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APPLICATION NUMBER:

21-130

21-131

21-132

MEDICAL REVIEW

Medical Officer Review of Study M1260/0033

Linezolid vs. ceftriaxone/cefepodoxime for community-acquired pneumonia in inpatients

General Information

Study Title: Linezolid (PNU-100766) in the Treatment of *Streptococcus pneumoniae* Pneumonia: An Open-Label Study of Intravenously Administered Linezolid with Oral Continuation Compared with Intravenously Administered Ceftriaxone Sodium Followed by Orally Administered Cefepodoxime Proxetil.

Study Objective: To assess the efficacy (clinical and microbiological) of linezolid when compared with cephalosporin therapy in the treatment of *Streptococcus pneumoniae* pneumonia, and to assess the safety and tolerance of linezolid in the treatment of *S. pneumoniae* pneumonia.

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

Study Period: 4 January 1998 – 25 May 1999

Investigators: One hundred and ten investigators participated (North America, Latin America, Asia, and Europe [including Australia and South Africa]); see Appendix 4 of sponsor's study report for details.

Study populations

Inclusion criteria

Patients at least 13 years of age with demonstrated or presumptive *S. pneumoniae* pneumonia were eligible for enrollment if they had at least 2 of the following symptoms: cough; production of purulent sputum or a change (worsening) in character of the sputum, auscultatory findings on pulmonary exam of rales and/or pulmonary consolidation (dullness on percussion, bronchial breath sounds, or egophony); dyspnea, tachypnea, or hypoxemia, particularly if any or all of these were progressive in nature; or an organism consistent with a respiratory pathogen isolated from sputum or blood cultures. In addition, eligible patients had at least 1 of the following conditions: fever, elevated total peripheral white blood cell (WBC) count $>10,000/\text{mm}^3$, $>15\%$ immature neutrophils (bands) regardless of total peripheral WBC, or leukopenia with total WBC $<4,500/\text{mm}^3$. A chest radiograph at baseline or within 48 hours had to be consistent with a diagnosis of pneumonia. Eligible patients had to provide a respiratory, blood, or pleural fluid specimen for microbiological evaluation that proved consistent with *S. pneumoniae* infection, and eligible patients had to have a survival expectancy of at least 60 days.

Medical Officer's Comment

The inclusion criteria are consistent with IDSA guidelines for study of anti-microbials for treatment of community-acquired pneumonia and with the draft FDA guidance for this indication.

Exclusion criteria

Patients were excluded from participation in the study if they had loculated empyema or lung abscess; cystic fibrosis or known or suspected tuberculosis; known bronchial obstruction or a history of post-obstructive pneumonia; untreated hyperthyroidism, pheochromocytoma, carcinoid syndrome, or uncontrolled or untreated hypertension; known or suspected pulmonary conditions, e.g., granulomatous diseases, lung cancer, or another malignancy.

nancy metastatic to the lungs; previous antibiotic treatment for the current episode of pneumonia for more than 24 hours, unless documented to be a treatment failure (72 hours treatment and not responding); 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 received another investigational drug within 30 days prior to baseline; had previously been enrolled in any study using linezolid; had hypersensitivity to oxazolidinones or any of the excipients in either the oral or IV formulation of linezolid, or hypersensitivity to aztreonam, ceftriaxone, or cefpodoxime; had liver disease or neutropenia as defined by laboratory criteria (total bilirubin > 5 X upper limit of normal, or neutrophil count < 500 cells/mm³; or infection due to organisms known to be resistant to either of the study medication regimens before study entry.

Study methods

Treatment assignment

Patients were randomized in a 1:1 ratio to receive either of the following regimens:

- Linezolid IV 600 mg every 12 hours followed by oral linezolid 600 mg every 12 hours for 7 to 14 consecutive days
- Ceftriaxone IV 1 g every 12 hours followed by oral cefpodoxime 200 mg every 12 hours for 7 to 14 consecutive days

Some patients continued on therapy for up to 28 days with sponsor's permission.

At the discretion of the investigator, patients in both treatment groups who received at least one dose of IV study medication and demonstrated clinical improvement (i.e., improvement in body temperature, peripheral white cell count, respiration rate, sputum production and sputum quality, severity of cough, pleuritic chest pain, rigors, or appearance of chest radiograph) could be switched to oral study medication.

Patients randomized to receive linezolid were permitted to receive aztreonam IV every 8 hours for the treatment of gram-negative organisms.

Medical Officer's Comment

Aztreonam is not active against Gram-positive pathogens, and thus its use should not obscure the treatment effect of study drug or comparator in patients with pneumonia due to S. pneumoniae or S. aureus. It would, however, confound attribution of efficacy in patients with H. influenzae pneumonia or with community-acquired pneumonia of unknown etiology.

Assessments

At the baseline/screening visit a medical history was obtained and physical examination performed. A chest X-ray was obtained, along with two sets of blood cultures and sputum for Gram's stain and culture. During the inpatient treatment phase, patients were to be assessed daily; during the outpatient phase, patients were to have a study visit at Day 7 (± 2 days) and an end-of-therapy (EOT) visit (if necessary, patients could be hospitalized for the entire study). The Test-of-Cure (TOC) evaluation was conducted at the follow-up visit, 15 to 21 days after the final dose of study medication. If blood cultures were initially positive, these were to be repeated at 48-72 hours after start of therapy, and then again within 48 hours if still positive; patients with three sets of positive blood cultures were to be discontinued from the study. Patients were to have a repeat chest X-ray at the time of switch to oral therapy, at the EOT visit, and at the TOC visit.

Clinical Observations

The investigator made the following objective and subjective clinical observations at each visit and recorded the findings on the CRF:

- cough
- chills
- dyspnea
- rales/crackles
- chest pain
- decreased breath sounds
- sputum amount

Radiography

The patient's chest radiograph (posterior-anterior and lateral) obtained at baseline was to be consistent with a diagnosis of pneumonia. The chest radiograph was to be repeated within 48 hours of initiation of study treatment if the initial chest radiograph was negative. A chest radiograph was also required at the time of switching to oral treatment, at the EOT and follow-up visits, and any other time the investigator deemed necessary.

Microbiology

A respiratory specimen (i.e., from expectorated sputum, transtracheal aspirate, bronchoalveolar lavage, protected bronchial specimen brushing, or pleural fluid) was collected for Gram's stain, culture, and susceptibility testing at baseline. If a specimen was obtainable, this was to be repeated at 48 to 72 hours after initiation of treatment, at the time the patient switched from IV to oral treatment, and at the EOT and follow-up visits. A sputum specimen with <10 squamous epithelial cells and ≥ 25 leukocytes per low power field (10x objective) was deemed suitable but not required for study entry. An organism was considered predominant if examination of a Gram's stain revealed 10 oil immersion fields (100x objective) with >10 organisms per field. Gram's stain, culture, and susceptibility evaluations were performed according to National Committee for Clinical Laboratory Standards (NCCLS) approved methods. Microbiological culture evaluations were performed by the central laboratory. The local laboratory cultured all specimens for any potential respiratory pathogens and may have performed susceptibility testing (minimum inhibitory concentration test [MIC] and/or disk susceptibility) against linezolid and other antibiotics. The local laboratory was to maintain frozen samples of all isolates (at -70°C) until P&U notified the investigator that the specimens could be discarded. Data from the central laboratory were used in all analyses unless data were available only from the local laboratory.

Medical Officer's Comment

Although the normal standards for high-quality sputum specimens (<10 epithelial cells and ≥ 25 leukocytes per low power field were not required for study entry, review of case report forms showed that a significant number of positive sputum cultures were obtained from specimens meeting these criteria. Sputum specimens with these characteristics have a diagnostic specificity approaching that of specimens obtained by invasive means (George et al. Ann. Intern. Med. (1966) 65:931-42); thus, the microbiologic results obtained from cultures associated with high quality Gram's stains are reasonably predictive of the presence of true lower respiratory tract pathogens.

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

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.

Initially, the study was evaluator-blinded. The protocol was amended in June 1998 to change the study to an open-label design. Ninety-one patients were enrolled under the evaluator-blind design. According to the study report,

“[the] complexities involved in blinding patients and investigators to several drugs (investigative study medication, concomitant, and comparators) in both intravenous and oral formulations as patients moved from an inpatient to an outpatient setting rendered blinding impractical. Some measurements used to assess efficacy, such as microbiological culture, body temperature, pulse, respiration rate, and WBC count, could be interpreted objectively, whether the evaluator was blinded or not.”

Medical Officer's Comment

The sponsor's rationale for changing the study to an open-label design is reasonable. Although an open-label design could allow introduction of bias into outcome assessments, the medical officer's review of the data did not show evidence that this occurred.

The sponsor defined the following analytic populations:

ITT – Patients who received at least one dose of study medication.

MITT – ITT patients who had a pathogen isolated at baseline.

Clinically evaluable (CE) – ITT patients who met the following criteria:

- The patient had a positive chest radiograph at baseline (within 48 hours of study entry) consistent with the diagnosis of pneumonia.
- The patient did not start taking a potentially effective antibiotic before taking the first dose of study medication that continued during treatment.
- The patient did not discontinue study medication, for any reason other than lack of efficacy, before 7 days and 14 doses.
- The patient received at least 80% of the prescribed study medications without missing 2 or more consecutive doses through the first 7 days of treatment.
- The patient did not receive a potentially effective concomitant noninvestigational antibiotic for an adverse event or intercurrent illness (unless the antibiotic was given due to lack of efficacy).
- The patient had a post-baseline assessment in the follow-up analysis window (12-28 days after end of treatment) unless the investigator's assessment of clinical outcome was a failure at the end of treatment, or the patient was given an antibiotic for lack of efficacy any time during study.

Microbiologically evaluable (ME) – CE patients who had a susceptible pathogen isolated at baseline.

Medical Officer's Comment

The FDA analysis generally used the same definitions for the ITT and MITT populations. However, patients who died before follow-up (from any cause) were generally considered missing and were excluded from the sponsor's ITT and MITT analyses; such patients were considered failures in the FDA analysis. In the sponsor's analysis, patients who had no post-baseline assessment of outcome (at EOT or follow-up) were considered failures; in the FDA analysis, such patients were assigned an outcome of missing.

The definition of the FDA clinically evaluable population was similar to the sponsor's; however, patients were considered clinically evaluable in the FDA analysis if they received at least 4 doses of study medication. In addition, patients who died of their initial infection before follow-up were considered failures in the FDA clinically evaluable analysis; such patients were generally considered missing by the sponsor unless they had been started on a new antibiotic or were scored as a failure at EOT by the investigator.

The sponsor's definition of clinical evaluability did not take into account whether patients met the inclusion criteria with respect to the presence of signs or symptoms of pneumonia at baseline. However, in the sample examined by the medical reviewer, all enrolled patients met these criteria.

According to the study report, no sample size calculations for the number of evaluable patients were performed. The sponsor assumed a microbiological evaluability rate of approximately 25%; 325 patients would therefore be needed for randomization into each of the 2 treatment groups to yield 80 microbiologically evaluable patients in each treatment group.

Medical Officer's Comment

In keeping with division policy, clinical outcome was used as the primary endpoint for review of this study. The implicit projected size of 80 microbiologically evaluable patients per treatment arm is consistent with the 1992 DAIDP Points to Consider regarding clinical trials of anti-infectives for community-acquired pneumonia. The final protocol did not give a statistical basis for this sample size in terms of the study's power to exclude a difference between treatment arms, i.e., no definition of equivalence was provided in the protocol. The sponsor's study report states that a lower bound of -10% for the 95% confidence interval around the difference in response rates between treatment arms, was used to define equivalence, assuming the confidence interval includes 0. However, it is not clear that this definition was implemented prospectively, since it was not specified in the final study protocol. For review purposes, a lower bound of -10% was accepted as indicating equivalence, since this is consistent with the Points to Consider.

Changes in study conduct

The original protocol was amended 10 times during the study. The major changes in the conduct of this study, implemented with Amendment 1, as well as analysis changes implemented with Amendment 2, are described below. Additionally, several site-/country-specific changes were made; these are described in section 9.9.1 of the sponsor's study report.

Amendment 1, 10 June 1998

From the time of protocol initiation to the implementation of this amendment, 93 patients were randomized, and 654 patients were randomized under Amendment 1. Protocol design changes included the following: change from evaluator-blinded study to open-label

design; reduction of the number of patients required to meet protocol goals; reduction of the minimum number of days of required hospitalization; elimination of Day 3 evaluations and moving of Day 9 evaluations to Day 7; modification of inclusion and exclusion criteria; addition of laboratory tests (serologic testing); modification to the wording of the monoamine oxidase inhibition and nonclinical toxicology sections; modification to the definitions of Clinically Cured and Failed endpoints and serious adverse events; and elimination of the Long Term Follow-up visit.

Amendment 2, 8 March 1999

The anticipated maximum number of patients and the assumptions regarding the microbiological and clinical evaluability rates obtainable from the treatment groups was changed. The criteria for serological evaluability were expanded and clarified, and analyses of efficacy variables were added for serologically evaluable patients. A notation was added that the TOC visit window to be used for efficacy analyses was 12-28 days post-therapy. The analyses of demographic and pretreatment population characteristic variables that used only the Microbiologically Evaluable patient subset were eliminated.

Medical Officer's Comment

The change in the TOC visit window is reasonable given the pharmacokinetics of linezolid (since patients would not be expected to have significant serum concentrations of linezolid at 12 days after end of therapy) and the natural history of community-acquired pneumonia. Although no rationale for this change was given, the presumed basis was to capture data from patients who would otherwise be considered unevaluable. Use of the wider window did not appear to significantly affect response rates.

Results

Demographics and disposition

Seven hundred and fifty-nine patients were enrolled; of these, 747 received study medication. There were eight patients in the linezolid arm and 4 in the ceftriaxone arm who were randomized but not treated; in general, these patients were discontinued from the study because of withdrawal of informed consent or failure to meet inclusion criteria on further review of enrollment data. There were 381 treated patients in the linezolid arm and 366 treated patients in the ceftriaxone/cefepodoxime arm. Table 33.1 shows the demographics of the ITT patient populations, as determined by the sponsor.

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Table 33.1. Sponsor's analysis of demographics of ITT patients – Study 33

| Parameters | Linezolid N = 381 | | Ceftriaxone/Cefpodoxime N = 366 | | P-value |
|---------------------------|----------------------|-------|------------------------------------|-------|---------|
| | n | % | n | % | |
| Age (years) | | | | | |
| Total Reporting | 381 | 100.0 | 366 | 100.0 | |
| < 18 | 8 | 2.1 | 5 | 1.4 | |
| 18-44 | 120 | 31.5 | 112 | 30.6 | |
| 45-64 | 110 | 28.9 | 113 | 30.9 | |
| ≥ 65 | 143 | 37.5 | 136 | 37.2 | |
| Mean ± SD | 54.6 ± 20.1 | | 54.7 ± 19.2 | | 0.9347 |
| Weight (kg) | | | | | |
| Total Reporting | 373 | 100.0 | 359 | 100.0 | |
| Not Reported | 8 | 2.1 | 7 | 1.9 | |
| Mean ± SD | 70.30 ± 17.60 | | 68.86 ± 19.15 | | 0.2887 |
| Race | | | | | |
| Total Reporting | 381 | 100.0 | 366 | 100.0 | 0.7665 |
| White | 246 | 64.6 | 241 | 65.8 | |
| Black | 46 | 12.1 | 44 | 12.0 | |
| Asian or Pacific Islander | 34 | 8.9 | 37 | 10.1 | |
| Mixed | 55 | 14.4 | 44 | 12.0 | |
| Sex | | | | | |
| Total Reporting | 381 | 100.0 | 366 | 100.0 | 0.4476 |
| Male | 228 | 59.8 | 209 | 57.1 | |
| Female | 153 | 40.2 | 157 | 42.9 | |
| Region | | | | | |
| Total Reporting | 381 | 100.0 | 366 | 100.0 | 0.6947 |
| North America | 135 | 35.4 | 142 | 38.8 | |
| Latin America | 99 | 26.0 | 83 | 22.7 | |
| Europe | 113 | 29.7 | 107 | 29.2 | |
| Other | 34 | 8.9 | 34 | 9.3 | |

†P-value is based on a one-way Analysis of Variance for age and weight and on χ^2 test for race, sex and region.

Table 33.2 shows the numbers of patients in each treatment arm completing treatment and completing follow-up, as determined by the sponsor.

