- Chemistry- AST, ALT, albumin, alkaline phosphatase, amylase, bilirubin, BUN, calcium, creatinine, creatine phosphokinase, sodium, potassium, bicarbonate, chloride, glucose, GGT, LDH, lipase, total protein and uric acid.
- Urinalysis- with microscopic.
- Pregnancy test for females of child bearing potential- A urine or serum b-HCG pregnancy test had to be performed at the site to qualify the patient for study entry, and a serum b-HCG assay was performed by the central laboratory at baseline and the Long Term Follow-up visit. The investigator baseline results had to be available and negative before the patient could take the first dose of study medication.
- Site culture and Gram stain- performed locally.
- Blood culture- Two sets (each set included aerobic and anaerobic; drawn from multiple sites at least 5 minutes apart) obtained at baseline; single sets thereafter.
- Bacterial isolate susceptibility testing- Susceptibility tests could be conducted (not required from the local investigator laboratory) to determine if pathogens were susceptible to linezolid, oxacillin sodium, and dicloxacillin sodium. Oxacillin sodium and dicloxacillin sodium susceptibility could be determined from the microtiter plates. Minimum inhibitory concentrations were determined from a panel of antibiotics by the central laboratory.

At baseline, the local laboratory had to perform a pregnancy test and also perform assays for hematology, chemistry, urinalysis, and microbiological culture evaluations to determine the patient's eligibility to enter the study. All laboratory and microbiological culture evaluations, including baseline, were performed by a central laboratory so that assay results were consistent and suitable for group analysis.

Deep culture specimens (such as from a biopsy, needle aspiration, surgically obtained specimens or fluids/pus) of the area contiguous to the primary infected area were to be obtained; swabs of intact skin surfaces or contaminated wounds were not acceptable. All potentially significant blood (aerobic and anaerobic) and infection site isolates were to be sent to the central laboratory for verification.
(M. O. Comment: The instruction for submission of potentially significant blood isolates resulted in many reports of bacteremia due to *Staphylococcus epidermidis*. Despite the instructions on deep culture specimens, there were still many isolates reported from swab samples. Other instructions for microbiological methods were provided in the protocol, but will not be repeated here.)

Screening Activities - After giving informed consent, eligible patients were randomized to either the linezolid or oxacillin sodium / dicloxacillin sodium treatment groups and provided suitable infection site specimens for gram stain, microbiological culture, and susceptibility testing; gram stain and culture samples were obtained before study medication administration. Blood was drawn for microbiological culture and laboratory assays. All patients provided a medical history (including the cause of infection, any underlying medical conditions, previous medical/surgical therapy for the infected site, and an evaluation of previous antibiotic exposure), urinalysis, and had a physical examination, vital signs, ECG, and clinical observations performed/obtained. Females of

child-bearing potential had a negative pregnancy test (performed locally) prior to receiving study medication.

Treatment Period Activities - All patients were initially hospitalized and could begin their study medication before laboratory results were available. Patients were allowed to receive their initial 12 hours of study medication while the safety laboratory tests were processed. If the safety laboratory criteria were not met, the patient was dropped from the study.
Patients whose microbiological cultures grew non-susceptible gram-positive or gram-negative pathogens could remain in the study if they showed clinical improvement and did not require concomitant antibiotic therapy (other than aztreonam). Patients with negative site cultures (no growth) at 72 hours but who were clinically improving, could remain in the study. After observed clinical signs and symptoms improvement, the patients were switched from intravenous to oral treatment. The sponsor recommended an infection site culture specimen be obtained at the switch from intravenous to oral treatment, if obtainable, and whenever clinically indicated. Positive baseline blood cultures were repeated at 48 to 72 hours and again 48 hours later if still positive. Subjects would have been dropped from the study if there were three positive cultures. Clinical observations and vital signs were recorded every 3 days while the patient was hospitalized, and/or at the switch from intravenous to oral treatment, and then every 6 days (+/- 48 hours) while treated as an outpatient. Laboratory assays were conducted on blood samples at Baseline, Days 3, 9, 15, End-of-Treatment, and Long Term Follow-up for all patients; laboratory assays also needed to be done when the patient was switched from intravenous to oral treatment unless this corresponded with a regularly scheduled visit. Patients that had their treatment extended had laboratory assays done on Day 21. Within 72 hours of treatment completion, a repeat infection site culture (if obtainable), clinical observations, vital signs, hematology, chemistry, a clinical response evaluation, and a treatment completion report were obtained/completed.

