.2
Vomiting	11	13.9	10	15.2
HEMIC AND LYMPHATIC				
Anemia	8	10.1	8	12.1
Thrombocytopenia	8	10.1	1	1.5
METABOLIC AND NUTRITIONAL				
Peripheral Edema	8	10.1	2	3.0
NERVOUS				
Somnolence	3	3.8	7	10.6
SKIN				
Erythema	1	1.3	7	10.6
Rash	6	7.6	7	10.6
UROGENITAL				
Infection Urinary Tract	8	10.1	5	7.6

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Table 54A.13. Study-Emergent Drug-Related Adverse Events by Body System: ITT				
	600 mg BID		200 mg BID	
		N = 79		N = 66
COSTART Body System/MET	**n**	**%**	**n**	**%**
Patients With at Least One	20	25.3	14	21.2
CARDIOVASCULAR				
Hypertension	1	1.3	2	3.0
DIGESTIVE				
Diarrhea	0	-	3	4.5
Incontinence Fecal	2	2.5	0	-
Vomiting	2	2.5	0	-
HEMIC AND LYMPHATIC				
Thrombocytopenia	3	3.8	1	1.5
SKIN				
Rash	2	2.5	2	3.0

Medical Officer's Comment

The numbers of patients with any particular drug-related adverse event were low. Attribution of a specific adverse event to linezolid administration in this patient population must be regarded as tentative, given the number of comorbid conditions and concomitant medications.

Analysis by the medical reviewer of potential MAOI-associated events did not find an excess of such events in the high-dose arm, or an association with use of potentially interacting concomitant medications.

Laboratory findings

Hematology

The sponsor analyzed changes in mean values of hematologic laboratory values over time. Mean values for WBC count, neutrophil count, and platelet count appeared lower in the 600 mg arm during therapy; the difference in WBC count and neutrophil count persisted after therapy.

Medical Officer's Comment

It is not clear if the decrease in leukocytes and neutrophils in the high-dose arm represents a myelosuppressive effect of linezolid or resolution of infection.

The sponsor also analyzed the frequency with which substantially abnormal hematologic laboratory values occurred; patients with abnormal values at baseline were considered to develop a substantial abnormality if values fell below a pre-specified threshold if the baseline was less than the lower limit of normal. The results are shown in Table 54A.14.

Table 54A.14. Incidence of substantially abnormal hematologic laboratory values							
Laboratory Assay	Criteria	Linezolid 600 mg BID			Linezolid 200 mg BID		
		n	N	%	n	N	%
Hemoglobin	<75% of LLN	15	78	19.23	15	66	22.73
Hematocrit	<75% of LLN	14	78	17.95	11	66	16.67
Platelet Count	<75% of LLN	13	77	16.88	4	64	6.25
WBC	<75% of LLN	2	78	2.56	1	66	1.52
Neutrophils	<0.5 LLN	2	78	2.56	0	66	0.00
Eosinophils	>= 10%	8	78	10.26	3	65	4.62
Reticulocyte Count	>2 x ULN	1	75	1.33	1	64	1.56

Medical Officer's Comment

Analysis of the hematology dataset by the medical officer using CrossGraphsled to similar conclusions. In particular, analysis of platelet counts revealed a higher incidence of thrombocytopenia in the high-dose arm than in the low-dose arm for patients with a normal platelet count at baseline (7/59 (11.9%) vs. 4/55 (7.3%)). Four patients in the high-dose arm and two in the low-dose arm had decreases in platelet counts to less than 50,000/mm^3; all but one of these had thrombocytopenia at baseline. Thrombocytopenia resolved in the majority of patients with laboratory follow-up. There were no clinical adverse events (e.g., gastrointestinal hemorrhage) related to development of thrombocytopenia, and no apparent requirement for platelet transfusion in patients who developed thrombocytopenia. While there was a slightly higher incidence of leukopenia and neutropenia in the high-dose arm, this was not as pronounced the development of thrombocytopenia.

Chemistry

The sponsor analyzed changes in mean values of chemistry laboratory values over time. These appeared comparable between treatment groups for all parameters analyzed. Mean lipase concentrations tended to be somewhat lower in the high-dose arm.

The sponsor also analyzed the frequency with which substantially abnormal chemistry laboratory values occurred; patients with abnormal values at baseline were considered to develop a substantial abnormality if values rose or fell a pre-specified amount (depending on the specific chemistry parameter) above or below baseline if the baseline value abnormal. The results are shown in Table 54A.15.

Table 54A.15. Incidence of substantially abnormal chemistry laboratory values							
Laboratory Assay	Criteria	Linezolid 600 mg BID			Linezolid 200 mg BID		
		n	N	%	n	N	%
Total Bilirubin	>2 x ULN	3	77	3.90	6	65	9.23
Total Protein	<0.75 x LLN	8	77	10.39	8	65	12.31
Albumin	<0.75 x LLN	12	77	15.58	12	65	18.46
AST	>2 x ULN	5	77	6.49	9	65	13.85
ALT	>2 x ULN	9	76	11.84	12	65	18.46
LDH	>2 x ULN	4	75	5.33	3	65	4.62
Alkaline Phosphatase	>2 x ULN	11	77	14.29	10	65	15.38
BUN	>2 x ULN	5	78	6.41	13	65	20.00
Creatinine	>2 x ULN	4	78	5.13	5	65	7.69
Sodium	<0.95 x LLN	5	78	6.41	4	66	6.06
	>1.05 x ULN	4	78	5.13	0	66	0.00
Potassium	<0.9 x LLN	5	77	6.49	4	66	6.06
	>1.1 x ULN	3	77	3.90	2	66	3.03
Chloride	<0.9 x LLN	2	78	2.56	0	66	0.00
	>1.1 x ULN	2	78	2.56	0	66	0.00
Bicarbonate	<0.9 x LLN	3	78	3.85	6	66	9.09
	>1.1 x ULN	6	78	7.69	2	66	3.03
Calcium	<0.9 x LLN	8	77	10.39	14	66	21.21
	>1.1 x ULN	2	77	2.60	0	66	0.00
Non Fasting Glucose	<0.6 x LLN	2	78	2.56	0	65	0.00
	>1.4 x ULN	15	78	19.23	18	65	27.69
Creatine Kinase	>2 x ULN	1	76	1.32	3	64	4.69
Lipase	>2 x ULN	4	76	5.26	9	64	14.06
Amylase	>2 x ULN	3	76	3.95	4	65	6.15

Medical Officer's Comment

The medical officer's review did not reveal any significant differences between treatment arms with respect to chemistry laboratory values for hepatic, pancreatic, and renal parameters, similar to that performed for hematologic laboratory values. One patient developed a significantly elevated lipase concentration associated with pancreatitis; however, this patient had had bowel surgery and may have been receiving total parenteral nutrition, which could have caused pancreatitis.