Table 33.2. Sponsor's analysis of patient disposition – Study 33

| Randomized population | Linezolid | | Ceftriaxone/Cefpodoxime | |
|--|-----------|-------|-------------------------|-------|
| | N = 389 | | N = 370 | |
| | n | % | n | % |
| Intent-to-treat patients (ITT) | 381 | 100.0 | 366 | 100.0 |
| Discontinued during treatment | 61 | 16.0 | 65 | 17.8 |
| Completed treatment | 320 | 84.0 | 301 | 82.2 |
| Discontinued during follow-up | 53 | 13.9 | 66 | 18.0 |
| Completed follow-up | 328 | 86.1 | 300 | 82.0 |
| Discontinued during treatment and/or follow-up | 75 | 19.7 | 79 | 21.6 |
| Completed treatment and follow-up | 306 | 80.3 | 287 | 78.4 |

Medical Officer's Comment

Patient disposition appeared to be balanced between treatment arms.

The frequencies of reasons for the discontinuation of treatment for the ITT population, as determined by the sponsor, are provided in Table 33.3.

Table 33.3. Sponsor's analysis of reasons for discontinuation – Study 33

| Reasons for Discontinuations | Linezolid | | Ceftriaxone/Cefpodoxime | |
|--|-----------|------|-------------------------|------|
| | N = 381 | | N = 366 | |
| | n | % | n | % |
| Discontinued patients | 61 | 16.0 | 65 | 17.8 |
| Lack of efficacy | 14 | 3.7 | 26 | 7.1 |
| Death | 4 | 1.0 | 4 | 1.1 |
| AE (serious) | 8 | 2.1 | 14 | 3.8 |
| AE (nonserious) | 11 | 2.9 | 2 | 0.5 |
| Ineligible, but started study medication | 8 | 2.1 | 7 | 1.9 |
| Protocol noncompliance | 3 | 0.8 | 3 | 0.8 |
| Subject's personal request | 4 | 1.0 | 1 | 0.3 |
| Lost to follow-up | 4 | 1.0 | 2 | 0.5 |
| Other | 5 | 1.3 | 6 | 1.6 |

Similar percentages of ITT patients discontinued treatment in the linezolid (16.0%, 61/381) and ceftriaxone/cefpodoxime (17.8%, 65/366) treatment groups. The most common reason for discontinuation in both groups was lack of efficacy. A greater percentage of patients in the ceftriaxone/cefpodoxime group (7.1%, 26/366) discontinued treatment due to lack of efficacy than in the linezolid group (3.7%, 14/381). While similar percentages of ITT patients in both groups discontinued treatment due to serious or nonserious adverse events, a greater percentage of patients in the ceftriaxone/cefpodoxime treatment group discontinued treatment due to serious adverse events, and a greater percentage of patients in the linezolid treatment group discontinued due to nonserious adverse events. There were 4 deaths during the treatment period in each treatment group.

Evaluability

Table 33.4 shows the evaluable populations in the FDA analysis, and Table 33.5 shows reasons for nonevaluability in the FDA analysis. Patients could be unevaluable for more than one reason.

| Table 33.4. FDA evaluable populations – Study 33 | | |
|---|--------------------------|-------------------------------------|
| Evaluation Group | Subjects Included | |
| | Linezolid | Ceftriaxone/ Cefpodoxime |
| All randomized subjects | 389 | 370 |
| ITT subjects | 381 (100%) | 366 (100%) |
| MITT subjects | 128 (33.6%) | 126 (34.4%) |
| Sponsor CE subjects | 276 (72.4%) | 258 (70.5%) |
| Sponsor ME subjects | 90 (23.6%) | 95 (26.0%) |
| FDA CE subjects | 285 (74.8%) | 274 (74.9%) |
| FDA ME subjects | 92 (24.1%) | 99 (27.0%) |

| Table 33.5. Reasons for clinical nonevaluability – FDA analysis – Study 33 | | | | |
|---|-------------------------------|----------|---|----------|
| Patient Subset/Reason for Exclusion | Linezolid N = 381 | | Ceftriaxone/ Cefpodoxime N = 366 | |
| | n | % | n | % |
| | Total nonevaluable population | 96 | 25.2 | 92 |
| Negative chest radiograph | 4 | 1.0 | 3 | 0.8 |
| Prior antibiotic usage | 3 | 0.8 | 8 | 2.2 |
| Insufficient therapy | 44 | 11.5 | 31 | 8.5 |
| Noncompliance with therapy regimen | 38 | 10.0 | 32 | 8.4 |
| Concomitant antibiotics | 6 | 1.6 | 9 | 2.5 |
| Lost to follow-up | 53 | 13.9 | 54 | 14.8 |
| Indeterminate outcome | 6 | 1.6 | 7 | 1.9 |

Medical Officer's Comment

The FDA clinically evaluable and microbiologically evaluable populations were similar in size to the sponsor's. Relatively few patients were excluded for baseline ineligibility. There were more patients excluded for insufficient therapy (i.e., failure to receive at least four doses) in the linezolid arm than in the comparator arm; this may reflect the higher percentage of patients discontinued for nonserious adverse events in the linezolid arm. The percentages of patients lost to follow-up or with indeterminate outcomes at follow-up were similar between treatment arms.

Efficacy

Table 33.6 shows clinical outcomes in the ITT and evaluable populations. The numbers of subjects listed in Table 33.6 exclude patients with missing or indeterminate outcomes, except for analyses where missing outcomes were changed to failures.

| FDA-Defined Study Population | Linezolid | | Ceftriaxone/cefepodoxime | | 95% C.I. |
|------------------------------|-----------|-------------------|--------------------------|-------------------|---------------|
| | N | Success Rates (%) | N | Success Rates (%) | |
| ITT | 330 | 80.9 | 313 | 77.0 | (-2.7, 10.5) |
| ITT (missing as failure) | 381 | 70.1 | 366 | 65.9 | (-2.7, 11.2) |
| MITT | 109 | 83.5 | 117 | 76.9 | (-4.7, 17.8) |
| MITT (missing as failure) | 128 | 71.1 | 126 | 71.4 | (-12.3, 11.6) |
| FDA CE | 285 | 86.3 | 274 | 82.1 | (-2.2, 10.6) |
| FDA ME | 92 | 87.0 | 99 | 81.8 | (-6.2, 16.4) |

Response rates in the FDA analyses were somewhat lower for both treatment arms than in the sponsor's analyses. The 95% confidence intervals around the difference in response rates between treatment arms were similar in both the FDA analysis and the sponsor's analysis.

Medical Officer's Comment

The results are consistent with equivalence between linezolid and ceftriaxone/cefepodoxime for the different analytic populations. The lower rates in the ITT analyses result largely from patients who were therapeutic failures but who received less than four doses of study drug and therefore were excluded from the CE and ME analyses. Analyses that counted patients with missing outcomes as failures yielded lower response rates, as expected. These analyses should be interpreted with caution, since there were a significant number of patients with missing outcomes, and many of these patients may not have been true therapeutic failures; the actual response rates that would have been obtained with complete follow-up would be likely to be higher.

Patients who died and whose death was assessed by the medical reviewer as being due to their initial infection were considered therapeutic failures. The mortality rate due to the initial infection was 4/381 (1.1%) in the linezolid arm and 6/366 (1.6%) in the ceftriaxone arm.

Table 33.7 shows clinical cure rates stratified by demographic factors.

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| Table 33.7. Clinical cure rates by demographic group – FDA CE population – Study 33 | | | | |
|--|----------------------|--|----------------|------------------------------|
| Subset | Linezolid (N=285) | Ceftriaxone/ Cefpodoxime (N=274) | 95% C.I. | Breslow- Day's P-value |
| Gender | | | | 0.913 |
| Male | 142/169 (84.0%) | 118/149 (79.2%) | (-4.3%, 14.0%) | |
| Female | 104/116 (89.7%) | 107/125 (85.6%) | (-5.1%, 13.2%) | |
| Age | | | | 0.764 |
| 13~44 yrs | 84/93 (90.3%) | 73/85 (85.9%) | (-6.2%, 15.1%) | |
| 45~64 yrs | 76/85 (89.4%) | 70/84 (83.3%) | (-5.4%, 17.6%) | |
| ≥ 65 yrs | 86/107 (80.4%) | 82/105 (78.1%) | (-9.6%, 14.1%) | |
| Race | | | | 0.454 |
| White | 155/184 (84.2%) | 149/183 (81.4%) | (-5.4%, 11.1%) | |
| Other | 91/101 (90.1%) | 76/91 (83.5%) | (-4.1%, 17.2%) | |
| Study site | | | | 0.711 |
| US | 75/87 (86.2%) | 77/96 (80.2%) | (-5.9%, 17.9%) | |
| Non-US | 171/198 (86.4%) | 148/178 (83.2%) | (-4.6%, 11.0%) | |

Medical Officer's Comment

Response rates appeared somewhat higher in women than in men, although the difference does not appear statistically significant. As would be expected from studies of prognostic factors for community-acquired pneumonia, response rates were lower in patients aged 65 years or older, but were still consistent with equivalence. Response rates were higher in non-white individuals; this population was composed primarily of black individuals. Response rates did not differ significantly when stratified by U.S. versus non-U.S. sites, suggesting that differences in hospitalization practices in different continents did not affect the outcome.

Table 33.8 shows clinical outcomes for clinically evaluable patients with baseline characteristics predicting a worse outcome (Fine *et al.* Am. J. Med (1990) 88:5). Similar results were obtained for the corresponding analysis of the MITT patient population

| Table 33.8. Clinical cure rates by baseline characteristics – FDA CE population – Study 33 | | |
|---|----------------------|--|
| Subset | Linezolid (N=285) | Ceftriaxone/ Cefpodoxime (N=274) |
| Age >50 | 146/171 (85.4%) | 128/160 (80.0%) |
| Bacteremia | 28/31 (92.3%) | 16/26 (61.5%) |
| Multilobar Pneumonia | 14/15 (93.3%) | 5/7 (71.4%) |
| Bilateral Pneumonia | 9/10 (90.0%) | 5/7 (71.4%) |
| Hypotension | 17/22 (77.3%) | 25/35 (71.4%) |
| Tachypnea (RR >30) | 23/29 (79.3%) | 23/31 (74.2%) |
| History of cancer | 75/87 (86.2%) | 55/70 (78.6%) |
| [BUN] > 7mM | 60/75 (80.0%) | 44/63 (69.8%) |
| HIV infection | 7/7 (100%) | 5/6 (83.3%) |

Medical Officer's Comment

The factors analyzed in Table 33.8 have been shown to be associated with an increased risk of mortality; it is reassuring that response rates in the linezolid arm were equal to or higher than those in the comparator arm for patients with such factors. It would be preferable to stratify patients for analysis using prospectively identified predictors of poor outcome (Fine et al. *New Engl. J. Med.* (1997) 336:243-50); the data collected in this study are not complete enough to make use of such prediction rules.

Because patients could receive concomitant aztreonam, which could have contributed to linezolid's treatment effect in patients without a documented Gram-positive pneumonia, response rates were analyzed in the clinically evaluable population according to aztreonam usage. There were 160 linezolid-treated patients who received aztreonam and 3 ceftriaxone-treated patients. The imbalance in the use of aztreonam is attributable to the differences in microbiologic spectra between linezolid and ceftriaxone; ceftriaxone is active against Gram-negative bacteria causing community-acquired pneumonia (e.g., *H. influenzae*), concomitant use of aztreonam would not normally be required or expected in the ceftriaxone arm. Linezolid-treated patients who received aztreonam had a cure rate of 136/160 (85.0%) v. 2/3 (66.7%) for ceftriaxone-treated patients. For patients who did not receive aztreonam, the response rates were 110/125 (88.0%) for linezolid-treated patients v. 223/271 (82.3%) for ceftriaxone-treated patients.

Table 33.9 shows microbiologic outcomes in the MITT and ME populations.

| FDA-Defined Study Population | Linezolid | | Ceftriaxone/cefepodoxime | | 95% C.I. |
|------------------------------|-----------|-------------------|--------------------------|-------------------|--------------|
| | N | Success Rates (%) | N | Success Rates (%) | |
| MITT | 110 | 82.7 | 118 | 75.4 | (-4.1, 18.7) |
| FDA ME | 92 | 87.0 | 99 | 81.8 | (-6.2, 16.4) |

Medical Officer's Comment

Microbiological responses were largely driven by clinical responses, since the majority of cured patients were no longer producing sputum at follow-up; a microbiological outcome of presumed eradication was inferred for such patients.

Table 33.10 shows clinical outcomes for microbiologically evaluable patients by specific pathogens.

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| Table 33.10. Clinical cure rates by pathogen – FDA ME population | | |
|--|-------------------|--|
| Subset | Linezolid (N=109) | Ceftriaxone/ Cefpodoxime (N=117) |
| <i>S. pneumoniae</i> | 63/73 (86.3%) | 62/73 (84.9%) |
| <i>S. pneumoniae</i> bacteremia | 27/30 (90.0%) | 15/24 (62.5%) |
| Penicillin-resistant <i>S. pneumoniae</i> | 3/5 (60.0%) | 2/2 (100.0%) |
| <i>Staphylococcus aureus</i> | 18/21 (85.7%) | 13/19 (68.4%) |
| <i>S. aureus</i> bacteremia | 1/1 (100.0%) | 1/2 (50%) |
| MRSA | 1/1 (100.0%) | 0/0 (–) |
| <i>H. influenzae</i> | 5/8 (62.5%) | 10/12 (83.3%) |
| <i>H. influenzae</i> without use of aztreonam | 4/7 (57.1%) | 9/10 (90.0%) |

Medical Officer's Comment

The cure rate in the linezolid arm for pneumococcal pneumonia was comparable to that for ceftriaxone. The subset of patients with pneumococcal bacteremia is particularly interesting. The majority of cases of pneumococcal pneumonia are diagnosed by Gram's stain and culture of sputum, but interpretation of the results of these tests is always problematic, given that *S. pneumoniae* may colonize the oropharynx in up to 50% of individuals (Hendley et al. *J. Infect. Dis.* (1975) 132:55-61). Growth of pneumococcus may therefore reflect colonization rather than infection by this organism. In contrast, patients with pneumococcal bacteremia show clear evidence of invasive disease; thus the cure rate for linezolid-treated patients with pneumococcal bacteremia in Study 33 provides strong evidence for the efficacy of linezolid in pneumococcal pneumonia. Although the response rate for cases associated with pneumococcal bacteremia was considerably higher than for ceftriaxone, it is unclear that this is a real difference – the response rate for ceftriaxone-treated patients with pneumococcal bacteremia is lower than one would expect on the basis of published data (Pallares et al. *New Engl. J. Med* (1995) 333:474-80).

With respect to penicillin-resistant isolates of *S. pneumoniae* (defined as those isolates with a penicillin MIC ≥ 2 $\mu\text{g/mL}$), there were relatively few cases of pneumonia due to PRSP in either arm, and none of these were associated with bacteremia, raising the issue of how many of these isolates represent true pathogens. The cure rate for linezolid in the few cases where PRSP was isolated was not impressive. Given the lack of confirmatory evidence from cases involving definite invasive disease due to PRSP (e.g., cases with concurrent bacteremia), these data do not provide convincing evidence for efficacy against PRSP.

The cure rates for cases where *Staphylococcus aureus* was isolated are misleading, since it is doubtful that the majority of these cases represent true staphylococcal pneumonia. Although *S. aureus* is a well-recognized, albeit unusual, cause of community-acquired pneumonia, accounting for 3-5% of cases (Bartlett and Mundy, *New Engl. J. Med.* (1995) 333:1618-24), it is also a common colonizer of the oropharynx. Thus, the distinction between colonization of the respiratory tract by *S. aureus* and infection by this organism is important.

To determine the likelihood that linezolid-treated patients who had a positive culture for *S. aureus* did in fact have staphylococcal pneumonia, the medical reviewer examined clinical, microbiologic, and radiographic data for such patients. There were 28 patients in the linezolid arm in the MITT population who had *S. aureus* isolated. The mean age of these

patients was 50.6 ± 20.6 years, which was similar to the mean age (54.6 years) for linezolid-treated patients as a whole. This is significant because elderly patients tend to be at higher risk for staphylococcal pneumonia. One patient had a positive blood culture for *S. aureus* in the setting of clinical signs and symptoms of pneumonia, which was accepted as definitive evidence of invasive staphylococcal disease involving the lungs. Of the others, 13/27 were afebrile at baseline and only 6/27 had a respiratory rate greater than 30. None had a history of recent influenza (either documented or suspected). With respect to microbiologic data, 10/27 patients did not have adequate Gram's stains of sputum specimens (defined as ≤ 10 epithelial cells and ≥ 25 leukocytes per low-power field, with either Gram-positive cocci or no organism predominating; only 10/27 showed predominantly Gram-positive organisms on Gram's stain; and only 9/27 grew *S. aureus* in pure culture. Only two patients with an adequate Gram stain showing predominantly Gram-positive cocci had growth of *S. aureus* in pure culture. Finally, although there are no typical radiographic signs of staphylococcal pneumonia, patients with this infection frequently have multiple areas of consolidation or abscesses (Rebhan and Edwards, *Can. Med. Assoc. J.* (1960) 82:513). Of the patient diagnosed with *S. aureus* pneumonia, 14/27 had involvement of only one lobe, and none had reports indicating air-fluid levels or other evidence of abscess formation.