Post-Treatment Activities - A long-term follow-up, or final visit, was completed between 15 and 21 days after treatment and considered the test-of-cure evaluation. Clinical observations, vital signs, hematology, and chemistry specimens were completed/obtained. A microbiological infection site specimen was cultured (if obtainable), blood culture (if positive at baseline), repeat pregnancy test, physical examination, and urinalysis were also performed/obtained. The clinical response evaluation and study completion report forms were completed at the long-term follow-up evaluation (or whenever a patient withdrew from the study. If any patient was noted to be a clinical failure or had any drainage from the infection site post treatment, the site was cultured and/or blood culture specimens were obtained as clinically indicated.
(M. O. Comment: The follow-up visit is the test-of cure visit. Although the follow-up visit remained at 15 and 21 days after treatment, amendment 1 of the protocol specified that the evaluable window was 12 to 28 days after treatment.)

Efficacy assessments: Efficacy assessments were based on patient disposition with regard to 1) clinical signs and symptoms assessed after treatment as compared with those observed at baseline and 2) microbiological assessments after treatment compared with

those conducted at baseline. Clinically evaluable patients were those who fulfilled the study entry criteria, received at least 80% of their total prescribed study medication without missing two consecutive doses during the first 7 days of treatment, and returned for a follow-up visit. Microbiologically evaluable patients were those who additionally had a confirmed pathogen at baseline from either the infection site and/or a blood culture. The confirmed pathogen could not be resistant to either study medication. The test-of-cure evaluation was conducted at the Long Term Follow-up visit.
Patients who withdrew from the study due to any of the following were classified as treatment failures:

- Lack of clinical improvement after at least 48 hours of treatment.
- Lack of microbiological improvement (such as three consecutive positive blood cultures).
- Disease progression such as septic shock and/or acute renal failure.

Patients who required an incision and drainage greater than 48 hours after the first dose of study medication were classified as indeterminate. Safety assessments were based on the evaluation of clinical observations, vital sign measurements, laboratory assays, and recorded adverse events.
(M.O. Comment: The protocol provides instructions for classification and reporting of adverse events in great detail. These portions of the protocol will not be repeated for this review. The criteria for clinical and microbiological evaluability above correspond roughly to criteria provided in the draft guidance for industry for skin and skin structure infections. The sponsor required at least 5 days and 20 doses of study medication before an assessment of cure or improvement could be made, and at least 2 days or 8 doses for an assessment of failure.)

Clinical Outcomes: At the End-of-Treatment and the Long Term Follow-up (test-of-cure) visits, the investigator assessed all patients for clinical outcome according to the following criteria:

- Cured- Resolution of infection signs and symptoms or improvement to such an extent that no further antimicrobial treatment was necessary.
- Improved- Partial resolution of clinical symptoms with no additional antimicrobial therapy required (this outcome category was only used at the EOT evaluation).
- Failed- Persistence, incomplete resolution, or worsening of entry signs and symptoms with emergence of new disease signs or symptoms and/or requiring additional antimicrobial therapy. Patients experiencing adverse event(s) that requires study medication discontinuation will be deemed clinical failures.
- Indeterminate- Extenuating circumstances that preclude classification to one of the above outcomes.

Microbiological Outcomes: Patient microbiological responses were based on central laboratory culture and sensitivity testing results and assessed according to the following definitions:

- Documented microbiologic eradication- The absence of the original pathogen or pathogens from the culture of the original site of infection at the test-of-cure visit.