Final conclusions

This was a randomized, dose-comparison study of two different doses of linezolid in the treatment of VRE infection. There were problems in conduct that complicate the interpretation of the results. These included what amounted to retrospective changes in inclusion criteria that decreased the likelihood that enrolled patients were truly infected, and a decision to present results from the trial after less than a third of the planned enrollment had been reached. Interpretation of differences between the treatment arms is complicated. Although there was a consistently higher response rate in the high-dose arm under a variety of analyses, (and consistency in the results from the second dataset of 82 patients) it is difficult to determine whether these represent real differences that would support the

conclusion that a high dose of linezolid is more effective than the low dose. It should be noted here that the question of efficacy only applies to E. faecium, *since there were too few cases of* E. faecalis *infection to gauge the efficacy of linezolid against the latter species.*

Given the current problematic situation with therapy of VRE infection and the mortality and morbidity associated with this indication, the medical reviewer is willing to accept the results of the current trial as substantial evidence of linezolid's efficacy in the treatment of vancomycin-resistant E. faecium *infection for the following reasons:*

1. In vitro *evidence of efficacy of linezolid against VRE.*
2. *Efficacy of linezolid in animal models of VRE infection.*
3. *Efficacy of linezolid against other Gram-positive infections at defined body sites.*
4. *A clinically acceptable response rate in the current trial for treatment of VRE infection when compared to historical series, although direct comparison with historical controls is not practical because of differences in study populations.*
5. *The difference in overall response rate between the high-dose and low-dose arms.*
6. *The consistency of response rates across different analyses, inlcuding subgroup analysies and analyses addressing the issue of nonsequential patient enrollment.*
7. *The consistency of results between Study 54A and Study 54 with respect to differences between the high-dose and low-dose arms.*
8. *The results from the combined 54A+54 dataset.*
9. *The decreased all-cause mortality rate in the high-dose arm, particularly in the population with VRE bacteremia.*
10. *An acceptable safety profile for this indication.*

These factors do not lessen the problems in interpreting the results of this trial, which are ably discussed by Dr. Brittain in her review. To address these problems, approval for this indication should be contingent on the following commitments by the applicant:

1. *Submission of the complete patient dataset from study 54 (i.e., data from all 331 patients).*
2. *Submission of the pharmacokinetic data from this study, including correlation with clinical outcomes, which would allow validation of the basic pharmacodynamic model undergirding this trial.*

Medical Officer's Review of Study M1260/0031 (Methicillin-resistant staphylococcal species infections)

General Information

Title of study: Linezolid for the Treatment of Methicillin-Resistant *Staphylococcus* Species (MRSS) Infections: A Randomized, Open-label Trial Comparing Linezolid IV/PO and Vancomycin IV

Objectives: To assess the efficacy (clinical and microbiological), safety, and tolerance of intravenously and orally administered linezolid when compared with vancomycin in the treatment of MRSS infections and to determine the direct medical costs required to achieve an acceptable clinical outcome in this population of patients with documented MRSS infections.

Study Design: Randomized, comparator-controlled, open-label, multi-center

Study period (years): 2 July 1998 - 21 July 1999

Investigator(s): One hundred and four investigators (North America, Europe, Latin America, Asia; see Appendix 4 of sponsor's study report for details).

Medical Officer's Comment

Anti-infective agents are generally approved by the FDA for treatment of infections at specific body sites caused by specific pathogens; anti-infective indications are generally not granted on a pathogen-specific basis. The objective of this study was to provide data supporting the inclusion of methicillin-resistant Staphylococcus aureus *under infections at specific anatomic sites in the Indications and Usage section. As discussed below, an important feature of the study design is the classification used prospective criteria to classify enrolled patients as having infections at specific body sites.*

Study population

Inclusion criteria

Hospitalized (including chronic care facilities) patients were eligible if they were at least 13 years of age and at least 40 kg in weight. Patients were also required to satisfy all of the following criteria: patients must have a known or suspected *Staphylococcus* infection as determined by laboratory findings consistent with *Staphylococcus* infection (e.g., Gram's stain or culture results) and have signs and symptoms of an active infection of pneumonia, skin and soft tissue infection, right-sided endocarditis, urinary tract infection, or bacteremia.

Medical Officer's Comment

The protocol provided specific clinical definitions for the various categories of infection. Those for pneumonia were consistent with the definition in Study 48A (hospital-acquired pneumonia); those for pneumonia were consistent with the definition in Study 39A (uncomplicated skin and skin/structure infection). Thus, although this was a pathogen-specific study, patients were studied in the context of infections at specified body sites, allowing data from the study to be used to support efficacy for linezolid against nosocomial pneumonia and skin/skin structure infections (SSSI) due to MRSA.

One problem with these definitions, however, is that the sponsor was not specific about whether patients in this study had community-acquired or hospital-acquired pneu-

monia, or whether skin infections were complicated or uncomplicated. In both cases, these are different indications with different epidemiology, microbiology, natural history, and requirements for therapy; thus, failure to distinguish between the two greatly complicated interpretation of results. Because MRSA is almost always a nosocomially-acquired pathogen and patients were hospitalized at entry, patients with a diagnosis of pneumonia were considered to have hospital-acquired pneumonia. The issue of skin/skin structure infection was more difficult. The criteria for skin/skin structure infection in this study were those for uncomplicated SSSI, but the pathogen studied was one generally associated with complicated SSSI. However, analysis of baseline characteristics suggested that this population was more similar with the study population in Study 55 (complicated SSSI); although the definition of complicated SSSI in that study was also problematic, SSSI patients in Study 31 were considered to have complicated SSSI.

Bacteremia of unknown origin (BUO) represented another problematic issue. The sponsor indicated that the diagnosis of 'bacteremia' applied to patients with BUO. The definition of this diagnosis in the protocol was unsatisfactory for a number of reasons. First, the sponsor used a vague clinical definition of this entity for patients with a positive culture; patients qualified for this diagnosis if they had fever, leukocytosis, increase in band forms, or 'change in vital signs' (no details on the latter were provided). While such a nonspecific definition is appropriate for patient care, this is not necessarily true for clinical trials. A recent study (Bossink et al. *Chest (1998) **113**:1533-41) showed that a majority of patients on a general medical or surgical service will meet two of the four clinical criteria for a systemic inflammatory response syndrome. Given this, the even looser criteria given in the protocol are likely to lead to enrollment of a number of patients who are not truly infected for those patients whose blood cultures grew coagulase-negative staphylococci, the most common blood culture contaminants. The original protocol contained a requirement for two positive blood cultures, which would have greatly added to the specificity of diagnosis. However, patients with a single blood culture positive for* S. aureus *may be regarded as having a true bloodstream infection in the appropriate clinical setting.*

In addition, the group of patients with this diagnosis may have been quite heterogeneous (Leibovici et al. *Clin. Inf. Dis. (1992) **14**:436-443), especially since the protocol did not require specific steps to identify the source of the bacteremia. Echocardiography was recommended but not required for this patient group. Catheters were to be removed and cultured, but no specific criteria were provided for the definition of catheter-associated bloodstream infection.*

Because results from the study were considered both as a whole and for specific infections, the definition of BUO was accepted for review purposes, but results for this group of patients should be interpreted with great caution, since these patients may not all have had true infection, and the underlying source of bacteremia (and expected response to therapy) may have varied significantly between patients.