With respect to methicillin-resistant *S. aureus* pneumonia, there were only three cases of infection with this organism in the MITT patient population, and none of these patients had an adequate sputum Gram stain obtained. In addition, it is worth noting that CAP due to this organism is a very uncommon entity; the epidemiologic and microbiologic features of CAP due to MRSA may be quite dissimilar to those of nosocomial MRSA infections (Herold et al. *J. Am. Med. Assoc.* (1998) 279:593-8). Thus, these data do not demonstrate efficacy against CAP due to MRSA.

Taken together these results suggest that many of the patients classified as having staphylococcal pneumonia actually were infected by another pathogen. While it is possible that some of these patients had polymicrobial infections, this is more typical of hospital-acquired pneumonia. Thus, these results, on their own, are insufficient to establish efficacy for community-acquired pneumonia due to *S. aureus*.

Linezolid has only modest activity against *H. influenzae* ($MIC_{90} = 8 \mu\text{g/mL}$); the low clinical success rate in patients who had this organism isolated is therefore to be expected.

Safety

Deaths, serious adverse events, and clinical adverse events

Deaths, serious adverse events, discontinuations due to adverse events, and clinical adverse events by body system are shown in Table 33.11.

| Table 33.11. Summary of deaths, SAEs, discontinuations, and clinical AEs – Study 33 | | | |
|--|------------------------------|---|-----------------------------|
| Safety Outcomes | Linezolid (N=381) | Ceftriaxone/ Cefpodoxime (N=366) | Fisher's P-value |
| Deaths | 15 (3.9%) | 19 (5.2%) | 0.484 |
| Infection-Related Deaths | 4 (1.1%) | 6 (1.6%) | 0.539 |
| Serious AEs | 51 (13.4%) | 54 (14.8%) | 0.600 |
| Discontinuation Due To AEs | 23 (6.0%) | 24 (6.6%) | 0.880 |
| Discontinuation Due To Drug related AEs | 9 (2.4%) | 1 (0.3%) | 0.021 |
| With Any AE | 218 (57.2%) | 200 (54.6%) | 0.507 |
| Digestive | 106 (27.8%) | 82 (22.4%) | 0.092 |
| Body | 87 (22.8%) | 76 (20.8%) | 0.535 |
| Respiratory | 51 (13.4%) | 74 (20.2%) | 0.014 |
| Skin | 44 (11.5%) | 27 (7.4%) | 0.061 |
| Nervous | 41 (10.8%) | 38 (10.4%) | 0.906 |
| Cardiovascular | 31 (8.1%) | 31 (8.5%) | 0.895 |
| Metabolic and Nutritional | 26 (6.8%) | 22 (6.0%) | 0.658 |
| Urogenital | 26 (6.8%) | 12 (3.3%) | 0.030 |
| Special Senses | 12 (3.1%) | 4 (1.1%) | 0.075 |
| Hemic and Lymphatic | 9 (2.4%) | 8 (2.2%) | 1.000 |
| Musculo-Skeletal | 5 (1.3%) | 4 (1.1%) | 1.000 |
| With Drug Related AE | 81 (21.3%) | 41 (11.2%) | < 0.001 |
| Digestive | 53 (13.9%) | 19 (5.2%) | < 0.001 |
| Body | 18 (4.7%) | 5 (1.4%) | 0.010 |
| Skin | 13 (3.4%) | 5 (1.4%) | 0.093 |
| Urogenital | 11 (2.9%) | 3 (0.8%) | 0.056 |
| Hemic and Lymphatic | 4 (1.0%) | 3 (0.8%) | 1.000 |
| Cardiovascular | 4 (1.0%) | 2 (0.5%) | 0.687 |
| Special Senses | 4 (1.0%) | 0 (0%) | 0.124 |
| Metabolic and Nutritional | 2 (0.5%) | 4 (1.1%) | 0.443 |
| Nervous | 2 (0.5%) | 0 (0%) | 0.500 |
| Respiratory | 0 (0%) | 2 (0.5%) | 0.240 |

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. The mortality rates for death to the primary infection were comparable between treatment arms. There was a higher incidence of discontinuations due to drug-related adverse events in the linezolid treatment arm. This appears to be largely due to the increased incidence of drug-related digestive events such as nausea and vomiting; 1.3% of linezolid treated patients discontinued treatment for drug-related digestive AEs, versus 0% of ceftriaxone-treated patients. It is worth noting, however, that the drug-related AE discontinuation rate was 2.4% in the linezolid arm.

Most serious adverse events were not drug-related. There were three drug-related SAEs in the linezolid arm (hypertension, thrombocytopenia, and a transient ischemic attack), and one in the ceftriaxone arm (pseudomembranous colitis). All of the linezolid patients with drug-related SAEs had comorbid conditions or were receiving concomitant medications that could have contributed to the SAE.

Specific adverse events and drug-related adverse events are shown in Tables 33.12 and 33.13, respectively.

| Table 33.12. Study-Emergent Adverse Events >2% Within Body Systems: ITT | | | | |
|---|------------------------------|----------|--|----------|
| | Linezolid N = 381 | | Ceftriaxone/Cefpodoxime N = 366 | |
| COSTART Body System/MET | n | % | n | % |
| Patients With at Least One | 218 | 57.2 | 200 | 54.6 |
| DIGESTIVE | | | | |
| Diarrhea | 42 | 11.0 | 33 | 9.0 |
| Nausea | 24 | 6.3 | 17 | 4.6 |
| Vomiting | 19 | 5.0 | 7 | 1.9 |
| Monilia Oral | 14 | 3.7 | 3 | 0.8 |
| Liver Function Tests Abnormal | 10 | 2.6 | 5 | 1.4 |
| NOS | | | | |
| Constipation | 8 | 2.1 | 8 | 2.2 |
| BODY | | | | |
| Headache | 28 | 7.3 | 21 | 5.7 |
| Chest Pain | 7 | 1.8 | 9 | 2.5 |
| Fever | 7 | 1.8 | 12 | 3.3 |
| Back Pain | 2 | 0.5 | 9 | 2.5 |
| SKIN | | | | |
| Rash | 10 | 2.6 | 12 | 3.3 |
| Herpes Simplex Dermatitis | 8 | 2.1 | 4 | 1.1 |
| NERVOUS | | | | |
| Insomnia | 9 | 2.4 | 12 | 3.3 |
| Anxiety | 8 | 2.1 | 2 | 0.5 |
| UROGENITAL | | | | |
| Moniliasis Vaginal | 9 | 2.4 | 2 | 0.5 |
| RESPIRATORY | | | | |
| Pneumonia | 5 | 1.3 | 14 | 3.8 |
| Dyspnea | 3 | 0.8 | 11 | 3.0 |
| Respiratory Failure | 3 | 0.8 | 8 | 2.2 |

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Table 33.13. Study-Emergent Drug-Related Adverse Events by Body System: ITT

| COSTART Body System/MET | Linezolid N = 381 | | Ceftriaxone/Cefpodoxime N = 366 | |
|-----------------------------------|----------------------|------|------------------------------------|------|
| | n | % | n | % |
| Patients With at Least One | 81 | 21.3 | 41 | 11.2 |
| DIGESTIVE | | | | |
| Diarrhea | 17 | 4.5 | 11 | 3.0 |
| Nausea | 13 | 3.4 | 5 | 1.4 |
| Monilia Oral | 10 | 2.6 | 2 | 0.5 |
| Liver Function Tests Abnormal NOS | 9 | 2.4 | 1 | 0.3 |
| UROGENITAL | | | | |
| Moniliasis Vaginal | 8 | 2.1 | 2 | 0.5 |

Medical Officer's Comment

The increased incidence of drug-related oral and vaginal candidiasis in linezolid-treated patients is somewhat surprising, given the narrow spectrum of linezolid; presumably this reflects the activity of linezolid against vaginal enterococci and against oral streptococci. The incidence of specific drug-related digestive system adverse events was generally higher in the linezolid arm, consistent with the incidences in Table 33.11.

Because linezolid is an inhibitor of monoamine oxidase (MAO), it may interact with indirect sympathomimetic amines to cause hypertensive crisis or with serotonergic drugs (e.g., dextromethorphan) to cause serotonin syndrome (hyperpyrexia, tremors, cognitive dysfunction). To address this issue, the medical reviewer independently examined the adverse event database, using techniques developed by Dr. Ana Szarfman of the Office of Biometrics. The analysis was performed using CrossGraphs 2.0.4 [REDACTED]. This analysis did not show any increased incidence of signs or symptoms in this study that would be expected with hypertensive crisis or serotonin syndrome, nor did there appear to be any increased incidence of adverse events in patients receiving medications that might interact with MAO inhibitors. This agreed with a similar analysis performed by the sponsor.

Laboratory findings

Hematology

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 33.14.

Table 33.14. Incidence of substantially abnormal hematologic laboratory values

| Laboratory Assay | Criterion | Linezolid | | Ceftriaxone/Cefpodoxime | |
|--|-------------|-----------|------|-------------------------|------|
| | | n/N | % | n/N | % |
| Hemoglobin (g/dL) | <75% of LLN | 13/353 | 3.68 | 8/336 | 2.38 |
| Hematocrit (%) | <75% of LLN | 7/353 | 1.98 | 5/336 | 1.49 |
| RBC ($\times 10^6/\text{mm}^3$) | <75% of LLN | 6/352 | 1.70 | 9/336 | 2.68 |
| Platelet Count ($\times 10^3/\text{mm}^3$) | <75% of LLN | 6/351 | 1.71 | 4/334 | 1.20 |
| WBC ($\times 10^3/\text{mm}^3$) | <75% of LLN | 7/353 | 1.98 | 7/336 | 2.08 |
| Neutrophils ($\times 10^3/\text{mm}^3$) | <0.5 LLN | 1/330 | 0.30 | 4/314 | 1.27 |
| Eosinophils (%) | >10% | 25/350 | 7.14 | 11/334 | 3.29 |
| Reticulocyte Count (%) | >2 x ULN | 0/350 | - | 1/332 | 0.30 |

Medical Officer's Comment

These results appear comparable between treatment arms; increases in eosinophils were more frequent in the linezolid arm, but the clinical significance of this is uncertain, since this represents relative rather absolute eosinophilia.

This is essentially a frequency shift table; the criteria used to define 'substantially abnormal' are arbitrary but are clinically reasonable. However, it would be preferable to use a recognized grading system for hematologic toxicity such as the WHO criteria or the National Cancer Institute's Common Toxicity Criteria.

Because such shift tables convert continuous data into a dichotomous form (i.e., substantially abnormal vs. not substantially abnormal), significant amounts of information are lost. To address this problem, the medical reviewer independently examined laboratory data, using CrossGraphs 2.0.4. This allowed an independent examination of not only the frequency of changes in hematologic laboratory values but also an assessment of the magnitude of these changes

This analysis showed no significant difference between linezolid and ceftriaxone in the frequency or magnitude of abnormally low laboratory values in patients with normal values at baseline for hemoglobin (33/369 (8.9%) v. 21/350 (6.0%)), white blood cells (18/379 (4.7%) v. 15/363 (4.1%)), or neutrophils (25/379 (6.6%) v. 19/366 (5.2%)). The same was true for patients with abnormally low values at baseline.

Analysis of platelet counts did reveal differences between the treatment groups. Among patients with a normal platelet count at baseline, there was a higher incidence of thrombocytopenia in the linezolid arm than in the ceftriaxone arm (12/353 (3.4%) vs. 0.9%). One patient each in the linezolid arm and in the ceftriaxone arm had decreases in platelet counts to less than $50,000/\text{mm}^3$ (grade III thrombocytopenia, NCI Common Toxicity Criteria). The patient in the linezolid arm had a history of idiopathic thrombocytopenic purpura and had a decreased platelet count at baseline. Thrombocytopenia resolved in all 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.

Chemistry

The sponsor analyzed changes in mean values of chemistry laboratory values over time. These appeared comparable between treatment groups for all parameters analyzed except for serum concentrations of alanine aminotransferase (ALT); for this parameter, mean

serum ALT concentrations were higher in the linezolid treatment arm, although the peak mean value was less than 50 U/L (see Figure 33.2). However, mean ALT concentrations returned to the normal range by follow-up in both arms. There were no cases of hyperbilirubinemia associated with elevated transaminase concentrations.

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 33.15.

Table 33.15. Incidence of substantially abnormal chemistry laboratory values

| Laboratory Assay | Criteria | Linezolid | | Ceftriaxone/Cefpodoxime | |
|----------------------------|-------------|-----------|-------|-------------------------|------|
| | | n/N | % | n/N | % |
| Total Bilirubin (mg/dL) | >2 x ULN | 0/356 | - | 2/338 | 0.59 |
| Total Protein (g/dL) | <0.75 x LLN | 2/357 | 0.56 | 0/340 | - |
| | >1.5 x ULN | 0/357 | - | 1/340 | 0.29 |
| Albumin (g/dL) | <0.75 x LLN | 13/356 | 3.65 | 13/338 | 3.85 |
| AST (U/L) | >2 x ULN | 19/335 | 5.67 | 20/319 | 6.27 |
| ALT (U/L) | >2 x ULN | 36/334 | 10.78 | 29/317 | 9.15 |
| LDH (U/L) | >2 x ULN | 4/355 | 1.13 | 2/338 | 0.59 |
| Alkaline Phosphatase (U/L) | >2 x ULN | 8/356 | 2.25 | 7/340 | 2.06 |
| BUN (mg/dL) | >2 x ULN | 4/357 | 1.12 | 3/339 | 0.88 |
| Creatinine (mg/dL) | >2 x ULN | 1/357 | 0.28 | 2/340 | 0.59 |
| Sodium (mEq/L) | <0.95 x LLN | 6/355 | 1.69 | 1/338 | 0.30 |
| | >1.05 x ULN | 1/355 | 0.28 | 1/338 | 0.30 |
| Potassium (mEq/L) | <0.9 x LLN | 4/354 | 1.13 | 3/338 | 0.89 |
| | >1.1 x ULN | 5/354 | 1.41 | 1/338 | 0.30 |
| Chloride (mEq/L) | <0.9 x LLN | 2/355 | 0.56 | 1/338 | 0.30 |
| Bicarbonate (mEq/L) | <0.9 x LLN | 13/353 | 3.68 | 12/336 | 3.57 |
| | >1.1 x ULN | 6/353 | 1.70 | 6/336 | 1.79 |
| Calcium (mg/dL) | <0.9 x LLN | 13/357 | 3.64 | 7/340 | 2.06 |
| Nonfasting Glucose (mg/dL) | <0.6 x LLN | 2/356 | 0.56 | 0/338 | - |
| | >1.4 x ULN | 28/356 | 7.87 | 26/338 | 7.69 |
| Creatine Kinase (U/L) | >2 x ULN | 15/354 | 4.24 | 6/335 | 1.79 |
| Lipase (U/L) | >2 x ULN | 12/353 | 3.40 | 12/336 | 3.57 |
| Amylase (U/L) | >2 x ULN | 9/357 | 2.52 | 9/339 | 2.65 |

Medical Officer's Comment

The medical officer conducted an independent review of chemistry laboratory values for hepatic, pancreatic, and renal parameters, similar to that performed for hematologic laboratory values. This review focused on patients with normal chemistry values at baseline who showed an increase to 2x the upper limit of normal (for BUN and creatinine, a more stringent criterion of 1.5x the upper limit of normal was used). In agreement with the sponsor's conclusions, this review did not show any significant differences between treatment arms for ALT, AST total bilirubin, amylase, lipase, BUN, or creatinine. A similar result was obtained for the limited numbers of patients with abnormal values at baseline.

Given the substantial numbers of patients with digestive system adverse events such as nausea and vomiting, the medical officer also examined whether these could have represented chemical hepatitis or pancreatitis. There was one patient with vomiting in the setting of mild elevation of serum ALT (112 U/L); there was no elevation of total bilirubin in this patient. There was one patient with a study-emergent elevated serum lipase concentration (346 U/L) who had an adverse event of pancreatitis; there were two patients with either an elevated amylase or lipase who had nausea or dyspepsia. These findings suggest that linezolid may be associated with pancreatitis, albeit at a low incidence.