- Presumed microbiologic eradication- The patient is clinically cured at the test-of-cure visit and no appropriate material is available for culture from the original site of infection
- Documented microbiologic persistence- The presence of at least one of the original pathogens from the culture of the original site of infection at the test-of-cure visit.
- Presumed microbiologic persistence- The patient is a clinical failure at the test-of-cure visit and no appropriate material is available for culture from the original site of infection.
- Superinfection- Any patient classified as clinically failed or clinically improved who has a pathogen isolated during therapy that is different than the original pathogen(s).
- Colonization- Isolation of an organism other than one isolated at baseline in a patient classified as a clinical cure.
- Reinfection- Any patient classified as a clinical failure who has a pathogen isolated after the End-of-Treatment visit that is different than the original pathogen(s).
- Indeterminate- Any patient who cannot be classified into one of the above categories.

(M. O. Comment: As with protocol 39/39A, the majority of subjects fall into the presumed eradication category. The M. O. focused on clinical outcome in the review of study results for reasons described with the microbiological outcome results of Study 39A.)

Statistical and Analytical Plan: Analyses of efficacy variables (primary and secondary) were done separately using clinically evaluable and microbiologically evaluable patients. Additionally, analyses of primary efficacy variables were done for the ITT group of patients, and analyses of primary and secondary efficacy variables were done for a modified intent-to-treat (MITT) group of patients. The ITT population was defined as all randomized patients who received at least one dose of study medication, while the MITT population was defined as a subset of the ITT population who also had an organism isolated at baseline. Analyses of safety variables were done using the ITT population.

Primary Variables - The primary efficacy variables in this study were patient clinical outcome, microbiologic outcome, and overall (combined clinical/microbiologic) outcome. The test-of-cure assessments were done at the long-term follow-up (LTFU) visit. The proportions of patients in each clinical outcome category were compared between treatment groups at LTFU using a chi-square test for homogeneity of proportions. The proportions of patients in relevant microbiologic outcome categories (as well as in the microbiologic success category) were compared between treatment groups at LTFU using a chi-square test for homogeneity of proportions (microbiologic success was defined as documented or presumed microbiologic eradication, or colonization). Patient overall outcome was measured as cure, failure, or indeterminate, with cure defined as a patient who was judged to be both a clinical cure and a microbiologic success, and failure defined as a patient who was a clinical failure and/or a microbiologic failure. The proportions of patients in these overall outcome categories were compared between treatment groups using a chi-square test for homogeneity of proportions. For all three primary efficacy variables, confidence intervals for the differences in success rates between the treatment groups were calculated. These confidence intervals were based on a normal approximation to the binomial distribution of success/failure.

Determination of Sample Size - Using a 2-sided test level of 5% and a desired statistical power of 80% under the assumption that each treatment group will yield a 90% success rate, 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 45%, this translates to a requirement of 316 enrolled patients per treatment group.

(M. O. Comment: The protocol sections that discussed the efficacy assessment and analytical plan were essentially the same as for the uncomplicated SSSI protocol, except that this protocol did not include plans for a futility analysis. Details of the plan for analyzing and reporting results for secondary variables, demographic factors, adverse events, and laboratory assays were included in the protocol. The sponsor was able to exceed the required number of enrolled and evaluable patients in each treatment group.)

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Results for Study 55

The sponsor's results are excerpted from the final study report for Study 55. The FDA analyses of the sponsor's data are provided together with the sponsor's results for comparison. A brief description of the methodology used by the FDA to produce these analyses is described in Appendix 1 of this document. Differences between the sponsor's results and FDA's results are discussed in the body of this section. Where the sponsor's results are provided alone, the reviewer did not perform a separate analysis or the reviewer's results are comparable.