Exclusion criteria

Patients were excluded from participation in the study if they met any of the following criteria: Females of childbearing potential who were unable to take adequate contraceptive precautions, were pregnant or breastfeeding; had left-sided endocarditis, osteomyelitis, or CNS infections; had infected devices that could not be removed; known to

have pheochromocytoma, carcinoid syndrome, untreated hyperthyroidism, or uncontrolled hypertension; were previously enrolled in this protocol or another linezolid protocol; were hypersensitive to linezolid or vancomycin or one of the excipients in either drug formulation; had absolute neutrophil count < 500/mm^3 , known liver disease with total bilirubin > 5.0x upper limit of normal (ULN); had more than 24 hours of treatment with a potentially effective antibiotic within 48 hours of study entry (unless the therapy had failed or the pathogen showed drug resistance, with the exception of vancomycin); concurrent use of another investigational medication, or had infection due to organisms known to be resistant to the study medications.

Study methods

Treatment assignment

Patients were randomized in a 1:1 ratio to receive one of the following treatment regimens for 7 to 28 consecutive days:

- linezolid IV 600 mg every 12 hours for the entire treatment period with an option to switch to linezolid oral 600 mg every 12 hours
- vancomycin IV 1 gram every 12 hours for the entire treatment period

Medical Officer's Comment

Originally, the protocol was designed as a three-arm study; patients in the third arm were to be treated with IV vancomycin and then switched when clinically indicated to PO linezolid. Enrollment in this arm was discontinued after 51 patients had been enrolled; the stated reason was to allow the study to focus on the comparison between vancomycin and linezolid.

Assessments

Clinical, microbiologic and safety assessments were similar to those in the other comparator-controlled studies. The test of cure visit was at 7-10 days for UTI patients, 15-21 days for pneumonia and SSSI patients, and 28-35 days for endocarditis and bacteremia of unknown origin patients.

Statistical considerations

The randomization scheme was performed by the sponsor; Each investigator received a unique set of patient numbers that were assigned sequentially to patients entering the study and used to identify study drug containers, CRFs, and all specimens for each given patient. Each investigator received a unique set of patient numbers.

Initially, the study was evaluator-blinded; the protocol was amended in December 1998 to change the study to an open-label design.

Medical Officer's Comment

The reasons underlying this change were unclear; although the applicant stated that this design was 'burdensome', it was feasible in Study 48A (hospital-acquired pneumonia). Although it would have been difficult to continue the blind after a switch to oral therapy, it should have been possible to blind evaluators (and patients) for the IV phase.

Using a 2-sided test level of 5% and a desired statistical power of 80% under the assumption that each treatment group would yield a 90% success rate, the number of

evaluable patients required per treatment group for a determination of equivalence between the 2 treatment groups to within 10% was 142 patients. Assuming an evaluability rate of 40%, this translates to a requirement of 355 enrolled patients per treatment group.

The primary endpoints were clinical outcome, microbiological outcome, and overall (combined clinical/microbiological) outcome. The sponsor defined analytic populations in a manner similar to the other phase 3 studies.

Medical Officer's Comment

The FDA review defined ITT, MITT, CE, and ME populations as in the FDA analysis of other phase 3 studies. Because this was a pathogen-driven study, the FDA analysis focused on the MITT and ME populations.

Changes in study conduct

Amendment 1: 07 July 1998

This protocol amendment was implemented to respond to regulatory agency recommendations, to ease certain study requirements without compromising safety, to update some protocol sections with new data, and to clarify certain protocol sections. The following changes were made:

- Inclusion criteria, by which eligibility was originally limited to patients with cultures positive for MRSA, were expanded to include known carriers of MRSA.

- Definitions of infection-specific enrollment criteria and infection-specific treatment and F-U periods for pneumonia, skin and soft tissue infections, urinary tract infections, right-sided endocarditis, and bacteremia of unknown source were added in response to recommendations from regulatory agencies.

- The upper age limit for eligibility was removed from the inclusion criteria after it was determined that linezolid clearance was not affected by changes in renal function.

- The lower age limit was dropped to 13 years with a weight restriction of 40 kg following completion of the initial pharmacokinetics study in pediatric patients.

- Criteria for exclusion of patients with abnormal ALT, AST, or creatinine values were dropped on the basis of new study results showing that linezolid metabolism is not dependent on hepatic or renal function. The exclusion criterion for patients with bilirubin values >3 x ULN was changed to specify known liver disease with bilirubin >5 x ULN.

- Exclusion criteria were modified to permit use of hormonal contraception, based on results of metabolism studies showing that linezolid is not a substrate for or an inhibitor of the human cytochrome P-450 enzymes.

- To improve safety, exclusion criteria were added for patients with uncontrolled hypertension or infection due to organisms known to be resistant to the study medications.

- An exclusion criterion was changed to allow up to 24 hours of treatment with a potentially effective antibiotic before enrollment; up to 3 days of such treatment were allowed for endocarditis, conditioned on sponsor consultation. Originally, patients were allowed only 12 hours of such treatment. This change is compatible with regulatory guidelines.

• Minimum requirements for length of hospital stay and IV dosing were reduced from 3 days and 4 doses to 1 day and 1 dose, respectively. This was based on the continuing adequate safety profile of linezolid coupled with customary practice in certain parts of the world.

• Recommended typical treatment durations were increased by 4 days for uncomplicated skin and soft tissue infections and UTI, and by 14 days for bacteremia.

• Instructions on concomitant therapy were updated as a result of interaction studies conducted with linezolid and drugs metabolized by MAO types A and B. In these studies, it was found that linezolid is a weak, nonselective, reversible inhibitor of MAO. This information plus the experience from Phase II studies provided a basis for the relaxation of the drug and diet restrictions that had been followed previously in Phase II studies. Also, cautions on concomitant use of phenytoin and warfarin were deleted based on results of an interaction study with warfarin.

• Topical steroids were permitted as adjunctive therapy for skin and soft tissue infections provided they were not in direct contact with the site infection.

• The list of screening activities was reworded to state specifically that chest radiographs were required for patients with suspected pneumonia only.

• A requirement for cultures of infected sites 48 to 72 hours after initiation of treatment was dropped, except for patients with bacteremia.