There were minor differences between treatment arms in the incidence of substantially abnormal laboratory values, but given the low numbers of patients, these do not appear to be significant. There were more patients in the linezolid arm with substantial elevations of creatine kinase; however, this finding is difficult to interpret, since such elevations could reflect release of creatine kinase from skeletal muscle due to persistent coughing caused by pneumonia.

Final conclusions

*This was a randomized, comparative trial of linezolid versus ceftriaxone/cefpodoxime in the treatment of inpatients with community-acquired pneumonia. The study design and definition of the study population were consistent with IDSA guidelines and divisional policy. The trial was weakened by its unblinded design; given the similar dosing schedules for linezolid and the comparator, it should have been possible to conduct this as a blinded study. However, there was no evidence of bias in assessment of outcomes between treatment arms. The change in the timing of the test-of-cure window represents another potential entry point for bias, given the unblinded design; again, however, there was no evidence of bias in assessment of outcomes between treatment arms. The trial was also weakened by the failure to prospectively specify the definition of equivalence; however, the sample size for the trial was determined based on pre-existing DAIDP policy. The trial was strengthened by the enrollment of a substantial number of patients with proven pneumococcal pneumonia (evidenced by positive blood cultures), as well as enrollment of a significant number of patients with risk factors for poor outcome (e.g., tachypnea). The comparators used are approved for treatment of pneumococcal pneumonia and both have good activity against *S. pneumoniae*. Given this, Study 33 represents an adequate and well-controlled trial.*

The results show evidence of efficacy for linezolid in the treatment of community-acquired pneumonia. Clinical and microbiologic response rates demonstrated therapeutic equivalence between linezolid and comparator across all analyses. Response rates were comparable between treatment arms when stratified by demographic factors. In addition, response rates were comparable for patients with predictors of poor outcome.

*With respect to specific pathogens, linezolid showed efficacy in patients with pneumonia due to penicillin-susceptible *S. pneumoniae* comparable to that for ceftriaxone/cefpodoxime. There was not enough evidence to demonstrate clinical efficacy against penicillin-resistant pneumococci, given the paucity of isolates and the lack of cases of PRSP bacteremia. Data supporting efficacy against *Staphylococcus aureus* in this indication were weak, given the lack of clinical, microbiologic, and radiologic evidence corroborating the presence of staphylococcal pneumonia in many patients who had *S. aureus* identified as a putative pathogen. There was minimal evidence supporting efficacy against CAP due to MRSA; in any event, it is unclear whether CAP due to MRSA is an entity that occurs at any appreciable incidence.*

No deaths were attributable to linezolid. The mortality rate due to the initial infection was low and comparable between treatment arms. There was a higher rate of drug-related discontinuations for linezolid in this study; there was a significant incidence of linezolid-related digestive system adverse events such as nausea and vomiting, which required discontinuation in 1.3% of linezolid-treated patients, and accounted for 4/9 discontinuations in the linezolid treatment arm. Laboratory abnormalities were comparable between treatment arms, except for ALT concentrations and platelet counts. ALT concentrations were higher in the linezolid arm during therapy, although the differences were small and were not consistent with chemical hepatitis. In a very small number of patients, nausea and vomiting may have reflected chemical pancreatitis. Although there was a somewhat higher rate of thrombocytopenia in linezolid-treated patients with normal platelet counts at baseline, there were no cases of grade IV thrombocytopenia and no related clinical adverse events. Taken together, these findings suggest an acceptable safety profile for the use of linezolid in the treatment of community-acquired pneumonia in patients requiring hospitalization.

In summary, these results support safety and efficacy of linezolid in the treatment of community-acquired pneumonia due to penicillin-susceptible Streptococcus pneumoniae, but do not provide substantial evidence of efficacy against penicillin-resistant S. pneumoniae. They provide marginal support for efficacy against Staphylococcus aureus in this indication; further support from another study would be required to demonstrate efficacy against this organism.

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Medical Officer's Review of Study M1260/0051

General Information

Study Title: Linezolid (PNU-100766) in the Treatment of Community-Acquired Pneumonia: an Investigator-Blind, Randomized, Comparator-Controlled Study in Outpatients.

Study Objective: To assess the comparative efficacy (clinical and microbiologic) of linezolid versus cephalosporin (cefepodoxime) therapy in the outpatient treatment of adult community-acquired pneumonia, and to assess safety and tolerance.

Study Design: Randomized, comparator-controlled, evaluator-blind, multi-center

Study Period: 30 September 1998 – 14 April 1999

Investigators: One hundred and three investigators participated (Canada, United States, Australia, Finland, Greece, Czech Republic, Hungary, South Africa, Switzerland, United Kingdom, Israel, Poland, Columbia, Chile, Peru, Mexico, Venezuela, and Brazil); see Appendix 4 of the sponsor's study report for details.

Study populations

Inclusion criteria

Adults patients were eligible for enrollment if they had at least 2 of the following symptoms: cough; production of purulent sputum or a change (worsening) in character of the sputum, auscultatory findings on pulmonary exam of rales and/or pulmonary consolidation (dullness on percussion, bronchial breath sounds, or egophony); dyspnea, tachypnea, or hypoxemia, particularly if any or all of these were progressive in nature; or an organism consistent with a respiratory pathogen isolated from sputum or blood cultures. In addition, eligible patients had at least 1 of the following conditions: fever, elevated total peripheral white blood cell (WBC) count $>10,000/\text{mm}^3$, $>15\%$ immature neutrophils (bands) regardless of total peripheral WBC, or leukopenia with total WBC $<4,500/\text{mm}^3$. Patients had to be deemed by the investigator to be clinically appropriate for outpatient therapy. A chest radiograph at Baseline or within 48 hours had to be consistent with a diagnosis of pneumonia. Eligible patients had to provide a respiratory, blood, or pleural fluid specimen for microbiological evaluation, and eligible patients had to have a survival expectancy of at least 60 days.

Medical Officer's Comment

*These inclusion criteria are similar to those in Study 33, except that the requirement that patients have documented or presumptive pneumococcal pneumonia was dropped. The criteria should have been more specific as to how to determine whether patients were appropriate for outpatient therapy; a significant number of enrolled patients had baseline characteristics (e.g., respiratory rate > 30) that predict a poor outcome and may not have been good candidates for outpatient treatment of their infection. Apart from the ethical issues raised by this factor, inclusion of such patients leads to much greater heterogeneity in the enrolled patient population. Since many such patients may have been treated more appropriately in the hospital setting, use of the term 'outpatient' population may not accurately describe the study sample. Use of the prediction rules published by the Pneumonia Outcome Research and Treatment Group (Fine et al. *New Engl. J. Med.* (1997) 336:243-50) would have better defined the study population.*

Exclusion criteria

Patients were excluded from participation in the study if they had a recent history of mechanical ventilation; loculated empyema or lung abscess; cystic fibrosis or known or suspected tuberculosis; known bronchial obstruction or a history of post-obstructive pneumonia; untreated hyperthyroidism, pheochromocytoma, carcinoid syndrome, or uncontrolled or untreated hypertension; known or suspected pulmonary conditions, e.g., granulomatous diseases, lung cancer, or another malignancy metastatic to the lungs; previous antibiotic treatment for the current episode of pneumonia for more than 24 hours, unless documented to be a treatment failure (72 hours treatment and not responding); known or suspected meningitis, endocarditis, or osteomyelitis; were receiving high doses of corticosteroids; were 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 received another investigational drug within 30 days prior to baseline; had previously been enrolled in any study using linezolid; had hypersensitivity to oxazolidinones or any of the excipients in either the oral or IV formulation of linezolid, or hypersensitivity to cefpodoxime; had liver disease or neutropenia as defined by laboratory criteria (total bilirubin > 5 X upper limit of normal, or neutrophil count < 500 cells/mm³; had a CD4 count of less than 200 cells/mm³ due to HIV infection; had unstable psychiatric condition or seizures requiring chronic medication (unless enrollment was authorized by the Clinical Trial Team Leader); or infection due to organisms known to be resistant to either of the study medication regimens before study entry.

Study methods

Treatment assignment

Patients were randomized in a 1:1 ratio to receive either of the following regimens:

- Oral linezolid 600 mg every 12 hours for 10 to 14 consecutive days
- Oral cefpodoxime 200 mg every 12 hours for 10 to 14 consecutive days

Some patients continued on therapy for up to 28 days with sponsor's permission.

Assessments

Assessment procedures were similar to those in Study 33, except that the on-therapy visits occurred at days 3 and 9 and considerations related to IV to oral switch in medication did not apply.

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.

The study was evaluator-blinded; unblinding could occur in emergency situations for patient care purposes.

The primary endpoint was clinical outcome. The analytic populations were defined by the sponsor using the same criteria as for Study 33.

Medical Officer's Comment

The FDA definitions of analytic populations were those used for review of Study 33.

Sample sizes were calculated 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. Under this assumption, the number of evaluable patients required per treatment group

for a determination of equivalence between the two treatment groups to within 10%, is 142 patients. Assuming an evaluability rate of 70%, this translated to a requirement of 203 enrolled patients per treatment group.

Changes in study conduct

The protocol was amended four times during the study; one amendment was not implemented.

Amendment 1, 8 March 1999

The statistical analysis was changed to widen the TOC window to 12 to 28 days after end of therapy. A category of serologically evaluable patients was defined; analysis of this patient population was not provided in the sponsor's study report.

Medical Officer's Comment

The potential impact of this amendment is less serious than in Study 33, since this was an evaluator-blind study.

Two country-specific amendments were made during the course of the study. First, the hepatic and hematologic exclusion criteria were tightened for patients enrolled at sites in South Africa because of regulatory requirements in that country; the impact of these changes was not indicated in the study report. Second, serologic studies were not required for sites in Brazil.

Results

Demographics and disposition

Five hundred forty-eight patients were enrolled; of these, 540 received study medication. There were 272 treated patients in the linezolid arm and 366 treated patients in the cefpodoxime arm. Table 55.1 shows the demographics of the ITT patient populations, as determined by the sponsor.

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| Table 51.1. Sponsor's analysis of demographics of ITT patients – Study 51 | | | | | | |
|--|-----------------------------------|------------------|-----------|--------------------|-----------|-----------------|
| | | Linezolid | | Cefpodoxime | | P-value† |
| Parameters | | N=272 | | N=268 | | |
| | | No. | %† | No. | %† | |
| Age (yr) | | | | | | |
| | Total Reporting | 272 | 100.0 | 268 | 100.0 | |
| | ≤17 | 0 | - | 1 | 0.4 | |
| | 18-44 | 126 | 46.3 | 120 | 44.8 | |
| | 45-64 | 93 | 34.2 | 86 | 32.1 | |
| | >65 | 53 | 19.5 | 61 | 22.8 | |
| | Mean ± SD | 47.6 ± 17.4 | | 48.8 ± 18.4 | | 0.4511 |
| Weight (kg) | | | | | | |
| | Total Reporting | 272 | 100.0 | 267 | 100.0 | |
| | Mean ± SD | 73.27 ± 17.49 | | 74.60 ± 18.99 | | 0.3982 |
| Race | | | | | | |
| | Total Reporting | 272 | 100.0 | 268 | 100.0 | 0.5164 |
| | White | 196 | 72.1 | 207 | 77.2 | |
| | Black | 30 | 11.0 | 28 | 10.4 | |
| | Asian or Pacific Islander | 1 | 0.4 | 2 | 0.7 | |
| | Mixed | 42 | 15.4 | 29 | 10.8 | |
| | Not allowed to ask per regulation | 3 | 1.1 | 2 | 0.7 | |
| Sex | | | | | | |
| | Total Reporting | 272 | 100.0 | 268 | 100.0 | 0.3887 |
| | Male | 132 | 48.5 | 140 | 52.2 | |
| | Female | 140 | 51.5 | 128 | 47.8 | |
| Region | | | | | | |
| | Total Reporting | 272 | 100.0 | 268 | 100.0 | 0.3776 |
| | North America | 115 | 42.3 | 123 | 45.9 | |
| | Latin America | 41 | 15.1 | 30 | 11.2 | |
| | Europe | 116 | 42.6 | 115 | 42.9 | |

†P-value was based on a one-way Analysis of Variance for continuous variables and a Chi-square test for categorical variables

Table 51.2 shows the numbers of patients in each treatment arm completing treatment and completing follow-up, as determined by the sponsor.

| | Linezolid N=278 | | Cefpodoxime N=270 | |
|--|--------------------|-------|----------------------|-------|
| | No. | %† | No. | %† |
| Population | | | | |
| Intent-To-Treat Patients (ITT) | 272 | 100.0 | 268 | 100.0 |
| Discontinued During Treatment | 55 | 20.2 | 29 | 10.8 |
| Completed Treatment | 217 | 79.8 | 239 | 89.2 |
| Discontinued During F-U | 41 | 15.1 | 32 | 11.9 |
| Completed F-U | 231 | 84.9 | 236 | 88.1 |
| Discontinued During Treatment and/or F-U | 56 | 20.6 | 38 | 14.2 |
| Completed Treatment and F-U | 216 | 79.4 | 230 | 85.8 |

Medical Officer's Comment

There was a substantially higher rate of discontinuation during treatment in the linezolid arm; as discussed below, this appears to be primarily due to adverse events.

The frequencies of reasons for the discontinuation of treatment for the ITT population, as determined by the sponsor, are provided in Table 51.3.

| | Linezolid N=272 | | Cefpodoxime N=268 | |
|--|--------------------|------|----------------------|------|
| | No. | %† | No. | %† |
| Reasons for Discontinuations | | | | |
| Discontinued patients | 55 | 20.2 | 29 | 10.8 |
| Lack of Efficacy | 15 | 5.5 | 9 | 3.4 |
| Death | 2 | 0.7 | 0 | 0 |
| SAE | 8 | 2.9 | 0 | 0 |
| AE (Non-serious) | 12 | 4.4 | 2 | 0.7 |
| Ineligible, but Started Study Medication | 5 | 1.8 | 8 | 3.0 |
| Subject's personal request | 5 | 1.8 | 2 | 0.7 |
| Lost to follow-up | 5 | 1.8 | 7 | 2.6 |
| Other | 3 | 1.1 | 1 | 0.4 |

Medical Officer's Comment

There was a higher rate of discontinuation due to lack of efficacy in the linezolid arm, as well as a substantially higher rate of discontinuations due to adverse events (both serious and nonserious). The discontinuation rates for AEs are higher in the linezolid arm even if only drug-related AEs are considered (10/272 (3.7%) v. 2/268 (0.7%), $p=0.037$). However, despite the imbalance in discontinuations due to serious adverse events, there was only one linezolid-treated patient who was discontinued for a drug-related serious adverse event (vomiting). There was no predominant drug-related adverse event responsible for discontinuation in the linezolid arm; linezolid-related AEs responsible for discontinuation included localized abdominal pain, headache, vomiting, and dizziness.

Evaluability

Table 51.4 shows the evaluable populations in the FDA analysis, and Table 51.5 shows reasons for nonevaluability in the FDA analysis. Patients could be unevaluable for more than one reason.

| Evaluation Group | Subjects Included | |
|-------------------------|-------------------|-------------|
| | Linezolid | Cefpodoxime |
| All randomized subjects | 278 | 270 |
| ITT subjects | 272 (100%) | 268 (100%) |
| MITT subjects | 60 (22.1%) | 60 (22.4%) |
| FDA CE subjects | 213 (78.3%) | 208 (77.6%) |
| FDA ME subjects | 50 (18.4%) | 48 (17.9%) |

Medical Officer's Comment

The FDA clinically evaluable and microbiologically evaluable populations were similar in size to the sponsor's. As with Study 33, the differences were largely related to exclusion from patients from the sponsor's analysis for insufficient therapy.

| Patient Subset/Reason for Exclusion | Linezolid N = 272 | | Cefpodoxime N = 268 | |
|-------------------------------------|----------------------|------|------------------------|------|
| | n | % | n | % |
| Total nonevaluable population | 59 | 21.7 | 60 | 22.4 |
| Negative chest radiograph | 2 | 0.7 | 5 | 1.9 |
| Prior antibiotic usage | 1 | 0.4 | 2 | 0.7 |
| Insufficient therapy | 23 | 8.5 | 14 | 5.2 |
| Noncompliance with therapy regimen | 28 | 10.3 | 16 | 6.0 |
| Concomitant antibiotics | 4 | 1.5 | 2 | 0.7 |
| Lost to follow-up | 42 | 15.4 | 37 | 13.8 |
| Indeterminate outcome | 4 | 1.6 | 9 | 1.9 |

Medical Officer's Comment

The treatment arms were roughly balanced with respect to reasons for nonevaluability; the higher rates of nonevaluability due to insufficient therapy or noncompliance in the linezolid arm most likely reflect the higher rates of discontinuations due to adverse events in linezolid-treated patients. As in Study 33, most exclusions from the per-protocol population were for post-baseline reasons.