Population Definitions

Discontinuation from Study - The first table shows the patient disposition for all randomized patients. Of the 826 patients who enrolled in the study, 403 patients were randomized to the linezolid treatment group, and 423 patients to the oxacillin treatment group. 819 patients received study medication and were in the ITT group: 400 patients received linezolid, and 419 patients received oxacillin. Comparable percentages of patients in each treatment group completed the study. Of the 400 patients in the linezolid treatment group, 336 (84.0%) subjects completed both the treatment and follow-up phases of the study; 357 (89.3%) completed treatment, and 346 (86.5%) completed the follow-up phase. Of the 419 patients in the oxacillin treatment group, 327 (78.0%) subjects completed both the treatment and follow-up phases of the study; 349 (83.3%) completed treatment, and 346 (82.6%) completed the follow-up phase.

Sponsor: Summary of Patient Disposition for all Randomized Patients

	Linezolid N = 403		Oxacillin/Dicloxacillin N = 423	
Population	**n**	**%**	**n**	**%**
Intent-To-Treat Patients (ITT)	400	100.0	419	100.0
Discontinued During Treatment	43	10.8	70	16.7
Completed Treatment	357	89.3	349	83.3
Discontinued During F-U	54	13.5	73	17.4
Completed F-U	346	86.5	346	82.6
Discontinued During Treatment and/or F-U	64	16.0	92	22.0
Completed Treatment and F-U	336	84.0	327	78.0

The sponsor provided reasons for discontinuation of subjects during treatment and during follow-up in the following two tables. A total of 64 (16.0%) patients in the linezolid group and 92 (22.0%) patients in the oxacillin group discontinued at some time during the study. The following two tables were provided by the sponsor to indicate reasons for discontinuations. Most of the subjects who discontinued are listed in both of the tables. The sponsor did not provide a table combining discontinuations during treatment and follow-up.

Sponsor: Reasons for Discontinuation During Treatment (ITT)

	Linezolid N = 400		Oxacillin/Dicloxacillin N = 419	
Reasons for Discontinuations	**n**	**%**	**n**	**%**
Discontinued Patients	43	10.8	70	16.7
Lack of Efficacy	9	2.3	15	3.6
Death	1	0.3	0	-
AE (Serious)	2	0.5	7	1.7
AE (Non-serious)	8	2.0	13	3.1
Ineligible, but Started Study Medication	4	1.0	3	0.7
Protocol Noncompliance	3	0.8	5	1.2
Subject's Personal Request	2	0.5	6	1.4
Lost to F-U	8	2.0	10	2.4
Other	6	1.5	11	2.6

Sponsor: Reasons for Discontinuation During Follow-up (ITT)

	Linezolid N = 400		Oxacillin/Dicloxacillin N = 419	
Reasons for Discontinuations	**n**	**%**	**n**	**%**
Discontinued Patients	54	13.5	73	17.4
Lack of Efficacy	8	2.0	10	2.4
Death	2	0.5	0	-
AE (Serious)	1	0.3	3	0.7
AE (Non-serious)	5	1.3	6	1.4
Ineligible, but Started Study Medication	2	0.5	4	1.0
Protocol Noncompliance	3	0.8	3	0.7
Subject's Personal Request	3	0.8	5	1.2
Lost to F-U	27	6.8	32	7.6
Other	3	0.8	10	2.4

Evaluable Populations - The following table provides the numbers of patients in the ITT, modified intent-to-treat (MITT), clinically evaluable, and microbiologically evaluable groups, as determined by the sponsor. The patient numbers in each group were balanced across the two treatment arms. The MITT patient population in each treatment arm consisted of all subjects with one or more organisms isolated from baseline cultures.