• Evaluability criteria for efficacy were revised to increase from 5 to 7 days, the interval (at start of therapy) during which evaluable patients were to have received 80% of prescribed study medication without missing 2 consecutive doses.

• Assignment of the clinical outcome "improved" was restricted to the EOT evaluation.

• Several changes were made to instructions on adverse event reporting and F-U based on revised standard operating procedures:

♦ A requirement for reporting pre-existing conditions as adverse events if they were considered to have become related to study medication was dropped.

Medical Officer's Comment

While this change did not appear to have an impact on the reporting of adverse events, it is illogical not to report pre-existing conditions if their severity or frequency changes because of study medication.

♦ Criteria for assessing the gravity of adverse events were revised; cancers, overdoses, and events causing permanent impairment of function or permanent structural damage were no longer explicitly defined as serious; and recommendations were added on assessing important adverse events not meeting the defined criteria for serious events.

♦ An instruction to use concise medical terminology in adverse event reporting was added.

♦ For eliciting adverse event information, an alternative question on events since the last clinic visit was added.

♦ A requirement was added for discontinuing study medication if a pregnancy was discovered during treatment and substituting an appropriate antibiotic labeled as safe for use during pregnancy.

• Other sections of the protocol were added or reworded for clarification, presentation of updated research results (for background and for support of study design rationales), or administrative purposes.

Amendment 2: 02 December 1998
In order to ensure timely and successful completion of the study, this amendment implemented the following changes:

• The original study objective of comparing the efficacy, safety and tolerance of vancomycin IV only with vancomycin IV followed by oral linezolid (step-down therapy) was removed, allowing efforts to be focused on fulfilling the other study objectives. This resulted in the removal of a vancomycin IV/linezolid oral treatment arm that was originally implemented, prompting changes in the sample size calculation (Section 9.8). References to the dropped treatment arm were deleted from the protocol title as were protocol sections describing primary objectives, overall trial design and plan, treatment schedule, oral dosing, randomization, and statistical and analytical plans.

Medical Officer's Comment

The amendment did not discuss the statistical implications of this change with respect to a mid-study change in the randomization scheme.

• A critical enrollment criterion was changed from documented MRSA infection (patients with cultures positive for MRSA or known MRSA carriers) to known or suspected methicillin-resistant Staphylococcus species infection as determined by laboratory findings consistent with such infection. Many investigators were having difficulty enrolling patients in the study because, in their institutions, patients with suspected MRSA are empirically treated with vancomycin. By the time culture results demonstrate MRSA, patients have often received vancomycin for greater than24 hours, making them ineligible to participate in the study. To help overcome this problem, all patients with suspected *Staphylococcus* species infections were deemed eligible for entry into the study. Patients who had culture results that did not confirm MRSA or methicillin-resistant Staphylococcus species were to be dropped from the study and considered nonevaluable. This prompted changes in enrollment targets as described in Section 9.8.12. References to MRSA in the protocol title and text were changed to MRSS as appropriate.

Medical Officer's Comment

This was a major change in the study design with respect to microbiology and epidemiology. The stated rationale is reasonable given the clinical realities of treating hospitalized patients. It is unlikely to have introduced a tendency towards equivalence by adding a different study population to the microbiologically evaluable population, given that patients who did not grow MRSS from cultures were to be dropped from the study and were not considered evaluable.

• The evaluator-blinded study design originally implemented was changed to an open-label design. The investigators had found implementation of the evaluator blinding procedures burdensome. Considering the differences in routes of administration, the effec-

tiveness of the blinding procedures was questionable. Double-blinding through use of double-dummy study treatments had been considered. However, this would have posed several problems, including difficulty in implementation while allowing for required vancomycin dosage adjustment, increased fluid volume administrations, and a significant decrease in the validity of the direct medical costs measurements. References to the study design as evaluator blinded were deleted or changed to reflect the revised design in the protocol title and protocol sections describing the rationale for study design, overall trial design and plan, and blinding.

Medical Officer's Comment

Please see the discussion of blinding above under Statistical Considerations.

Other protocol changes not directly related to the revisions in design and objectives described above were as follows:

• For UTI patients, an inclusion criterion requiring specific symptoms was waived for patients unable to provide a history. In addition, a urine sample collected from a catheter was specified as an acceptable source for culture.

• For patients with bacteremia of unknown source, an inclusion criterion requiring at least 2 positive blood cultures was changed to require at least 2 blood cultures drawn from different sites (one from each site) prior to initiation of therapy.

Medical Officer's Comment

Please see the discussion of this issue under Inclusion Criteria. Dropping the requirement for two positive blood cultures greatly decreases the likelihood that these patients are truly infected for those patients whose cultures grow coagulase-negative staphylococci.

• A provision was added prohibiting patients from receiving >96 hours of study medication unless cultures documented MRSS; patients were allowed to receive study medication before culture results were obtained.

• A requirement was added that any bacteremia patient with an IV catheter in place at the onset of symptoms was to have the catheter removed and the catheter tip cultured.

• An option was added for a blinded independent evaluator to conduct a rating of illness severity at Baseline using the Mortality Probability Model II (MPM-II) scale.

Several protocol sections were revised for clarification, to correct typographical errors, or for administrative purposes, with no substantive effect on study conditions.

Amendment 3: 11 May 1999

For purposes of statistical analysis, the TOC windows were expanded. It was decided that if more than one clinical/microbiological evaluation was made within a window for a particular visit, the worst assessment would be used as the assessment for that window. The TOC window to be used for ITT, MITT, and evaluable patient analyses is provided in the table below.

	F-U Visit	F-U Analysis Window	LTFU Visit	LTFU Analysis Window
Infection				
Skin/Soft Tissue	15-21 d*	7-28 d	NA	NA
Pneumonia	15-21 d*	12-28 d	NA	NA
Urinary Tract Infection	7-10 d*	7-27 d	28-42 d	28-42 d
Right-Sided Endocarditis	28-35 d*	7-60 d	84-98 d	61-98 d
Bacteremia with SST	NA	7-28 d	NA	NA
Bacteremia with pneumonia	NA	12-28 d	NA	NA
Bacteremia with UTI	NA	7-27 d	NA	28-42 d
Other	NA	7-60 d	NA	NA
Bacteremia with known other source	NA	7-60 d	NA	NA
Bacteremia (source unknown)	28-35 d*	7-60 d	84-98 d	61-98 d

F-U = Follow-up; LTFU = Long-term Follow-up; NA = Not applicable; SST = Skin and Soft Tissue; UTI = Urinary tract infection; d = days.

Medical Officer's Comment

These changes in evaluability windows were made for all phase 3 protocols between March and May 1999. While the windows are not unreasonable, it would have been preferable to incorporate them in the study design from the beginning.