Efficacy

Table 51.6 shows clinical outcomes in the ITT and evaluable populations. The numbers of subjects listed in Table 51.6 exclude patients with missing or indeterminate outcomes, except for analyses where missing outcomes were changed to failures.

Table 51.6. FDA analysis of clinical outcome - Study 51

| FDA-Defined Study Population | Linezolid | | Cefpodoxime | | 95% C.I. |
|------------------------------|-----------|-------------------|-------------|-------------------|---------------|
| | N | Success Rates (%) | N | Success Rates (%) | |
| ITT | 227 | 82.8 | 222 | 86.5 | (-10.8, 3.4) |
| ITT (missing as failure) | 272 | 69.1 | 268 | 71.6 | (-10.6, 5.5) |
| MITT | 54 | 85.2 | 52 | 80.8 | (-11.8, 20.6) |
| MITT (missing as failure) | 60 | 76.7 | 60 | 70.0 | (-10.8, 24.1) |
| FDA CE | 213 | 84.5 | 208 | 89.9 | (-12.2, 1.4) |
| FDA ME | 50 | 88.0 | 48 | 81.3 | (-9.5, 23.0) |

Response rates in the FDA analyses were somewhat lower for both treatment arms than in the sponsor's analyses. The 95% confidence intervals around the difference in response rates between treatment arms were similar in both the FDA analysis and the sponsor's analysis, except for the clinically evaluable population.

Medical Officer's Comment

The results are consistent with equivalence between linezolid and cefpodoxime for the different analytic populations. In contrast to Study 33, the response rates for linezolid were lower than the comparator in a number of the analyses. The lower rates in the ITT analyses result largely from patients who were failures but who received less than four doses of study drug and therefore were excluded from the CE and ME analyses. Analyses that counted patients with missing outcomes as failures yielded lower response rates, as expected. These analyses should be interpreted with caution, since there were a significant number of patients with missing outcomes (45 linezolid, 46 cefpodoxime), and many of these patients may not have been true therapeutic failures; the actual response rates that would have been obtained with complete follow-up would be likely to be higher.

With respect to patients who died from their initial infection, there was 1/272 (0.4%) such patients in the linezolid arm and none in the cefpodoxime arm.

Table 51.7 shows response rates stratified by demographic factors.

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

Medical Officer's Comment

Response rates were comparable by gender between treatment arms. It is not clear why response rates were higher for linezolid-treated patients older than 65, although the difference was significantly different. Response rates were lower in non-white individuals in the cefpodoxime arm; again, the reason for this effect is unclear.

Table 51.8 shows clinical outcomes for clinically evaluable patients with baseline characteristics predicting a worse outcome (Donowitz and Mandell 1995). Similar results were obtained for the corresponding analysis of the MITT patient population.

| Subset | Linezolid (N=213) | Cefpodoxime (N=208) |
|-----------------------|----------------------|------------------------|
| Age >50 | 78/91 (85.7%) | 92/98 (93.9%) |
| Bacteremia | 3/3 (100%) | 3/5 (60%) |
| Multilobar Pneumonia | 37/46 (80.4%) | 34/39 (87.2%) |
| Bilateral Pneumonia | 25/30 (83.3%) | 24/27 (88.9%) |
| Hypotension | 6/8 (75.0%) | 10/12 (83.3%) |
| Respiratory rate > 30 | 8/9 (88.9%) | 6/7 (85.7%) |
| [BUN] > 7 mM | 20/26 (76.9%) | 22/23 (95.7%) |
| HIV infection | 3/4 (75.0%) | 2/2 (100%) |

Medical Officer's Comment

While the response rates for oral linezolid in these patient subsets were generally comparable to those for cefpodoxime, they were lower for several subsets (e.g., [BUN] > 7 mM). It is disturbing that patients with certain of these characteristics (e.g., respiratory rate > 30) were enrolled in this trial and treated as outpatients, since such characteristics are linked to increased mortality from pneumonia. However, there were relatively few patients with these characteristics, and the numbers of patients with such characteristics were similar between treatment arms.

Table 51.9 shows microbiologic outcomes in the MITT and ME populations.

| FDA-Defined Study Population | Linezolid | | Cefpodoxime | | 95% C.I. |
|------------------------------|-----------|-------------------|-------------|-------------------|-----------------|
| | N | Success Rates (%) | N | Success Rates (%) | |
| MITT | 55 | (81.8%) | 53 | (84.9%) | (-19.0%, 12.8%) |
| FDA ME | 50 | 86.0% | 48 | 87.5% | (-17.0%, 14.0%) |

Medical Officer's Comment

As in Study 33, microbiological responses were largely driven by clinical responses, since the majority of cured patients were no longer producing sputum at follow-up; a microbiological outcome of presumed eradication was inferred for such patients. The wide confidence intervals reflect the relatively low proportion of patients who had a pathogen isolated in this study.

Table 51.10 shows clinical outcomes for microbiologically evaluable patients by specific pathogens.

| Subset | Linezolid (N=50) | Cefpodoxime (N=48) |
|---|------------------|--------------------|
| <i>S. pneumoniae</i> | 25/27 (92.6%) | 19/21 (90.5%) |
| <i>S. pneumoniae</i> bacteremia | 3/3 (100%) | 3/5 (60.0%) |
| Penicillin-resistant <i>S. pneumoniae</i> | 0/0 (NA) | (0/0) NA |
| <i>S. aureus</i> | 11/12 (91.7%) | 9/12 (75.0%) |
| <i>S. aureus</i> bacteremia | 0/0 (NA) | 0/0 (NA) |
| MRSA | 1/1 (100%) | 0/1 (0%) |
| <i>H. influenzae</i> | 11/13 (84.6%) | 13/15 (86.7%) |

Medical Officer's Comment

*As in Study 33, linezolid showed efficacy similar to comparator for cases of pneumococcal pneumonia. Although there were few cases of pneumococcal bacteremia, the results in these cases were consistent with those of Study 33, with 3/3 linezolid-treated patients cured. There were no cases of pneumonia in which penicillin-resistant *S. pneumoniae* was isolated.*

*Although, there were a reasonable number of cases in which *S. aureus* was isolated, as in Study 33 it is doubtful that the majority of these represented true staphylococcal pneumonias. Of 15 MITT patients in whom *S. aureus* was isolated, only six had sputum Gram's stains of good quality showing predominantly Gram-positive cocci, and only one of these represented a case in which methicillin-resistant *S. aureus* was isolated. Of these, only four showed growth of *S. aureus* in pure culture; the MRSA case was not one of these. None of these cases were associated with radiographic signs of cavitation. Thus, as with study 33, the evidence for efficacy in *S. aureus* pneumonia is weak, given the lack of microbiologic and radiographic data to support enrollment of substantial numbers of patients with this diagnosis.*

*The high success rate of linezolid for cases in which *H. influenzae* was isolated is misleading; as with *S. aureus*, in most cases the evidence that *H. influenzae* was the true pathogen is weak. Of 13 patients in the MITT population who had isolation of *H. influenzae*,*

only two showed predominantly Gram-negative organisms on sputum Gram stains; neither of these Gram stains was of good quality. In 8/13 cases, Gram-positive cocci were predominant on the sputum Gram stain, suggesting that H. influenzae was not the pathogen. Thus, there is little evidence of efficacy against true cases of H. influenzae pneumonia

Safety

Deaths, serious adverse events, and clinical adverse events

Deaths, serious adverse events, discontinuations due to adverse events, and clinical adverse events by body system are shown in Table 51.11. An AE that met one or more of the following criteria/outcomes was classified as serious: death; life-threatening (i.e., immediate risk of death); in-patient hospitalization or prolongation of existing hospitalization; persistent or significant disability/incapacity; congenital anomaly/birth defect; any other event that the investigator or the Applicant judged to be serious or that was defined as serious by the regulatory agency in the country in which the event occurred. The assessment of gravity was made independently of the severity rating.

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Table 51.11. Summary of deaths, SAEs, discontinuations, and clinical AEs – Study 51

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

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. The mortality rates for death to the primary infection were low, as would be expected for this patient population, and were comparable between treatment arms. There was a markedly higher incidence of discontinuations due to any adverse event and due to drug-related adverse events in the linezolid treatment arm. As noted earlier, there was no single drug-related adverse event that was predominant in the linezolid treatment arm.

Most serious adverse events were not drug-related. However, the most common serious adverse event in the linezolid arm was worsening of pneumonia, which is of concern in light of the finding that discontinuations for lack of efficacy were more common in the linezolid arm.

There was a substantially higher rate of all adverse events and drug-related adverse events in the linezolid arm. This appears to be due in part to a higher incidence of digestive system adverse events, such as nausea, vomiting, and diarrhea, in linezolid-treated patients. It may also be due an increase in skin system adverse events, which would include rash.

Specific adverse events and drug-related adverse events are shown in Tables 51.12 and 51.13, respectively.

| COSTART Body System/MET | Linezolid N=272 | | Cefpodoxime N=268 | |
|-----------------------------------|--------------------|------|----------------------|------|
| | No. | % | No. | % |
| Patients With at Least One | 164 | 60.3 | 115 | 42.9 |
| DIGESTIVE | | | | |
| Diarrhea | 27 | 9.9 | 24 | 9.0 |
| Dyspepsia | 11 | 4.0 | 2 | 0.7 |
| Liver Function Tests Abnormal NOS | 6 | 2.2 | 0 | - |
| Nausea | 22 | 8.1 | 13 | 4.9 |
| Vomiting | 11 | 4.0 | 6 | 2.2 |
| BODY | | | | |
| Abdominal Pain, Generalized | 9 | 3.3 | 0 | - |
| Chest Pain | 9 | 3.3 | 7 | 2.6 |
| Fatigue | 6 | 2.2 | 4 | 1.5 |
| Headache | 28 | 10.3 | 20 | 7.5 |
| RESPIRATORY | | | | |
| Abnormal Lung Sounds | 3 | 1.1 | 9 | 3.4 |
| Cough | 10 | 3.7 | 9 | 3.4 |
| Dyspnea | 9 | 3.3 | 3 | 1.1 |
| Pneumonia | 12 | 4.4 | 6 | 2.2 |
| Rhinitis | 10 | 3.7 | 4 | 1.5 |
| Sputum Increased | 3 | 1.1 | 8 | 3.0 |
| NERVOUS | | | | |
| Dizziness | 8 | 2.9 | 8 | 3.0 |
| Insomnia | 12 | 4.4 | 7 | 2.6 |
| SKIN | | | | |
| Rash | 6 | 2.2 | 0 | - |

| COSTART Body System/MET | Linezolid N=272 | | Cefpodoxime N=268 | |
|----------------------------|--------------------|------|----------------------|------|
| | No. | % | No. | % |
| Patients With at Least One | 86 | 31.6 | 48 | 17.9 |
| DIGESTIVE | | | | |
| Diarrhea | 22 | 8.1 | 16 | 6.0 |
| Nausea | 15 | 5.5 | 9 | 3.4 |
| Vomiting | 6 | 2.2 | 2 | 0.7 |
| BODY | | | | |
| Headache | 11 | 4.0 | 8 | 3.0 |
| NERVOUS | | | | |
| Insomnia | 7 | 2.6 | 5 | 1.9 |

Medical Officer's Comment

As in Study 33, the incidence of digestive system drug-related adverse events (nausea, vomiting, and diarrhea) was higher in the linezolid arm. With respect to all adverse events, there was a higher incidence of abdominal pain and increased liver function tests in the linezolid arm, although these were not attributed to drug administration. An analysis by the medical reviewer of whether these results might reflect chemical hepatitis or pancreatitis (see below under Chemistry) did not show an increased incidence of abnormalities in transaminase, bilirubin, amylase, or lipase concentrations.

As in Study 33, an independent analysis using CrossGraphs was performed to examine whether the MAO inhibitory activity of linezolid was associated with potential adverse events such as hypertensive syndrome or serotonin syndrome. No evidence was found for such an association, either with or without concomitant medications that might interact with linezolid.

Laboratory findings

Hematology

The sponsor analyzed changes in mean values of hematologic laboratory values over time. These appeared comparable between treatment groups for WBC count and neutrophil count. Mean hemoglobin concentration was lower in the linezolid arm than in the cefpodoxime arm at all time points; however, this difference did not appear statistically or clinically significant. 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 51.14.

Table 51.14. Incidence of substantially abnormal hematology laboratory values

| Laboratory Assay | Criterion | Linezolid | | | Cefpodoxime | | |
|------------------|-------------|-----------|-----|------|-------------|-----|------|
| | | n | N | % | n | N | % |
| Hemoglobin | <75% of LLN | 2 | 266 | 0.75 | 1 | 266 | 0.38 |
| Hematocrit | <75% of LLN | 1 | 266 | 0.38 | 3 | 266 | 1.13 |
| Platelet Count | <75% of LLN | 4 | 265 | 1.51 | 1 | 266 | 0.38 |
| WBC | <75% of LLN | 11 | 266 | 4.14 | 4 | 266 | 1.50 |
| Neutrophils | <0.5 LLN | 9 | 266 | 3.38 | 2 | 266 | 0.75 |
| Eosinophils | >= 10% | 10 | 266 | 3.76 | 13 | 266 | 4.89 |

Medical Officer's Comment

The medical reviewer independently analyzed the hematology laboratory data with CrossGraphs as outlined for Study 33, focusing on patients with normal values at baseline.

The incidence of decreased hemoglobin concentrations was similar between linezolid and cefpodoxime (14/251 (5.6%) v. 12/243 (4.9%)). There was a somewhat higher incidence of leukopenia in linezolid-treated patients than in cefpodoxime-treated patients with normal platelet counts at baseline (29/266 (10.9%) vs. 20/261 (7.7%)). Two linezolid-treated patients and no cefpodoxime-treated patients developed grade III leukopenia (i.e., WBC count < 2000/mm³; one of the linezolid-treated patients had resolution of leukopenia, while the other did not have laboratory follow-up past their leukocyte nadir. One of these patients developed mucosal moniliasis, but this was not attributed to the leukopenia.

M.O. Review of M1260/0051 (Linezolid vs. cefpodoxime for outpatient CAP)

Among patients with a normal neutrophil count at baseline, 41/269 (15.2%) in the linezolid arm and 26/265 (9.8%) developed neutropenia. 7/272 (2.6%) of linezolid-treated patients and 3/268 (1.1%) cefpodoxime-treated patients developed grade at least grade III neutropenia (absolute neutrophil count < 1000/mm³), while one linezolid-treated patient developed grade IV neutropenia (ANC < 500/mm³). With the exception of the patient mentioned above who developed moniliasis, there were no adverse events that could be related to the development of neutropenia.

Among patients with a normal platelet count at baseline, there was a slightly higher incidence of thrombocytopenia in the linezolid arm than in the cefpodoxime arm (8/268 (3.0% vs. 4/261 (1.5%)). No patients had decreases in platelet counts to less than 50,000/mm³. Patients with laboratory follow-up showed resolution of thrombocytopenia. 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.