Sponsor: Evaluable Populations

	Linezolid		Oxacillin/Dicloxacillin	
Population	**N**	**%**	**n**	**%**
All Randomized Patients	403	-	423	-
Never Received Study Medication	3	-	4	-
ITT Patients	400	100.0	419	100.0
No Baseline Pathogen	188	47.0	200	47.7
MITT Patients	212	53.0	219	52.3
Clinically Evaluable Patients	298	74.5	302	72.1
Microbiologically Evaluable Patients	143	35.8	151	36.0

The number and percentage of patients in the evaluable populations as determined by the FDA analyses are shown in the following table. The ITT patient populations are the same in the FDA and sponsor analyses. The ITT group was defined as all patients who received at least one dose of study medication. The clinically evaluable population is also similar in the sponsor's and reviewer's analyses. The microbiologically evaluable population defined by the FDA is much smaller than that used by the sponsor. The sponsor included *Staphylococcus epidermidis, Staphylococcus haemolyticus,* and other organisms in the ME population. The FDA ME population included *Staphylococcus aureus, Streptococcus pyogenes, Streptococcus agalactiae, Enterococcus faecalis*, and *Enterococcus faecium.* Most of the other organisms reported by the sponsor were likely contaminants or were isolated in too few cases to contribute greatly.

The FDA reviewer also identified an ITT-prime population. This consists of subjects who met all baseline inclusion and exclusion criteria. As noted in the protocol review, the inclusion criteria required some indication of systemic inflammatory response (fever, WBC count >10,000/mm^3, or immature neutrophils >15%). The main reason for exclusion from the ITT-prime population is lack of this inflammatory response. Roughly 20% of linezolid subjects and 25% of oxacillin subjects did not meet this inclusion criterion.

M. O.: Evaluable Populations

	Linezolid N=400		Oxacillin/Dicloxacillin N=419	
Population	**N**	**%**	**N**	**%**
ITT Patients	400	100.0	419	100.0
ITT-Prime Patients	316	79.0	313	74.7
Clinically Evaluable Patients (CE)	245	61.3	242	57.8
Microbiologically Evaluable Patients (ME)	101	25.3	108	25.8

The first table on the following page shows the reasons that subjects were considered non-evaluable. A single subject could have multiple reasons for non-evaluability. Subjects who were not clinically evaluable fell into three main categories. These categories are insufficient therapy, non-compliance, or outcome assessment not in evaluable window. This last category included subjects lost to follow-up and subjects whose outcome assessment was not between 12 and 28 days after end of therapy, and was the main reason for clinical non-evaluability. Most microbiologically non-evaluable patients did not have any baseline pathogens, were clinically non-evaluable, or had an organism resistant to oxacillin. Oxacillin-resistant organisms included *Staphylococcus aureus* and *Staphylococcus epidermidis*. None of the baseline pathogens were reported as resistant to linezolid.

Sponsor: Reasons for Non-Evaluability

	Linezolid N = 400		Oxacillin/Dicloxacillin N = 419	
Patient Subset/Reason for Exclusion	**n**	**%**	**n**	**%**
Clinically Evaluable Patients	298	74.5	302	72.1
Clinically Not Evaluable Patients	102	25.5	117	27.9
Prior Antibiotic Usage	3	0.8	4	1.0
Insufficient Therapy	29	7.3	43	10.3
Noncompliance With Therapy Regimen	39	9.8	47	11.2
Concomitant Antibiotics	11	2.8	15	3.6
No Post-Baseline Clinical Outcome in Evaluable Window	64	16.0	64	15.3
Modified Intent-to-Treat Patients	212	53.0	219	52.3
Not Modified Intent-to-Treat Patients (No Baseline Pathogen)	188	47.0	200	47.7
Microbiologically Evaluable Patients	143	35.8	151	36.0
Microbiologically Not Evaluable Patients	257	64.3	268	64.0
Clinically Not Evaluable Patients	102	25.5	117	27.9
No Baseline Pathogens in the Evaluable Window	189	47.3	201	48.0
All Baseline Pathogens Resistant to Study Medication	11	2.8	11	2.6

The M. O. reasons for non-evaluability were based in part on the algorithm used by the sponsor. Therefore, the reasons for non-evaluability are similar. However, in the FDA analysis, subjects who were not included in the ITT-prime population were considered clinically non-evaluable. A total of 48 (14.2%) linezolid subjects and 66 (19.6%) oxacillin subjects were excluded from the FDA clinically evaluable population for this reason. A few patients considered non-evaluable by the sponsor were considered evaluable by the reviewer, and vice versa. These few patients did not have a significant effect on the overall reasons for clinical non-evaluability in the FDA analysis. In the FDA analysis, the number of patients who were microbiologically non-evaluable because there was no baseline pathogen increases, based on the organisms considered pathogens by the FDA reviewer. The number of subjects who were microbiologically non-evaluable because of exclusion from the clinically evaluable population also increased slightly.