Other changes included the following:

• The microbiological outcome of "recurrence" was dropped. It was determined that this outcome was not required in Phase III of the linezolid program.

Medical Officer's Comment

It is not clear why this change was introduced; the sponsor did not provide any evidence that patients in the phase III program could not show microbiologic recurrence.

• When Amendment 2 was prepared, a few phrases regarding evaluator blinding were inadvertently left in the text of the protocol. These phrases were deleted in Amendment 3 to reflect that research staff will not be blinded to plasma vancomycin concentrations and adjustment of dosing.

Results

Demographics and disposition

A total of 529 patients were enrolled; 243 patients were randomized to linezolid and 225 patients were randomized to vancomycin; 51 patients were randomized to an arm of the study that was discontinued and not included in this analysis. Two hundred forty-patients were treated in the linezolid arm and 220 in the vancomycin arm. Table 31.1 shows the demographics of patients enrolled in the first two arms, and Table 31.2 shows their diagnoses.

Table 31.1. Sponsor's analysis of demographics of ITT patients – Study 31					
		Linezolid	Vancomycin		
Parameters		N = 240		N = 220	P-value‡
	n	%	n	%	
Age (years)					
Total Reporting	240	100.0	220	100.0	
15-44	32	13.3	59	26.8	
45-64	78	32.5	52	23.6	
≥ 65	130	54.2	109	49.5	
Mean ± SD		63.9 ± 16.1		59.8 ±20.2	0.0157*
Weight (kg)					
Total Reporting	220	100.0	199	100.0	
Mean ± SD		73.33 ± 20.31		73.10 ± 20.31	0.9068
Race					
Total Reporting	240	100.0	220	100.0	0.1605
White	195	81.3	168	76.4	
Black	18	7.5	30	13.6	
Asian or Pacific Islander	4	1.7	5	2.3	
Mixed	23	9.6	17	7.7	
Sex					
Total Reporting	240	100.0	220	100.0	0.9934
Male	143	59.6	131	59.5	
Female	97	40.4	89	40.5	
Region					
Total Reporting	240	100.0	220	100.0	0.9212
North America	113	47.1	98	44.5	
Latin America	55	22.9	51	23.2	
Europe	68	28.3	66	30.0	
Other	4	1.7	5	2.3	

Medical Officer's Comment

The treatment arms appear comparable with respect to baseline demographics; although the mean age was higher in the linezolid group, this does not appear to be a clinically significant difference.

Table 31.2. Sponsor's analysis of diagnoses of ITT patients – Study 31					
	Linezolid		Vancomycin		
					P-Value †
	N = 240		N = 220		
Primary Source of MRSS Infection	**n**	**%**	**n**	**%**	
Pneumonia	50	20.8	49	22.3	0.7075
Pneumonia With Bacteremia	8	3.3	7	3.2	0.9272
SST Infection	122	50.8	108	49.1	0.7089
SST Infection With Bacteremia	8	3.3	5	2.3	0.4929
UTI	12	5.0	15	6.8	0.4073
UTI With Bacteremia	1	0.4	1	0.5	0.9508
Other	30	12.5	23	10.5	0.4925
Other With Bacteremia	11	4.6	15	6.8	0.2998
Bacteremia of Unknown Source	26	10.8	24	10.9	0.9792

Medical Officer's Comment

To address the issue of whether patients with MRSA skin/skin structure infections had complicated or uncomplicated infections, the medical officer analyzed the degree of involvement, medical histories, and concomitant medications. In the ITT population about two-thirds of the patients in both arms had deep or extensive involvement of skin or skin/structures, meeting the definition of complicated SSSI. Of the remainder, there were 74 patients with SSSI who had superficial involvement of the skin. Of these, 37 were recorded as having growth of MRSA as a pathogen. Of these, 12 had a history of diabetes; 6 had acute or chronic renal dysfunction; 5 had a history compatible with peripheral vascular disease; 3 had neoplastic disease; and 2 had a history of HIV infection or other immunosuppressed state. With respect to concomitant medications, 6 of the MRSA SSSI patients were receiving glucocorticosteroids or other immunosuppressive medications. Given these factors in combination with the focus of the study on hospitalized patients who would be expected to have multiple co-morbidities, the MRSA SSSI patients appear to consist primarily of subjects with complicated SSSI.

Table 31.3 shows the numbers of patients in each treatment arm completing treatment and completing follow-up, as determined by the sponsor.

Table 31.3. Sponsor's analysis of patient disposition – Study 31				
		Linezolid	Vancomycin	
Population		N = 243		N = 225
	n	%	n	%
Intent-To-Treat Patients (ITT)	240	100.0	220	100.0
Discontinued During Treatment	78	32.5	69	31.4
Completed Treatment	162	67.5	151	68.6
Discontinued During Follow-Up‡	87	36.3	75	34.1
Completed Follow-Up‡	153	63.8	145	65.9
Discontinued During Treatment and/or Follow-Up‡	97	40.4	83	37.7
Completed Treatment and Follow-Up‡	143	59.6	137	62.3

Medical Officer's Comment

Patient discontinuations appeared balanced between treatment arms.

Reasons for discontinuation, as determined by the sponsor, are shown in Table 31.4.

Table 31.4. Sponsor's analysis of reasons for discontinuation – Study 31				
		Linezolid	Vancomycin	
Reasons for Discontinuation		N = 240		N = 220
	N	%†	n	%†
Discontinued Patients	78	32.5	69	31.4
Lack of Efficacy	7	2.9	3	1.4
Death	16	6.7	13	5.9
Adverse Event (Serious)	4	1.7	3	1.4
Adverse Event (Nonserious)	5	2.1	4	1.8
Ineligible, but Started Study Medication	32	13.3	38	17.3
Protocol Noncompliance	2	0.8	2	0.9
Subject's Personal Request	2	0.8	0	-
Other‡	10	4.2	6	2.7

† Percentages are based on the total number of patients in each treatment group.
‡ Not specified

Medical Officer's Comment

Discontinuations for death or lack of efficacy were higher in the linezolid arm, but given the small numbers of patients involved, the difference is not significant. It should be kept in mind that open-label designs may have a bias against an investigational agent if the patient or physician is aware that there is an approved therapy available. Discontinuations for adverse events were similar between arms.

Evaluability

Table 31.5 shows the evaluable populations in the FDA analysis, and Table 31.6 shows reasons for nonevaluability in the FDA analysis. Patients could be unevaluable for more than one reason.