Chemistry

The sponsor analyzed changes in mean values of chemistry laboratory values over time. Only those for ALT and lipase were reported in the main body of the study report. Mean values for ALT were significantly higher at the end of therapy in the linezolid arm, but the difference did not appear to be clinically significant. Values for lipase were consistently lower during therapy in the linezolid 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 51.15.

| Table 51.15. Incidence of substantially abnormal chemistry laboratory values | | | | | | | |
|---|------------------|------------------|----------|----------|--------------------|----------|----------|
| Laboratory Assay | Criterion | Linezolid | | | Cefpodoxime | | |
| | | n | N | % | n | N | % |
| Total Bilirubin | >2 x ULN | 1 | 265 | 0.38 | 0 | 266 | 0.00 |
| Albumin | <0.75 x LLN | 4 | 265 | 1.51 | 1 | 266 | 0.38 |
| AST | >2 x ULN | 8 | 265 | 3.02 | 8 | 266 | 3.01 |
| ALT | >2 x ULN | 13 | 265 | 4.91 | 14 | 266 | 5.26 |
| Alkaline Phosphatase | >2 x ULN | 1 | 266 | 0.38 | 0 | 266 | 0.00 |
| BUN | >2 x ULN | 1 | 266 | 0.38 | 0 | 266 | 0.00 |
| Sodium | <0.95 x LLN | 2 | 266 | 0.75 | 0 | 266 | 0.00 |
| | >1.05 x ULN | 0 | 266 | 0.00 | 2 | 266 | 0.75 |
| Potassium | >1.1 x ULN | 3 | 264 | 1.14 | 2 | 266 | 0.75 |
| Bicarbonate | <0.9 x LLN | 1 | 265 | 0.38 | 1 | 266 | 0.38 |
| | >1.1 x ULN | 1 | 265 | 0.38 | 0 | 266 | 0.00 |
| Calcium | >1.1 x ULN | 1 | 266 | 0.38 | 0 | 266 | 0.00 |
| | <0.6 x LLN | 0 | 263 | 0.00 | 1 | 265 | 0.38 |
| Non Fasting Glucose | >1.4 x ULN | 5 | 263 | 1.90 | 19 | 265 | 7.17 |
| | >2 x ULN | 9 | 265 | 3.40 | 5 | 266 | 1.88 |
| Lipase | >2 x ULN | 6 | 266 | 2.26 | 7 | 264 | 2.65 |
| Amylase (U/L) | >2 x ULN | 1 | 266 | 0.38 | 2 | 266 | 0.75 |

Medical Officer's Comment

The medical officer conducted an independent review of chemistry laboratory values for hepatic, pancreatic, and renal parameters, similar to that performed for Study 33. This review did not show any significant differences between treatment arms. One linezolid patient with an elevated serum lipase (260 U/L) had an adverse event of dyspepsia; however, this resolved despite continued elevation of serum lipase, arguing against the possibility that this represented drug-induced pancreatitis. There was no laboratory evidence for chemical hepatitis.

Final conclusions

*This was a randomized, comparative trial of linezolid versus cefpodoxime in the outpatient treatment community-acquired pneumonia. The study design and definition of the study population were consistent with the IDSA guidelines for this indication and divisional policy, although as noted above, characterization of the study sample as an 'outpatient' population may not be accurate given that a number of patients were enrolled with baseline indicators of severe infection. The trial was strengthened by an evaluator-blinded design, although a double-blind design would have been preferable, and should have been possible given the similar dosing schedules of linezolid and the comparator. However, it is worth noting in this regard that there were no instances documented of the blind being broken. The comparator is approved for treatment of pneumococcal pneumonia and has good activity against *S. pneumoniae*. Given this, Study 51 may be regarded as an adequate and well-controlled trial.*

The results show evidence of efficacy for linezolid in the treatment of community-acquired pneumonia. Clinical and microbiologic response rates were consistent with equivalence between linezolid and comparator across all analyses. Response rates were comparable between treatment arms when analyses were stratified by demographic factors. In addition, response rates were comparable for patients with predictors of poor outcome. However, it is important to note that the rate of discontinuation for lack of efficacy was higher in the linezolid arm than the comparator arm, in contrast to Study 33. This difference may have been due to the single-blinded design of this study, which would reduce evaluator bias in favor of continuing patients on linezolid. When taken together with the adverse event profile of linezolid (see below), this suggests that linezolid may not have as favorable a risk-benefit ratio in the outpatient treatment of CAP as cephalosporins.

*With respect to specific pathogens, linezolid showed efficacy against patients with pneumonia due to penicillin-susceptible *S. pneumoniae* comparable to that for cefpodoxime. There was no evidence to demonstrate clinical efficacy against penicillin-resistant pneumococci, given the lack of PRSP. As with Study 33, data supporting efficacy against *Staphylococcus aureus* in this indication was weak, given the lack of corroboration of the presence of staphylococcal pneumonia in many patients who had *S. aureus* identified as a putative pathogen. There was little or no evidence supporting efficacy against CAP due to MRSA.*

No deaths were attributable to linezolid, and the mortality rate due to the initial infection was low in both treatment arms. The adverse event profile for linezolid in this study showed a substantially higher rate of drug-related discontinuations, as well as of all adverse events and of drug-related adverse events; Laboratory abnormalities were notable for a significant incidence of leukopenia and neutropenia in the linezolid arm, although there were no clearly related clinical adverse events, and these abnormalities were not seen to the same

extent in the other Phase 3 clinical studies. Although there was a somewhat higher rate of thrombocytopenia in linezolid-treated patients with normal platelet counts at baseline, there were no cases of grade IV thrombocytopenia and no related clinical adverse events.

In summary, these results support the safety and efficacy of linezolid in the treatment of community-acquired pneumoniae due to penicillin-susceptible Streptococcus pneumonia, although they suggest that its usefulness may be limited in the outpatient treatment of CAP because of its adverse event profile and because it is not clear that a significant number of enrolled patients were suitable candidates for outpatient treatment. They do not provide substantial evidence of efficacy against penicillin-resistant S. pneumoniae, nor do they provide strong support for the efficacy of linezolid against S. aureus community-acquired pneumonia.

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Medical Officer's Review of Study M1260/0048A (Hospital-acquired Pneumonia)

General Information

Study title: Linezolid (PNU-100766) in the Treatment of Patients with Nosocomial Pneumonia: A Double-Blind, Randomized, Comparator-Controlled Study

Study Objectives: To assess the comparative efficacy (clinical and microbiological) of linezolid plus aztreonam therapy versus vancomycin plus aztreonam therapy in the treatment of nosocomial pneumonia in hospitalized adults, to assess safety and tolerance, and to assess the prevalence of vancomycin-resistant enterococci (VRE) in patients receiving broad-spectrum antibiotic therapy.

Study Design: Randomized, double-blind, multi-center, comparator-controlled.

Investigators: 90 investigator sites participated (North America, Europe [including Israel, South Africa, Australia], and Latin America); a list of all participating investigators is presented in Appendix 5 of the sponsor's clinical study report.

Study period: 13 October 1998 to 16 July 1999.

Study Population

Inclusion criteria

Adult patients with a clinical picture compatible with pneumonia (acquired in an in-patient health care facility or chronic care facility) were required to satisfy at least two of the following criteria: cough; production of purulent sputum or a change (worsening) in character of the sputum; auscultatory findings on pulmonary exam of rales and/or pulmonary consolidation; dyspnea, tachypnea, or hypoxemia, particularly if any or all of these were progressive in nature; and an organism consistent with a respiratory pathogen isolated from respiratory, sputum, or blood cultures; the patient was also expected to survive at least 7 days. Each patient should also have had at least two of the following: fever; respiratory rate >30 breaths per minute; systolic hypotension; pulse rate > 120 beats per minute; altered mental status; requirement for mechanical ventilation; elevated total peripheral white blood cell (WBC) count > 10,000/mm³; > 15% immature neutrophils (bands) regardless of total peripheral WBC; leukopenia with total WBC < 4,500/mm³; the patient had a chest radiograph at baseline/screening or within 48 hours of initiation of treatment consistent with a diagnosis of pneumonia (new or progressive infiltrates, consolidation, or pleural effusion); provided a suitable invasive respiratory specimen and a sputum specimen for Gram's stain and culture; venous access available for intravenous dosing; and was willing to complete all study-related activities and F-U visit.

Medical Officer's Comment

Although the criteria used in this study are appropriate, they do not guarantee that the population studied truly has hospital-acquired pneumonia. Distinguishing nosocomial pneumonia from other medical conditions affecting pulmonary function can be difficult, particularly in critically ill patients and in those who are mechanically ventilated. For example, intubated patients with pulmonary infarction due to emboli can show all of the clinical and radiographic signs and symptoms listed above (and even have an organism isolated due to colonization of the ventilator circuit) but not have a true respiratory tract infection. Nonintubated but debilitated patients who are bedbound may have fever, cough, and infiltrates on chest X-ray due to atelectasis.

MO Review of 48A (Linezolid 600 mg q12h + Aztreonam vs. Vancomycin 1 g q12h + Aztreonam)

Quantitative cultures of respiratory specimens obtained by invasive methods have been proposed as one method for increasing the specificity (and perhaps sensitivity) of diagnosis. The protocol makes use of such cultures for intubated patients; however, it is difficult ethically to justify use of these procedures in most nonintubated patients who can produce a sputum sample.

Exclusion criteria

Patients were to be excluded for the following reasons: infection due to organisms known to be resistant to either of the study medication regimens before study entry; known or suspected meningitis, endocarditis, or osteomyelitis; pheochromocytoma, untreated hyperthyroidism, untreated or uncontrolled hypertension, or carcinoid syndrome; unstable psychiatric conditions or seizure disorders requiring chronic administration of medication without consultation and consent of the Trial Conduct Team Leader (TCTL); CD4 cell count < 200 cells/mm³ secondary to human immunodeficiency virus (HIV) infection; previous antibiotic treatment received for more than 24 hours, unless documented to be a treatment failure (72 hours treatment and not responding) or if the isolated pathogen for the current pneumonia was resistant *in vitro* to previous nonstudy antibiotic therapy; coagulopathy; known liver disease and total bilirubin > 5 X the upper limit of normal (ULN); severe neutropenia < 500 cells/mm³.

Study methods

Treatment assessment

Patients were randomized in a 1: 1 ratio to receive intravenously (IV) either of the following regimens for 7 to 21 days:

- Linezolid IV 600 mg every 12 hours plus aztreonam IV 1-2 g every 8 hours. Aztreonam use was optional if no gram-negative pathogens were identified.
- Vancomycin IV 1 g every 12 hours plus aztreonam IV 1-2 g every 8 hours. Aztreonam use was optional if no gram-negative pathogens were identified.

Medical Officer's Comment

Vancomycin is often used for the empiric therapy of nosocomial pneumonia in settings where methicillin-resistant staphylococci are prevalent, because of its activity against Gram-positive organisms, especially MRSA. For a comparative trial of this sort it has the advantage of having a spectrum of activity and dosing schedule similar to that of linezolid, facilitating blinding. While vancomycin is not a drug of first choice for treatment of infections due to methicillin-susceptible staphylococci, its use as a comparator for this trial is acceptable.

Almost all patients received aztreonam. Because it is not active against Gram-positive organisms, its use should not confound the treatment effect of linezolid or vancomycin against Gram-positive pathogens.

Assessments

Basic assessment procedures were similar to those in Study 33. In addition, an [] was determined at baseline for each patient. An [] anteroposterior chest radiograph was considered acceptable for patients who were mechanically ventilated. An invasive respiratory specimen was also required within 24 hours of study entry for patients who were intubated; such specimens could be obtained by protected specimen brush (PSB), bronchoalveolar lavage (BAL), transthoracic aspirate, transtracheal aspirate, or pleural fluid. Quantitative cultures were to be performed by the local laboratory on PSB, BAL, and

transtracheal aspirates.

Statistical considerations

Randomization followed the same principles as those for Study 33. The sponsor used the same definitions for analytic populations as in Study 33. Additional microbiologically evaluable subpopulations (ME1 and ME2) were also defined based on the isolation of pathogens at baseline by invasive procedures, either without (ME1) or with (ME2) specified quantitative criteria.

The primary endpoints were clinical outcome, microbiologic outcome, and overall (clinical + microbiologic) outcome. All 95% confidence intervals were based on the normal approximation to the binomial distribution and were considered consistent with equivalence if the following conditions were met: 1) there were at least 83 patients per treatment group, 2) the confidence interval included zero, and 3) the lower limit of the confidence interval exceeded -20%.

Medical Officer's Comment

The definition of equivalence employed here (i. e., a confidence interval lower bound of -20%) reflects the relatively low response rates seen in studies of hospital-acquired pneumonia, as well as the relative difficulty of enrolling seriously ill patients in trials of this sort. However, given the seriousness of this infection and its associated mortality, a response rate that may be 20% lower than that of the comparator arm is not necessarily clinically acceptable.

Changes in study conduct

There were four implemented amendments of the protocol; one of these was specific to South Africa and concerned tightening of laboratory exclusion criteria in response to regulatory requirements. The other three were as follows:

Amendment 1, 25 March 1999

The TOC (F-U) visit window to be used for efficacy analysis of ITT, MITT, and evaluable patients was changed from 15 to 21 days post-therapy to 12 to 28 days posttherapy. This administrative amendment applied to all patients.

Amendment 2, 19 April 1999

Protocol changes addressed the following issues: 1) discontinuation of the requirement for an invasive respiratory procedure in non-endotracheally intubated patients, and 2) clarification of exclusion criterion regarding previous antibiotic treatment. Sixty-nine patients were enrolled under this amendment.

Amendment 3, 14 July 1999

This was described by the sponsor as an 'administrative' amendment and applied to all patients. There were no changes to the design or scope of the study. Two data sets were defined for analysis purposes. Patients enrolled on or prior to 20 June 1999 and whose CRFs were received by 21 July 1999 were analyzed separately and the protocol was referred to as M/1260/0048A. A second analysis was planned be done for all patients enrolled after 20 June 1999 and/or whose CRF were received after 21 July 1999 and the protocol will be referred to as M/1260/0048. Patients in the first data set were included in the NDA submission. The second data set will be analyzed separately.

MO Review of 48A (Linezolid 600 mg q12h + Aztreonam vs. Vancomycin 1 g q12h + Aztreonam)

Results

Demographics and disposition

Four hundred and two patients were enrolled. Of these, 396 received study medication. There were 203 treated patients in the linezolid arm and 193 treated patients in the vancomycin arm. Table 48A.1 shows the demographics of the ITT patient populations, as determined by the sponsor.

| Table 48A.1. Sponsor's analysis of demographics of ITT patients – Study 48A | | | | | |
|--|--------------------|---------------|---------------------|---------------|---------|
| Parameters | Linezolid N=203 | | Vancomycin N=193 | | P-value |
| | n | % | n | % | |
| Age (years) | | | | | |
| Total reporting | 203 | 100.0 | 193 | 100.0 | |
| 18-44 | 34 | 16.7 | 43 | 22.3 | |
| 45-64 | 53 | 26.1 | 48 | 24.9 | |
| ≥ 65 | 116 | 57.1 | 102 | 52.8 | |
| Mean ± SD | | 62.8 ± 18.0 | | 61.3 ± 18.7 | 0.4178 |
| Intubated at baseline | | | | | |
| Total reporting | 201 | 100.0 | 191 | 100.0 | |
| 0-11 | 63 | 31.3 | 50 | 26.2 | |
| 12-15 | 46 | 22.9 | 59 | 30.9 | |
| 16-19 | 40 | 19.9 | 36 | 18.8 | |
| 20-39 | 52 | 25.9 | 46 | 24.1 | |
| Mean ± SD | | 15.7 ± 6.5 | | 15.4 ± 6.9 | 0.7430 |
| Weight (Kg) | | | | | |
| Total Reporting | 198 | | 188 | | |
| Mean ± SD | | 73.64 ± 18.19 | | 73.34 ± 17.90 | 0.8701 |
| Race | | | | | |
| Total Reporting | 203 | 100.0 | 193 | 100.0 | 0.9289 |
| White | 181 | 89.2 | 170 | 88.1 | |
| Black | 11 | 5.4 | 10 | 5.2 | |
| Asian/Pacific Islander | 1 | 0.5 | 1 | 0.5 | |
| Mixed | 7 | 3.4 | 10 | 5.2 | |
| Not asked per local regulation | 3 | 1.5 | 2 | 1.0 | |
| Sex | | | | | |
| Total reporting | 203 | 100.0 | 193 | 100.0 | 0.6556 |
| Male | 142 | 70.0 | 131 | 67.9 | |
| Female | 61 | 30.0 | 62 | 32.1 | |
| Region | | | | | |
| Total reporting | 203 | 100.0 | 193 | 100.0 | 0.4198 |
| North America | 93 | 45.8 | 78 | 40.4 | |
| Latin America | 10 | 4.9 | 14 | 7.3 | |
| Europe | 100 | 49.3 | 101 | 52.3 | |

† P-value is based on a one-way analysis of variance for age, category, and weight, and is based on a chi-square test for race, sex, and region.

Medical Officer's Comment

The treatment arms were well balanced with respect to demographic factors and severity of illness at baseline. The latter is crucial, since this is a key predictor of outcome in nosocomial pneumonia. The [redacted] score takes into account both the patient's acute illness and comorbid conditions. The pattern of [redacted] scores for enrolled patients indicates a broad distribution of baseline severity of illness, ranging from patients with mild disease with few or no comorbid conditions (score < 10) to those at very high risk for death (score > 25).