Patient Characteristics

Patient Demographics – The following table provides comparisons of age, weight, race, gender, and geographic region across the two treatment arms of the study. Demographic factors were comparable in the two treatment arms, except that the proportion of subjects 65 years of age or older is slightly higher in the oxacillin treatment arm.

Sponsor: Patient Demographics (ITT)

	Linezolid N = 400		Oxacillin/Dicloxacillin N = 419		
Parameters	**n**	**%**	**n**	**%**	**P-Value †**
Age (years)					
Total Reporting	400	100.0	419	100.0	
16-44	194	48.5	180	43.0	
45-64	139	34.8	133	31.7	
≥ 65	67	16.8	106	25.3	
Mean ± SD	46.8 ± 17.1		49.2 ± 18.5		0.0544
Weight (kg)					
Total Reporting	396	100.0	414	100.0	
Not Reported	4	1.0	5	1.2	
Mean ± SD	79.13 ± 22.67		78.97 ± 23.03		0.9229
Race					
Total Reporting	400	100.0	419	100.0	0.4672
White	227	56.8	230	54.9	
Black	49	12.3	69	16.5	
Asian or Pacific Islander	38	9.5	42	10.0	
Mixed	84	21.0	76	18.1	
Not Allowed to Ask	2	0.5	2	0.5	
Sex					
Total Reporting	400	100.0	419	100.0	0.5283
Male	252	63.0	255	60.9	
Female	148	37.0	164	39.1	
Region					
Total Reporting	400	100.0	419	100.0	0.6498
North America	99	24.8	120	28.6	
Latin America	98	24.5	100	23.9	
Europe	167	41.8	163	38.9	
Other	36	9.0	36	8.6	

† P-value is based on a one-way Analysis of Variance for mean age and weight, based on a chi-square test for race, gender, and region.

The sponsor also provided comparisons of the number of subjects in each treatment arm noted with abnormalities in medical history or physical examination. Comparisons of whether or not an abnormality was reported in a body system were made across treatment arms. No significant differences were noted between the two treatment arms. The sponsor compared the means of baseline vital signs across treatment arms. No differences were noted. Comparisons of mean laboratory values for chemistry, hematology, and urinalysis results were also made. Again, no differences were noted. The mean WBC counts were 11.46 x 10^3 /mm^3 in the linezolid group and 11.78 x 10^3 /mm^3 in the oxacillin group.

Anti-microbial use (topical and systemic), prior to and during study, was compared. Subjects in both treatment arms used non-investigational antibiotics prior to the first dose of study medication, 39.8% in the linezolid group and 43.7% in the oxacillin group. Concomitant medications other than antibiotics were used by 85.5% of linezolid subjects and 88.1% of oxacillin subjects. Medications used by 5% or more of patients in both treatment groups prior to or during treatment were: acetaminophen, angiotensin converting enzyme inhibitors, antianginal agents, antifungal agents, antianxiety medications, antiemetic/antivertigo agents, systemic antihistamines, beta-adrenergic blocking agents, calcium channel blocking agents, heparin, histamine H_2 antagonist, insulin, loop diuretics, narcotic agonist analgesics, narcotic analgesic combinations, non-barbiturates sedatives and hypnotics, non-steroidal anti-inflammatory agents, oral potassium, salicylates, sulfonylureas, and unknown medications and/or combinations. **(M. O. Comment: Compared to the pivotal study for uncomplicated infections, a higher proportion of subjects were using concomitant medications. These medications included sulfonylureas, insulin, loop diuretics, and beta blockers, indicating the inclusion of subjects with significant co-morbidities.)**