Table 31.5. FDA evaluable populations – Study 31		
Evaluation Group	**Subjects Included**	
	Linezolid	**Vancomycin**
All randomized subjects	243	225
ITT subjects	240 (100%)	220 (100%)
MITT subjects	157 (65.4%)	144 (65.5%)
FDA CE subjects	116 (48.3%)	125 (56.8%)
FDA ME subjects	59 (24.6%)	67 (30.5%)

Table 31.6. Reasons for clinical nonevaluability – FDA analysis – Study 31				
	Linezolid		**Vancomycin**	
Patient Subset/Reason for Exclusion†	**n**	**%**	**n**	**%**
Clinically Nonevaluable Patients	124	51.7	95	43.2
Negative Chest Radiograph	2	0.8	3	1.4
Prior Antibiotic Usage	13	5.4	6	2.7
Insufficient Therapy	53	22.1	47	21.4
Noncompliance With Therapy Regimen	48	20.0	24	10.0
Concomitant Antibiotics	11	4.6	3	1.4
No Post-Baseline Clinical Outcome in Evaluable Window	74	30.8	60	27.3
Indeterminate outcome	12	5.0	13	4.5

Medical Officer's Comment

Linezolid-treated patients were twice as likely to be unevaluable as vancomycin-treated patients because of noncompliance. The applicant's explanation for this was unequal application of the criterion for noncompliance; patients in the vancomycin arm who were dosed less frequently because of renal insufficiency were permitted to receive doses less frequently than every 12 hours and still be considered evaluable.

However, if the rates of noncompliance were truly comparable, one would expect more vancomycin-treated patients to be noncompliant without this adjusted application of the criterion, and equal numbers with the adjusted application. It is more likely that the difference reflects the higher number of patients who died in the linezolid arm (40 vs. 30), the slightly higher number of patients who discontinued for adverse events in the linezolid arm (9 patients vs. 7 patients), the higher numbers of patients who discontinued for 'other' reasons in the linezolid arm (10 patients v. 6 patients) and the higher number of linezolid patients who requested to leave the protocol (2 patients vs. 0 patients).

Efficacy

Table 31.7 shows clinical outcomes in the ITT and evaluable populations. The numbers of subjects listed in Table 31.7 exclude patients with missing or indeterminate outcomes, except for analyses where missing outcomes were changed to failures.

Table 31.7. FDA analysis of clinical outcome - Study 31			
Population	**Linezolid** n/N (%)	**Vancomycin** n/N (%)	**C.I.**
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 CE	93/116 (80.2%)	90/125 (72.0%)	-3.4%, 19.7%
FDA ME	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			

Medical Officer's Comment

There was a marked difference between the MITT and ME analyses, with the response rate for linezolid being lower than that for vancomycin in the MITT analysis, and higher in the ME analysis.

In interpreting these results, it is important to remember that deaths prior to follow-up were considered failures in the FDA analysis; the MITT contains patients who died prior to follow-up, while such patients are excluded from the ME analysis. Ten more patients died in the linezolid arm than in the vancomycin arm; if one excludes these patients the response rates rise in both arms, the difference between arms falls, and the confidence interval around the difference in response rates narrows.

Table 31.8 shows response rates for the FDA clinically evaluable population stratified by demographic factors.

Table 31.8. Clinical cure rates by demographic group – FDA CE population – Study 31				
Subset	**Linezolid (N=116)**	**Vancomycin (N=125)**	**95% C.I.**	**Breslow-Day's P-value**
Gender				**0.847**
Male	56/70 (80.0%)	56/77 (72.7%)	(-7.8%, 22.3%)	
Female	37/46 (80.4%)	34/48 (70.8%)	(-9.8%, 29.0%)	
Age				**0.878**
13-44 y	16/20 (80.0%)	27/35 (77.1%)	(-23.5%, 29.2%)	
45-64 y	33/41 (80.5%)	18/26 (69.2%)	(-13.4%, 35.9%)	
≥ 65 y	44/55 (80.0%)	45/64 (70.3%)	(-7.4%, 26.8%)	
Race				**0.945**
White	74/92 (80.4%)	69/95 (72.6%)	(-5.4%, 21.0%)	
Other	19/24 (79.2%)	21/30 (70.0%)	(-17.7%, 36.0%)	
Study site				**0.651**
US	33/45 (73.3%)	28/47 (59.6%)	(-7.5%, 35.0%)	
Non-US	60/71 (84.5%)	62/78 (79.5%)	(-8.6%, 18.7%)	

Medical Officer's Comment

Demographic factors did not appear to significantly affect response rate, except for study site location. There is no obvious explanation for this.

Tables 31.9 and 31.10 show clinical outcomes for patients with MRSA infection

by source of diagnosis for the MITT and ME populations

TABLE 31.9. Clinical cure rates for FDA MITT subjects by source of MRSA infection		
MRSA Infection Source	**Subjects Included**	
	Linezolid	**Vancomycin**
All sources	58/104 (55.8%)	58/88 (65.9%)
Pneumonia	12/28 (42.9%)	15/28 (53.6%)
- with bacteremia	4/8 (50.0%)	2/5 (40.0%)
Skin and soft tissue infection	36/52 (69.2%)	34/44 (77.3%)
- with bacteremia	3/7 (42.9%)	3/3 (100%)
Urinary tract infection	2/6 (33.3%)	4/4 (100%)
- with bacteremia	0/1 (0%)	0/0 (NA)
Other	6/13 (46.2%)	3/7 (42.9%)
- with bacteremia	3/6 (50.0%)	3/6 (50.0%)
Bacteremia of unknown origin	2/5 (40.0%)	2/5 (40.0%)

TABLE 31.9. Clinical cure rates for FDA ME subjects by source of MRSA infection		
MRSA Infection Source	**Subjects Included**	
	Linezolid	**Vancomycin**
All sources	40/51 (78.4%)	41/57 (71.9%)
Pneumonia	9/10 (90.0%)	12/17 (70.6%)
- With bacteremia	3/3 (100%)	2/3 (66.7%)
Skin and soft tissue infection	26/33 (78.8%)	24/33 (72.7%)
- With bacteremia	2/4 (50.0%)	2/2 (100%)
Urinary tract infection	0/0 (NA%)	2/2 (100%)
- With bacteremia	0/0 (NA)	0/0 (NA)
Other	3/6 (50.0%)	2/4 (50.0%)
- With bacteremia	1/3 (33.3%)	2/4 (50.0%)
Bacteremia of unknown origin	2/2 (100%)	1/1 (100%)

Medical Officer's Comment

As with the overall cure rates, response rates for linezolid were lower than those for vancomycin in the MITT analysis when analyzed by source of infection, and higher in the ME analysis. As discussed, this likely reflects the somewhat higher all-cause mortality rate in the linezolid arm. The differences between treatment arms are not significant for any particular class of infection, given the small numbers of patients involved; for example, a shift of outcome for two MRSA pneumonia patients in each arm would have resulted in a higher response rate for linezolid.

Table 31.11 shows response rates adjusted for co-administration of aminoglycosides in the MITT and ME analyses.