Table 48A.2 shows the numbers of patients in each treatment arm completing treatment and completing follow-up, as determined by the sponsor.

| Population | Linezolid | | Vancomycin | |
|--|-----------|-------|------------|-------|
| | n | % | n | % |
| All Randomized Patients | 205 | - | 197 | - |
| Never Received Study Medication | 2 | - | 4 | - |
| Intent-to-Treat Patients (ITT) | 203 | 100.0 | 193 | 100.0 |
| Discontinued During Treatment | 61 | 30.0 | 68 | 35.2 |
| Completed Treatment | 142 | 70.0 | 125 | 64.8 |
| Discontinued During F-U | 56 | 27.6 | 67 | 34.7 |
| Completed F-U | 147 | 72.4 | 126 | 65.3 |
| Discontinued During Treatment and/or F-U | 79 | 38.9 | 89 | 46.1 |
| Completed Treatment and F-U | 124 | 61.1 | 104 | 53.9 |

Medical Officer's Comment

The rates of discontinuation during treatment and during follow-up were somewhat lower in the linezolid arm.

The frequencies of reasons for the discontinuation of treatment for the ITT population, as determined by the sponsor, are provided in Table 48A.3.

| Reason for Discontinuation | Linezolid (N=203) | | Vancomycin (N=193) | |
|--|-------------------|------|--------------------|------|
| | n | % | n | % |
| Any reason | 61 | 30.0 | 68 | 35.2 |
| Lack of efficacy | 10 | 4.9 | 11 | 5.7 |
| Death | 14 | 6.9 | 17 | 8.8 |
| Adverse event (serious) | 3 | 1.5 | 6 | 3.1 |
| Adverse event (nonserious) | 6 | 3.0 | 8 | 4.1 |
| Ineligible, but started study medication | 4 | 2.0 | 7 | 3.6 |
| Protocol noncompliance | 0 | 0.0 | 1 | 0.5 |
| Subject's personal request | 3 | 1.5 | 2 | 1.0 |
| Other | 21 | 10.3 | 16 | 8.3 |

Medical Officer's Comment

In contrast to the community-acquired pneumonia trials (Studies 33 and 51), the rate of discontinuation for adverse events was lower in the linezolid arm. Discontinuations for 'other' primarily represent those patients from whom only Gram-negative pathogens were isolated.

Evaluability

Table 48A.4 shows the evaluable populations in the FDA analysis, and Table 48A.5

MO Review of 48A (Linezolid 600 mg q12h + Aztreonam vs. Vancomycin 1 g q12h + Aztreonam)

shows reasons for nonevaluability in the FDA analysis. Patients could be unevaluable for more than one reason.

| | Linezolid | Vancomycin |
|-------------------------|------------------|-------------------|
| All randomized subjects | 205 | 197 |
| ITT | 203 (100%) | 193 (100%) |
| MITT | 94 (46.3%) | 83 (43.0%) |
| FDA CE | 122 (60.1%) | 103 (53.4%) |
| FDA ME | 54 (26.6%) | 41 (21.2%) |
| FDA ME2 | 22 (10.8%) | 20 (10.4%) |

| Reason | Linezolid (N=203) | | Vancomycin (N=193) | |
|------------------------------------|--------------------------|----------|---------------------------|----------|
| | n | % | n | % |
| Any | 81 | 39.9 | 90 | 46.6 |
| Negative chest radiograph | 0 | 0.0 | 3 | 1.6 |
| Prior antibiotic usage | 2 | 1.0 | 3 | 1.6 |
| Insufficient therapy | 36 | 17.7 | 38 | 19.7 |
| Noncompliance with therapy regimen | 31 | 15.3 | 36 | 18.7 |
| Concomitant antibiotics | 21 | 10.3 | 10 | 5.2 |
| No test of cure assessment | 46 | 22.7 | 57 | 29.5 |
| Indeterminate outcome | 2 | 1.0 | 7 | 3.6 |

Patients could be non-evaluable for more than one reason; therefore percentages add to more than 100.0.

Medical Officer's Comment

Although the sizes of the ITT and MITT populations were identical in the sponsor's and FDA's analysis, the assignment of outcomes differed; patients who died before the test of cure visit were considered missing by the sponsor, but were scored as failures in the FDA analysis. Given the relatively high mortality rate in this study in both treatment arms, this generally lowered response rates in both arms, and had a significant impact on differences between treatment arms, since there was higher all-cause mortality in the vancomycin arm.

The FDA clinically evaluable (CE) population was larger for both treatment arms than the sponsor's CE population. This was primarily due to the inclusion in the FDA CE analysis of patients who died from their initial infection; such patients were excluded from the sponsor's CE analysis by being assigned an outcome of missing. As with the ITT analyses, this had a significant impact on response rates.

Most patients were excluded from the clinically evaluable population for post-baseline reasons, rather than baseline ineligibility. Patients without a test of cure assessment were generally those who died prior to the TOC visit. The reasons for exclusion were relatively balanced between treatment arms, although more patients were discontinued for concomitant antibiotics in the linezolid arm.

Efficacy

Table 48A.6 shows clinical outcomes in the ITT and evaluable populations. The numbers of subjects listed in Table 48A.6 exclude patients with missing or indeterminate outcomes, except for analyses where missing outcomes were changed to failures.

MO Review of 48A (Linezolid 600 mg q12h + Aztreonam vs. Vancomycin 1 g q12h + Aztreonam)

| Population | Linezolid | Vancomycin | 95% C.I. |
|---------------------------|----------------|----------------|---------------|
| | n/N (%) | n/N (%) | |
| ITT | 85/174 (48.9%) | 73/164 (44.5%) | -6.9%, 15.6% |
| ITT (missing as failure) | 85/203 (41.9%) | 73/193 (37.8%) | -6.1%, 14.2% |
| MITT | 47/82 (57.3%) | 33/72 (45.8%) | -5.5%, 28.5% |
| MITT (missing as failure) | 47/94 (50.0%) | 33/83 (39.8%) | -5.5%, 26.0% |
| FDA CE | 70/122 (57.4%) | 62/103 (60.2%) | -16.6%, 11.0% |
| FDA ME | 36/54 (66.7%) | 26/41 (63.4%) | -18.3%, 24.8% |
| FDA ME2 | 16/22 (72.7%) | 13/20 (65.0%) | -25.0%, 40.5% |

Medical Officer's Comment

In the MITT analysis, linezolid has a higher response rate than does vancomycin. In the ME analysis, vancomycin has a slightly higher response rate. This difference is largely due to a higher response rate for vancomycin in the ME analysis compared to the vancomycin response rate in the MITT analysis. Patients who died before follow-up were considered failures in the FDA analysis; given the higher all-cause mortality rate in the vancomycin arm (see below) this would tend to drive response rates for vancomycin down in the MITT analysis. Most patients in the MITT analysis met the baseline clinical and radiographic criteria for diagnosis of pneumonia.

The response rates in the ME2 subpopulation – the group with the strongest evidence for the presence of HAP – were comparable between treatment arms.

Of note, there was a lower mortality rate due to the initial infection in the linezolid arm. There was also a lower all-cause mortality rate in the linezolid arm (see below under Safety).

Table 48A.7 shows clinical response rates stratified by demographic group.

| Subset | Linezolid (N=122) | Vancomycin (N=103) | 95% C.I. | Breslow-Day's P-value |
|-------------------|----------------------|-----------------------|-----------------|--------------------------|
| Gender | | | | 0.39 |
| Male | 49/86 (57.0%) | 44/69 (63.8%) | (-23.5%, 9.9%) | |
| Female | 21/36 (58.3%) | 18/34 (52.9%) | (-20.7%, 31.5%) | |
| Age | | | | 0.852 |
| 18-44 y | 12/21 (57.1%) | 12/23 (52.2%) | (-29.0%, 38.9%) | |
| 45-64 y | 19/29 (65.5%) | 22/31 (71.0%) | (-32.3%, 21.4%) | |
| ≥ 65 y | 39/72 (54.2%) | 28/49 (57.1%) | (-22.7%, 16.8%) | |
| Race | | | | 0.104 |
| White | 65/112 (58.0%) | 55/95 (57.9%) | (-14.3%, 14.6%) | |
| Other | 5/10 (50.0%) | 7/8 (87.5%) | (-87.3%, 12.3%) | |
| Study site | | | | 0.784 |
| US | 19/43 (44.2%) | 13/27 (48.2%) | (-31.0%, 23.0%) | |
| Non-US | 51/79 (64.6%) | 49/76 (64.5%) | (-16.3%, 16.4%) | |

Medical Officer's Comment

Response rates were comparable when stratified by demographic group. In addition, there were no interactions by age or gender. Interestingly, response rates were higher in both arms in the CE population at non-US sites; it is not clear if this reflects exclusion of patients who died before follow-up from the CE population.

MO Review of 48A (Linezolid 600 mg q12h + Aztreonam vs. Vancomycin 1 g q12h + Aztreonam)

Table 48A.8 shows clinical response rates stratified by score.

| Table 48A.8. Clinical cure rates by <u> </u> score – Study 48A | | |
|--|------------------|-------------------|
| <u> </u> score | Linezolid | Vancomycin |
| ITT | 85/174 (48.9%) | 73/164 (44.5%) |
| 0-11 | 38/57 (66.7%) | 26/39 (66.7%) |
| 12-15 | 19/38 (50.0%) | 27/50 (54.0%) |
| 16-19 | 13/34 (38.2%) | 11/32 (34.4%) |
| 20-39 | 14/43 (32.6%) | 8/41 (19.5%) |
| Missing score | 1/2 (50.0%) | 1/2 (50.0%) |
| MITT | 47/82 (57.3%) | 33/72 (45.8%) |
| 0-11 | 15/21 (71.4%) | 14/19 (73.7%) |
| 12-15 | 11/19 (57.9%) | 13/23 (56.5%) |
| 16-19 | 8/15 (53.3%) | 3/12 (25.0%) |
| 20-39 | 12/26 (46.2%) | 3/18 (16.7%) |
| Missing score | 1/1 (100.0%) | 0/0 (-) |
| FDA CE | 70/122 (57.4%) | 62/103 (60.2%) |
| 0-11 | 35/49 (71.4%) | 22/29 (75.9%) |
| 12-15 | 14/25 (56.0%) | 26/37 (70.3%) |
| 16-19 | 10/22 (45.5%) | 7/17 (41.2%) |
| 20-39 | 10/24 (41.7%) | 6/18 (33.3%) |
| Missing score | 1/2 (50.0%) | 1/2 (50.0%) |
| FDA ME | 36/54 (66.7%) | 26/41 (63.4%) |
| 0-11 | 13/18 (72.2%) | 10/12 (83.3%) |
| 12-15 | 8/12 (66.7%) | 12/16 (75.0%) |
| 16-19 | 6/10 (60.0%) | 2/5 (40.0%) |
| 20-39 | 8/13 (61.5%) | 2/8 (25.0%) |

Medical Officer's Comment

Although it is not possible to draw conclusions about the relative efficacy of linezolid and vancomycin from this analysis, given the small sizes of the subgroups, it is reassuring that those linezolid-treated patients at highest risk of death (baseline score of 20 or greater) showed a response rate that was similar to or higher than vancomycin in all analyses.

Table 48A.9 shows clinical response rates for patient subgroups of interest. Results are presented for the MITT and ME populations.

| Table 48A.9. Clinical cure rates for clinically relevant subgroups – Study 48A | | |
|---|------------------|-------------------|
| Subset | Linezolid | Vancomycin |
| MITT | | |
| Bacteremia | 5/10 (50.0%) | 4/10 (40.0%) |
| Ventilator-associated pneumonia | 30/56 (53.6%) | 14/46 (30.4%) |
| Ventilator-associated MRSA pneumonia | 11/21 (52.4%) | 5/17 (29.4%) |
| Non-ventilator-associated pneumonia | 17/26 (65.4%) | 19/26 (73.1%) |
| Aminoglycosides given | 10/22 (45.5%) | 9/23 (39.1%) |
| Aminoglycosides not given | 37/60 (61.7%) | 24/49 (49.0%) |
| Pseudomonas aeruginosa present | 4/5 (80.0%) | 4/10 (40.0%) |
| Pseudomonas aeruginosa not present | 43/77 (55.8%) | 29/62 (46.8%) |

MO Review of 48A (Linezolid 600 mg q12h + Aztreonam vs. Vancomycin 1 g q12h + Aztreonam)

| Subset | Linezolid | Vancomycin |
|---|---------------|---------------|
| ME | | |
| Bacteremia | 2/4 (50.0%) | 4/6 (66.7%) |
| Ventilator-associated pneumonia | 20/33 (60.6%) | 9/22 (40.9%) |
| Ventilator-associated MRSA pneumonia | 10/16 (62.5%) | 3/5 (60.0%) |
| Non-ventilator-associated pneumonia | 16/21 (76.2%) | 17/19 (89.5%) |
| Aminoglycosides given | 4/9 (44.4%) | 5/12 (41.7%) |
| Aminoglycosides not given | 32/45 (71.7%) | 21/29 (72.4%) |
| <i>Pseudomonas aeruginosa</i> present | 3/3 (100.0%) | 2/6 (33.3%) |
| <i>Pseudomonas aeruginosa</i> not present | 33/51 (64.7%) | 24/35 (68.6%) |

Medical Officer's Comment

For patients with predictors of poor outcome (ventilated at baseline, documented or presumed Gram-negative infection), the response rates for linezolid were higher than those for vancomycin in both the MITT and ME analyses. For patients without these risk factors, the linezolid rates were lower than but similar to those in the vancomycin arm. This analysis also demonstrates that the response rates for linezolid were comparable to those for vancomycin if aminoglycosides were not administered.

Table 48A.10 shows microbiologic outcomes in the FDA analysis.

| FDA-Defined Study Population | Linezolid | | Vancomycin | | 95% C.I. |
|------------------------------|-----------|------------------|------------|------------------|-----------------|
| | N | Success rate (%) | | Success rate (%) | |
| MITT | 82 | 54.9 | 74 | 50.0 | (-12.1%, 21.8%) |
| FDA ME | 54 | 64.8 | 41 | 65.9 | (-22.5%, 20.4%) |

Table 48A.11 shows clinical outcomes by pathogen in the FDA analysis for the MITT and ME populations.

| Subset | Linezolid | Vancomycin |
|---|---------------|---------------|
| MITT | | |
| <i>Staphylococcus aureus</i> | 27/53 (50.9%) | 19/48 (39.6%) |
| Methicillin-resistant <i>S. aureus</i> | 14/27 (51.9%) | 10/26 (38.5%) |
| Methicillin-susceptible <i>S. aureus</i> | 13/26 (50.0%) | 9/22 (40.9%) |
| <i>Streptococcus pneumoniae</i> | 11/14 (78.6%) | 10/13 (76.9%) |
| Penicillin-resistant <i>S. pneumoniae</i> | 2/2 (100.0%) | 0/0 (-) |
| ME | | |
| <i>Staphylococcus aureus</i> | 23/38 (60.5%) | 14/23 (60.9%) |
| Methicillin-resistant <i>S. aureus</i> | 13/22 (59.1%) | 7/10 (70.0%) |
| Methicillin-susceptible <i>S. aureus</i> | 10/16 (62.5%) | 7/13 (53.8%) |
| <i>Streptococcus pneumoniae</i> | 9/9 (100.0%) | 9/10 (90.0%) |
| v Penicillin-resistant <i>S. pneumoniae</i> | 2/2 (100.0%) | 0/0 (-) |

Medical Officer's Comment

Overall, microbiologic response rates were comparable between treatment arms. With regard to individual pathogens, response rates for linezolid were comparable to or higher than those for vancomycin for MRSA and *S. pneumoniae*. Although response rates for vancomycin for MRSA were higher in the ME analysis, this appears to be due to an increase in the response rate for vancomycin in moving from the MITT to ME analysis, and most likely reflects the exclusion of vancomycin patients who died before follow-up from the ME analysis.

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 48A.12.

| Table 48A.12. Summary of deaths, SAEs, discontinuations and clinical AEs – Study 48A | | | |
|---|------------------------------|-------------------------------|-------------------------|
| Safety Outcomes | Linezolid (N=203) | Vancomycin (N=193) | Fisher's P-value |
| Died | 36 (17.7%) | 49 (25.4%) | 0.067 |
| Died with infection related by TOC | 11 (5.4%) | 17 (8.8%) | 0.240 |
| Serious AE | 63 (31.0%) | 65 (33.7%) | 0.592 |
| Discontinuation due to AE | 13 (6.4%) | 20 (10.4%) | 0.203 |
| Discontinuation due to drug-related AE | 3 (1.5%) | 4 (2.1%) | 0.718 |
| Any AE | 143 (70.4%) | 143 (74.1%) | 0.434 |
| Body | 58 (28.6%) | 56 (29.0%) | 1.000 |
| Cardiovascular | 54 (26.6%) | 45 (23.3%) | 0.487 |
| Digestive | 58 (28.6%) | 50 (25.9%) | 0.574 |
| Hemic and Lymphatic | 20 (9.9%) | 15 (7.8%) | 0.485 |
| Metabolic and Nutritional | 20 (9.9%) | 17 (8.8%) | 0.734 |
| Musculo-skeletal | 2 (1.0%) | 0 (0.0%) | 0.499 |
| Nervous | 31 (15.3%) | 31 (16.1%) | 0.890 |
| Respiratory | 50 (24.6%) | 54 (28.0%) | 0.494 |
| Skin | 27 (13.3%) | 31 (16.1%) | 0.479 |
| Special senses | 4 (2.0%) | 3 (1.6%) | 1.000 |
| Urogenital | 31 (15.3%) | 23 (11.9%) | 0.380 |
| Any drug-related AE | 27 (13.3%) | 30 (15.5%) | 0.568 |
| Body | 3 (1.5%) | 4 (2.1%) | 0.718 |
| Cardiovascular | 0 (0.0%) | 4 (2.1%) | 0.056 |
| Digestive | 14 (6.9%) | 15 (7.8%) | 0.848 |
| Hemic and Lymphatic | 3 (1.5%) | 3 (1.6%) | 1.000 |
| Metabolic and Nutritional | 3 (1.5%) | 5 (2.6%) | 0.494 |
| Respiratory | 1 (0.5%) | 0 (0.0%) | 1.000 |
| Skin | 5 (2.5%) | 7 (3.6%) | 0.567 |
| Urogenital | 2 (1.0%) | 1 (0.5%) | 1.000 |

Medical Officer's Comment

As noted earlier, all-cause and infection-specific mortality rates were lower in the linezolid arm. While these results must be interpreted cautiously, since death in patients with hospital-acquired pneumonia can rarely be attributed definitively to a specific cause, they are reassuring with respect to use of linezolid in this population. None of the deaths were considered directly attributable to linezolid or vancomycin.

MO Review of 48A (Linezolid 600 mg q12h + Aztreonam vs. Vancomycin 1 g q12h + Aztreonam)

The rates of serious, non-serious, and drug-related adverse events were comparable between treatment arms. None of the SAEs in the linezolid arm were felt to be drug-related.

Specific adverse events are shown in Table 48A.13.

| Table 48A.13. Study-Emergent Adverse Events >2% Within Body Systems: ITT | | | | | |
|--|------------------------------|----------|-------------------------------|----------|----------------|
| | Linezolid (N=203) | | Vancomycin (N=193) | | P-value |
| | n | % | n | % | |
| Patients With at Least One | 143 | 70.4 | 143 | 74.1 | 0.4176 |
| BODY | | | | | |
| Chest pain | 1 | 0.5 | 4 | 2.1 | 0.1593 |
| Fever | 8 | 3.9 | 7 | 3.6 | 0.8701 |
| Generalized edema | 6 | 3.0 | 3 | 1.6 | 0.3497 |
| Infection bacterial NOS | 1 | 0.5 | 4 | 2.1 | 0.1593 |
| Inject./vascular catheter site infection | 4 | 2.0 | 1 | 0.5 | 0.1957 |
| Localized Pain | 4 | 2.0 | 2 | 1.0 | 0.4469 |
| Microbiological test abnormal NOS | 6 | 3.0 | 6 | 3.1 | 0.9292 |
| Reaction unevaluable | 4 | 2.0 | 1 | 0.5 | 0.1957 |
| Sepsis | 11 | 5.4 | 8 | 4.1 | 0.5533 |
| Septic shock | 5 | 2.5 | 5 | 2.6 | 0.9355 |
| Trauma | 8 | 3.9 | 4 | 2.1 | 0.2783 |
| CARDIOVASCULAR | | | | | |
| Atrial fibrillation | 3 | 1.5 | 4 | 2.1 | 0.6535 |
| Bradycardia NOS | 5 | 2.5 | 3 | 1.6 | 0.5206 |
| Cardiac arrest NEC | 3 | 1.5 | 5 | 2.6 | 0.4314 |
| Congestive heart failure | 9 | 4.4 | 2 | 1.0 | 0.0398 |
| Deep vein thrombosis | 4 | 2.0 | 4 | 2.1 | 0.9425 |
| Hypertension | 7 | 3.4 | 0 | 0.0 | 0.0092 |
| Hypotension | 5 | 2.5 | 5 | 2.6 | 0.9355 |
| Myocardial infarction | 4 | 2.0 | 4 | 2.1 | 0.9425 |
| DIGESTIVE | | | | | |
| Constipation | 8 | 3.9 | 9 | 4.7 | 0.7230 |
| Diarrhea | 19 | 9.4 | 15 | 7.8 | 0.5730 |
| Gastrointestinal bleeding | 4 | 2.0 | 6 | 3.1 | 0.4705 |
| Ileus | 5 | 2.5 | 1 | 0.5 | 0.1133 |
| Monilia oral | 4 | 2.0 | 5 | 2.6 | 0.6789 |
| Multiple organ failure | 5 | 2.5 | 2 | 1.0 | 0.2815 |
| Nausea | 7 | 3.4 | 4 | 2.1 | 0.4050 |
| Vomiting | 6 | 3.0 | 4 | 2.1 | 0.5756 |
| HEMIC AND LYMPHATIC | | | | | |
| Anemia | 10 | 4.9 | 7 | 3.6 | 0.5238 |
| Thrombocytopenia | 2 | 1.0 | 4 | 2.1 | 0.3760 |
| METABOLIC AND NUTRITIONAL | | | | | |
| Hyperglycemia | 5 | 2.5 | 3 | 1.6 | 0.5206 |
| Hypokalemia | 4 | 2.0 | 2 | 1.0 | 0.4469 |
| NERVOUS | | | | | |
| Agitation | 6 | 3.0 | 6 | 3.1 | 0.9292 |
| Anxiety | 4 | 2.0 | 4 | 2.1 | 0.9425 |
| Confusion | 4 | 2.0 | 2 | 1.0 | 0.4469 |

Table 48A.13. Study-Emergent Adverse Events >2% Within Body Systems: ITT

| COSTART Body System /MET | Linezolid (N=203) | | Vancomycin (N=193) | | P-value |
|-------------------------------|-------------------|-----|--------------------|-----|---------|
| | n | % | n | % | |
| NERVOUS | | | | | |
| Convulsion | 6 | 3.0 | 1 | 0.5 | 0.0658 |
| Depressive symptoms | 4 | 2.0 | 3 | 1.6 | 0.7535 |
| Encephalopathy | 6 | 3.0 | 2 | 1.0 | 0.1748 |
| Insomnia | 7 | 3.4 | 2 | 1.0 | 0.1074 |
| RESPIRATORY | | | | | |
| Dyspnea | 6 | 3.0 | 5 | 2.6 | 0.8252 |
| Effusion pleural | 3 | 1.5 | 4 | 2.1 | 0.6535 |
| Pneumonia | 13 | 6.4 | 11 | 5.7 | 0.7690 |
| Respiratory distress syndrome | 3 | 1.5 | 5 | 2.6 | 0.4314 |
| Respiratory failure | 14 | 6.9 | 8 | 4.1 | 0.2322 |
| SKIN | | | | | |
| Dermatitis fungal | 2 | 1.0 | 4 | 2.1 | 0.3760 |
| Erythema | 1 | 0.5 | 5 | 2.6 | 0.0876 |
| Pressure sore | 6 | 3.0 | 5 | 2.6 | 0.8252 |
| Rash | 4 | 2.0 | 11 | 5.7 | 0.0520 |
| Skin erosion NEC | 4 | 2.0 | 2 | 1.0 | 0.4469 |
| UROGENITAL | | | | | |
| Failure Kidney Acute | 6 | 3.0 | 1 | 0.5 | 0.0658 |
| Infection Urinary Tract | 12 | 5.9 | 6 | 3.1 | 0.1808 |
| Kidney failure | 0 | 0.0 | 4 | 2.1 | 0.0392 |

The only drug-related adverse event occurring at a frequency of >2% was diarrhea, which occurred in 9/203 (4.4%) patients in the linezolid arm and 4/193 (2.6%) patients in the vancomycin arm.

Medical Officer's Comment

Although the incidence of adverse events was generally comparable between treatment arms, there was a higher incidence of hypertension and congestive heart failure in linezolid-treated patients. Although none of these were attributed to linezolid, this result raises the issue of whether the patients involved were receiving concomitant medications that could have interacted with linezolid vis-a-vis its MAO inhibitory activity.

To address this issue, the treatment arms were compared using CrossGraphs to determine if there was evidence of an association between concomitant medication use and hypertension or CHF. This analysis included examination of adverse events such as myocardial infarction that could be pathophysiologically related to CHF or hypertension. Classes of medications examined included indirect-acting sympathomimetic amines, MAO inhibitors, amphetamines and other stimulants, inhaled bronchodilators, and vasopressors. There was a higher rate of concomitant use of inhaled sympathomimetic bronchodilators in linezolid-treated patients who had an AE of CHF versus vancomycin-treated patients (6/8 vs. 1/3), and in those who had an AE of hypertension (2/5 vs. 0/0). However, there did not appear to be a temporal correlation between use of bronchodilators and either of these AEs. In each instance, the adverse event appeared to be related to a pre-existing condition. While this analysis does not exclude the possibility that use of bronchodilators together with linezolid could exacerbate pre-existing CHF or hypertension, it suggests that the differences between treatment arms are most consistent with

MO Review of 48A (Linezolid 600 mg q12h + Aztreonam vs. Vancomycin 1 g q12h + Aztreonam)

random effects, given the small numbers of patients involved. However, it would be important in post-marketing surveillance to address the possibility of a true interaction.

Laboratory findings

Hematology

The sponsor analyzed changes in mean values of hematologic laboratory values over time. These appeared comparable between treatment groups for hematocrit, hemoglobin, WBC count, neutrophil count, and platelet 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 48A.14.

Table 48A.14. Incidence of substantially abnormal hematologic laboratory values – Study 48A

| Laboratory Assay | Criteria | Linezolid | | | Vancomycin | | |
|--------------------|-------------|-----------|-----|-------|------------|-----|-------|
| | | n | N | % | n | N | % |
| Hemoglobin | <75% of LLN | 33 | 201 | 16.42 | 35 | 187 | 18.72 |
| Hematocrit | <75% of LLN | 25 | 200 | 12.50 | 28 | 186 | 15.05 |
| Platelet Count | <75% of LLN | 5 | 200 | 2.50 | 13 | 186 | 6.99 |
| WBC | <75% of LLN | 0 | 201 | 0.00 | 4 | 187 | 2.14 |
| Neutrophils | <0.5 LLN | 0 | 199 | 0.00 | 3 | 186 | 1.61 |
| Eosinophils | >= 10% | 5 | 199 | 2.51 | 7 | 186 | 3.76 |
| Reticulocyte Count | >2 x ULN | 0 | 196 | 0.00 | 5 | 183 | 2.73 |

Medical Officer's Comment

As with other studies, the medical officer independently reviewed the hematology dataset using CrossGraphs. In contrast to the community-acquired pneumonia studies (Studies 33 and 51) and the MRSA study (Study 31), the linezolid arm had a lower incidence of thrombocytopenia than the comparator arm in this study in patients with a normal platelet count at baseline (8/166 (4.8%) vs. 10/172 (5.8%)). This may reflect the fact that vancomycin has been associated with thrombocytopenia, as well as use of multiple other medications that can affect platelet count (e.g., heparin) in this study.

The medical officer's analysis did not find any significant difference with respect to WBC counts, neutrophil counts or hemoglobin concentrations, in agreement with the sponsor's analysis.

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 48A.15.

| Laboratory Assay | Criteria | Linezolid | | | Vancomycin | | |
|----------------------|-------------|-----------|-----|-------|------------|-----|-------|
| | | n | N | % | n | N | % |
| Total Bilirubin | >2 x ULN | 8 | 200 | 4.00 | 4 | 188 | 2.13 |
| Total Protein | <0.75 x LLN | 23 | 202 | 11.39 | 15 | 188 | 7.98 |
| Albumin | <0.75 x LLN | 20 | 198 | 10.10 | 14 | 188 | 7.45 |
| AST | >2 x ULN | 20 | 200 | 10.00 | 21 | 188 | 11.17 |
| ALT | >2 x ULN | 37 | 200 | 18.50 | 32 | 188 | 17.02 |
| LDH | >2 x ULN | 12 | 199 | 6.03 | 8 | 187 | 4.28 |
| Alkaline Phosphatase | >2 x ULN | 26 | 201 | 12.94 | 17 | 189 | 8.99 |
| BUN | >2 x ULN | 11 | 202 | 5.45 | 7 | 189 | 3.70 |
| Creatinine | >2 x ULN | 2 | 201 | 1.00 | 2 | 189 | 1.06 |
| Sodium | <0.95 x LLN | 8 | 202 | 3.96 | 5 | 189 | 2.65 |
| | >1.05 x ULN | 3 | 202 | 1.49 | 2 | 189 | 1.06 |
| Potassium | <0.9 x LLN | 8 | 201 | 3.98 | 6 | 189 | 3.19 |
| | >1.1 x ULN | 4 | 201 | 1.99 | 3 | 189 | 1.60 |
| Chloride | <0.9 x LLN | 0 | 202 | 0.00 | 1 | 189 | 0.53 |
| | >1.1 x ULN | 0 | 202 | 0.00 | 1 | 189 | 0.53 |
| Bicarbonate | <0.9 x LLN | 5 | 199 | 2.51 | 5 | 188 | 2.66 |
| | >1.1 x ULN | 7 | 199 | 3.52 | 9 | 188 | 4.79 |
| Calcium | <0.9 x LLN | 19 | 202 | 9.41 | 21 | 188 | 11.17 |
| | >1.1 x ULN | 0 | 202 | 0.00 | 1 | 188 | 0.53 |
| Non-Fasting Glucose | <0.6 x LLN | 0 | 200 | 0.00 | 1 | 187 | 0.53 |
| | >1.4 x ULN | 28 | 200 | 14.00 | 30 | 187 | 16.04 |
| Creatine Kinase | >2 x ULN | 15 | 198 | 7.58 | 10 | 188 | 5.32 |
| Lipase | >2 x ULN | 32 | 199 | 16.08 | 22 | 188 | 11.70 |
| Amylase | >2 x ULN | 10 | 199 | 5.03 | 6 | 188 | 3.19 |

Medical Officer' Comment

The medical officer's analysis did not find any difference between treatment arms with respect to abnormal chemistry laboratory values. However, two patients with significantly elevated lipase concentrations (> 500 U/L) were noted who had symptoms consistent with pancreatitis. One of these patients had undergone substantial abdominal surgery and presumably was receiving total parenteral nutrition; the lipid component of TPN has been associated with pancreatitis. One patient developed hyperbilirubinemia and significant elevations of transaminases while on linezolid. However, this occurred in the setting of sepsis and massive hemorrhage, both of which can cause severe hepatic dysfunction.

Final conclusions

This was a randomized, comparative trial of linezolid versus vancomycin in the treatment of hospital-acquired pneumonia. The trial was designed according to IDSA and divisional guidelines for this indication. One of the major strengths of the trial was its double-blind design, as well as use of appropriate clinical and microbiologic criteria to define the study population. The trial was weakened, however, by the decision to submit a portion of the data as a completed trial but continue the study under a separate designation. This has the potential to introduce bias. However, the impact of this decision was greatly reduced by the double-blind nature of the trial, and its implementation before the study blind was broken, which allows the conclusion that

this was an adequate and well-controlled trial.

The results show efficacy for linezolid in the treatment of hospital-acquired pneumonia. Response rates were comparable between treatment arms, both overall, and for clinically relevant subgroups of interest (such as patients with high [redacted] scores), although the response rates were quite low, as would be expected in this seriously ill patient population. Linezolid showed efficacy against S. aureus (both methicillin-resistant and susceptible strains) comparable to that for vancomycin, as well as for S. pneumoniae, although it should be kept in mind that vancomycin does not represent optimal therapy for infections due to methicillin-susceptible S. aureus or pneumococcus. There were too few isolates of PRSP to demonstrate efficacy against this organism.

With respect to safety, the incidence of adverse events was generally comparable between treatment arms. The increased incidence of hypertension and CHF in the linezolid arm did not appear to be associated with use of concomitant medications such as indirect-acting amines. The treatment arms were also comparable in both the sponsor's and medical officer's analyses with respect to laboratory abnormalities.

In summary, this study provides evidence of safety and efficacy for linezolid in the treatment of hospital-acquired pneumonia. When combined with the data from the studies of community-acquired pneumonia (see Integrated Summary of Efficacy), the NDA contains substantial evidence of safety and efficacy that would support approval for this indication.

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