Table 31.11. Clinical outcomes stratified by aminoglyoside use		
Subset	Linezolid	Vancomycin
FDA MITT		
Aminoglycosides	14/30 (46.7%)	15/27 (55.6%)
No aminoglycosides	61/98 (62.2%)	59/85 (69.4%)
FDA ME		
Aminoglycosides	9/11 (81.8%)	9/14 (64.3%)
No aminoglycosides	36/48 (75.0%)	39/53 (73.6%)

Medical Officer's Comment

It is interesting that response rates are higher in both arms in the MITT analysis for patients who did not receive aminoglycosides versus those that did. This suggests that aminoglycosides did not contribute to the treatment effect of either linezolid or vancomycin. The lower response rates in patients treated with aminoglycosides may reflect the use of these antibiotics to treat presumed or documented Gram-negative infections. The differences between patients treated with or without aminoglycosides in the ME analysis are not significant, given the small numbers of patients in this analysis who received aminoglycosides.

Table 31.12 shows overall microbiologic outcomes.

Table 31.12. FDA analysis of microbiologic outcomes – Study 31			
	Linezolid	**Vancomycin**	**95% C.I.**
MITT	62/134 (46.3%)	62/125 (49.6%)	-16.3%, 9.6%
ME	38/59 (64.4%)	41/67 (61.2%)	-15.3%, 21.7%

Table 31.13 shows clinical outcomes for specific staphylococcal strains for the MITT and ME populations.

Table 31.13. Clinical outcomes by staphylococcal strain – Study 31		
MITT		
	Linezolid	**Vancomycin**
MRSA	58/104 (55.8%)	58/88 (65.9%)
MSSA	3/4 (75.0%)	2/3 (66.7%)
MRSE	8/14 (57.1%)	10/13 (76.9%)
ME		
	Linezolid	**Vancomycin**
MRSA	40/51 (78.4%)	41/57 (71.9%)
MSSA	0/1 (0%)	1/1 (100%)
MRSE	5/7 (71.4%)	7/9 (77.8%)

Medical Officer's Comment

The results for MRSA have been presented above (Tables 31.8 and 31.9, under All sources). There were too few isolates of MSSA to draw any conclusions. Similarly, the number of isolates of MRSE are too few to draw conclusions about the relatively efficacy of linezolid and vancomycin; furthermore, because of the lack of microbiologic and clinical specificity in the definition of bacteremia of unknown origin, the diagnosis in most cases of MRSE infection, it is not clear how many of these patients were truly infected.

Safety

Deaths, serious adverse events, discontinuations and clinical adverse events

Deaths, serious adverse events, discontinuations due to adverse events, and clinical adverse events by body system are shown in Table 31.14.

Table 31.14. Summary of deaths, SAEs, discontinuations, and clinical AEs – Study 31

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

Medical Officer's Comment

There was a higher all-cause mortality rate in the linezolid arm, as discussed earlier in the efficacy section of this review. Infection-specific mortality rates were comparable between arms. None of the deaths were directly attributable to linezolid or vancomycin. Four serious adverse events were possibly related to linezolid; pancreatitis (2 cases), renal failure (1 case), elevated liver enzymes (1 case)

Although the incidence of serious adverse events and all adverse events was comparable between treatment arms, there was a markedly higher drug-related adverse event rate in the linezolid arm, largely due to the incidence of digestive system AEs such nausea, vomiting, and diarrhea in linezolid-treated patients. Drug-related AEs responsible

for linezolid discontinuation included thrombocytopenia (2 cases) tachycardia (1 case), nausea (1 case), abnormal liver function tests (1 case).

Specific AEs and drug-related AEs are shown in Tables 31.15 and 31.16.

Table 31.15. Study-Emergent Adverse Events >2% Within Body Systems: ITT Patients

		Linezolid		Vancomycin
		N = 240		N = 220
COSTART Body System /MET	**n**	**%**	**n**	**%**
Patients With at Least One	164	68.3	136	61.8
BODY				
Abdominal Pain Generalized	2	0.8	5	2.3
Fever	7	2.9	5	2.3
Headache	7	2.9	5	2.3
Infection Bacterial NOS	8	3.3	3	1.4
Localized Edema	6	2.5	4	1.8
Localized Pain	10	4.2	7	3.2
Microbiological Test Abnormal NOS	3	1.3	5	2.3
Sepsis	11	4.6	11	5.0
Trauma	10	4.2	7	3.2
CARDIOVASCULAR				
Congestive Heart Failure	5	2.1	2	0.9
Hypotension	7	2.9	5	2.3
Thrombosis	5	2.1	0	-
DIGESTIVE				
Constipation	11	4.6	6	2.7
Diarrhea	26	10.8	9	4.1
Multiple Organ Failure	4	1.7	5	2.3
Nausea	23	9.6	10	4.5
Vomiting	15	6.3	8	3.6
HEMIC AND LYMPHATIC				
Anemia	13	5.4	8	3.6
Thrombocytopenia	5	2.1	1	0.5
METABOLIC AND NUTRITIONAL				
Healing Abnormal	1	0.4	5	2.3
NERVOUS				
Agitation	5	2.1	4	1.8
Insomnia	6	2.5	3	1.4
RESPIRATORY				
Dyspnea	7	2.9	6	2.7
Pharyngitis	2	0.8	5	2.3
Pneumonia	7	2.9	7	3.2
Respiratory Failure	8	3.3	6	2.7
SKIN				
Pruritus Non-application Site	5	2.1	6	2.7
Rash	9	3.8	8	3.6
UROGENITAL				
Infection Urinary Tract	13		16	7.3
Kidney Failure	6		4	1.8

Table 31.16. Study-Emergent Drug-Related Adverse Events by Body System: ITT Patients					
			Linezolid		Vancomycin
			N = 240		N = 220
	COSTART Body System/MET	n	%	n	%
Patients With at Least One		44	18.3	18	8.2
DIGESTIVE					
	Diarrhea	9	3.8	0	-
	Nausea	6	2.5	1	0.5

Medical Officer's Comment

As noted above, there was a much higher incidence of drug-related diarrhea in the linezolid arm. There was also a higher incidence of thrombocytopenia in the linezolid arm.

Analysis by the medical officer of potential MAOI-associated adverse events did not reveal any increased incidence of such events in the linezolid arm or association with administration of potentially interacting concomitant medications.

Laboratory findings

The sponsor analyzed changes in mean values of hematologic laboratory values over time. These appeared comparable between treatment groups for hematocrit, hemoglobin, WBC count and neutrophil count. However, mean platelet values during therapy appeared lower in the linezolid arm, although the difference in mean values did not appear clinically significant.

The sponsor also analyzed the frequency with which substantially abnormal hematologic laboratory values occurred; patients with abnormal values at baseline were considered to develop a substantial abnormality if values fell below a pre-specified threshold if the baseline was less than the lower limit of normal. The results are shown in Table 31.17.

Table 31.17. Incidence of substantially abnormal hematologic laboratory values							
Laboratory Assay	Criteria		Linezolid		Vancomycin		
		n	N	%	n	N	%
Hemoglobin	<75% of LLN	37	232	15.95	25	212	11.79
Hematocrit	<75% of LLN	27	231	11.69	15	212	7.08
Platelet Count	<75% of LLN	23	230	10.00	6	210	2.86
WBC	<75% of LLN	3	232	1.29	2	212	0.94
Neutrophils	<0.5 LLN	2	231	0.87	4	211	1.90
Eosinophils	>= 10%	9	232	3.88	16	211	7.58
Reticulocyte Count	>2 x ULN	1	231	0.43	3	209	1.44

Medical Officer's Comment

The medical officer's analysis of the hematology dataset showed a substantially higher incidence of thrombocytopenia in the linezolid arm. Of patients with normal platelet counts at baseline, thrombocytopenia developed in 25/218 (11.5%) of linezolid-treated patients but only 5/206 (2.4%) of vancomycin-treated patients. With respect to

development of severe thrombocytopenia (<50,000/mm^3), the incidence was 6/240 (2.5%) for linezolid-treated patients vs. 1/220 (0.5%) for vancomycin-treated patients. One patient with a platelet count of 63,000 at nadir had an adverse event of epistaxis; this was not considered serious or drug-related. Patients with laboratory follow-up showed resolution of thrombocytopenia.

Chemistry

The sponsor analyzed changes in mean values of chemistry laboratory values over time. These appeared comparable between treatment groups for all parameters analyzed.

The sponsor also analyzed the frequency with which substantially abnormal chemistry laboratory values occurred; patients with abnormal values at baseline were considered to develop a substantial abnormality if values rose or fell a pre-specified amount (depending on the specific chemistry parameter) above or below baseline if the baseline value abnormal. The results are shown in Table 31.18.

Table 31.18. Incidence of substantially abnormal chemistry laboratory values

Laboratory Assay	Criteria		Linezolid			Vancomycin	
		n	N	%	n	N	%
Total bilirubin	>2 x ULN	4	231	1.73	9	216	4.17
Total protein	<0.75 x LLN	11	233	4.72	2	218	0.92
Albumin	<0.75 x LLN	14	231	6.06	10	216	4.63
AST	>2 x ULN	9	231	3.90	17	215	7.91
ALT	>2 x ULN	13	231	5.63	19	216	8.80
LDH	>2 x ULN	5	233	2.15	6	218	2.75
Alkaline phosphatase	>2 x ULN	12	233	5.15	10	218	4.59
BUN	>2 x ULN	12	233	5.15	11	217	5.07
Creatinine	>2 x ULN	0	233	0.00	5	218	2.29
Sodium	<0.95 x LLN	8	233	3.43	12	218	5.50
	>1.05 x ULN	0	233	0.00	2	218	0.92
Potassium	<0.9 x LLN	7	232	3.02	5	218	2.29
	>1.1 x ULN	5	232	2.16	1	218	0.46
Chloride	<0.9 x LLN	0	233	0.00	4	218	1.83
	>1.1 x ULN	0	233	0.00	1	218	0.46
Bicarbonate	<0.9 x LLN	15	230	6.52	19	215	8.84
	>1.1 x ULN	8	230	3.48	10	215	4.65
Calcium	<0.9 x LLN	17	233	7.30	17	218	7.80
Non-fasting glucose	<0.6 x LLN	5	230	2.17	1	215	0.47
	>1.4 x ULN	33	230	14.35	27	215	12.56
Creatine kinase	>2 x ULN	3	231	1.30	4	215	1.86
Lipase	>2 x ULN	9	232	3.88	9	216	4.17
Amylase	>2 x ULN	8	233	3.43	6	218	2.75

Medical Officer's Comment

The medical officer's analysis of the chemistry laboratory database did not find any significant differences between treatment arms with respect to abnormal laboratory values. There was no evidence to suggest linezolid-associated chemical hepatitis. Two

linezolid-treated patients had significantly elevated lipase concentrations (593 U/L and 314 U/L), with a clinical diagnosis of pancreatitis.

Final conclusions

This was a randomized, comparative trial of linezolid in the treatment of patients with methicillin-resistant staphylococcal infections. An important feature of the trial was the use of specific criteria for classifying patients as having infections at defined anatomic sites. This allowed data from this trial to be used in support of the efficacy of linezolid in the treatment of nosocomial pneumonia or complicated SSSI due to MRSA. The criteria used for bacteremia of unknown origin were not very specific. Another weakness of the trial was the lack of blinding; although the IV to oral switch would have made it difficult to implement this for a given patient's entire treatment course, it could have been implemented for the IV phase of therapy. Changing the objective of the trial from study of linezolid in the treatment of MRSA infections to its clinical activity against MRSS infections also shifted the nature of the patient population, although analysis on the basis of baseline characteristics permitted focus on MRSA.

Overall cure rates were relatively low in both arms for MRSA infection (56% for linezolid vs. 66% for vancomycin). The majority of patients enrolled with MRSA infection had nosocomial pneumonia or cSSSI; in these groups of patients, response rates for linezolid were similar to those for vancomycin, although generally lower in the MITT analysis and higher in the ME analysis. The lower response rates for linezolid in the MITT analysis derived partly from a higher rate of discontinuations for lack of efficacy and partly from a higher all-cause mortality rate in the linezolid arm. There were too few patients with infection due to methicillin-susceptible S. aureus to draw any conclusions. With respect to methicillin-resistant S. epidermidis, response rates were lower in the linezolid arm than in the vancomycin arm, but again, there were too few cases to draw firm conclusions. The treatment effect of linezolid appeared to be independent of the use of aminoglycosides.

The adverse event profile of linezolid in this trial was notable for a high incidence of drug-related digestive system adverse events such as nausea and diarrhea, although these did not result in higher rates of drug-related discontinuations. There was a substantial incidence of thrombocytopenia in this trial, more so than in any other of the phase 3 trials. Of note, this trial provided for the longest duration of therapy; the applicant has provided analyses showing that the incidence of substantially abnormal platelet counts begins to differ between linezolid and all phase 3 comparators after about 16 days of treatment. The mechanism by which linezolid-associated thrombocytopenia occurs is not known. The only potential thrombocytopenia-related adverse event was epistaxis in one patient; there were no cases of gastrointestinal or cerebral hemorrhage. It is important to keep in mind that patients in this trial frequently received multiple concomitant medications (e.g., heparin) that could affect platelet count.

In summary, this study provides data supporting the efficacy of linezolid in nosocomial pneumonia and complicated SSSI due to MRSA, with an acceptable safety profile in this ill population. It does not provide evidence of efficacy against MRSE, but future studies focusing on catheter-related bloodstream infection may yield more data.