Characteristics of the Skin Infection at Baseline - Clinical symptoms and signs of skin infection at baseline were compared between the two treatment arms. The investigators graded clinical symptoms and signs on a four-point scale: none, mild, moderate or severe. The clinical signs and symptoms were chills, erythema, drainage/discharge, swelling/induration, tenderness/pain to palpation, heat/localized warmth, and fluctuance. The frequency of these clinical signs and symptoms were comparable across the two treatment arms. Pain/tenderness, erythema, and swelling/induration were reported in 97%-99% of subjects in the ITT population. The least frequent symptom reported was chills, which occurred in roughly 44% of subjects.

The following table shows the clinical diagnoses at baseline and the degree of involvement (superficial vs. deep). Results were comparable across treatment arms.

Sponsor: Clinical Diagnosis and Degree of Involvement at Baseline (ITT)

Variable Result	Linezolid N = 400		Oxacillin/Dicloxacillin N = 419		P-Value
	n	%	n	%	
Total Number Reporting	397	100	417	100	
Not Reported	3	-	2	-	
Diagnosis					
Infected Wound	24	6.0	40	9.6	0.5295
Cellulitis	178	44.8	186	44.6	
Erysipelas	41	10.3	40	9.6	
Skin Ulcer	15	3.8	14	3.4	
Skin Abscesses	58	14.6	64	15.3	
Infected Bite	7	1.8	3	0.7	
Infected Surgical Incision	25	6.3	26	6.2	
Other	49	12.3	43	10.3	
Missing	0	-	1	0.2	
Degree of Involvement					
Superficial	78	19.6	95	22.8	0.2745
Deep	319	80.4	322	77.2	

Cellulitis and skin abscesses were the most common diagnoses. While these clinical diagnoses were also included in the uncomplicated SSSI trials, patients with (furuncles, impetigo, folliculitis, paronychial infections, and carbuncles) were not included in this trial. Subjects in the "other" category commonly included burn subjects (2.7% of ITT), or subjects with descriptions of cellulitis (e.g., cellulitis/phlegmon of abdomen) or skin abscesses (e.g., peri-anal abscess). Roughly 78% of all infections were considered deep infections by the investigator.

The following table summarizes data on the duration of infection and lesion area. Mean values were comparable across the two treatment arms. Mean values for the area of lesions are larger by an order of magnitude compared to the uncomplicated SSSI studies. Again, this suggests more extensive infections for subjects enrolled in this trial.

Sponsor: Duration of Infection and Area of Lesion (ITT)

Pretreatment Variable	Results	Linezolid	Oxacillin/Dicloxacillin	P-Value
Duration of Infection (Days)	N	397	416	
	Mean	5.6	6.2	0.4948
	Standard Deviation	7.8	15.1	
Area of Lesion (cm^2)	N	388	403	
	Mean	408.4	413.4	0.9457
	Standard Deviation	1325.9	599.6	

Dosage Information – The following table shows the total duration of treatment for both treatment arms as the number of days of treatment.

Sponsor: Total Duration of Treatment in Days (ITT)

Duration Assessment	Linezolid N = 400		Oxacillin/Dicloxacillin N = 419	
Number of Days Treated	n	%	n	%
<5	24	6.0	32	7.6
5	2	0.5	7	1.7
6	4	1.0	9	2.1
7	8	2.0	9	2.1
8	19	4.8	17	4.1
9	30	7.5	35	8.4
10	26	6.5	29	6.9
11	40	10.0	35	8.4
12	35	8.8	33	7.9
13	22	5.5	24	5.7
14	30	7.5	36	8.6
15	51	12.8	50	11.9
16	14	3.5	17	4.1
17	13	3.3	8	1.9
18	9	2.3	17	4.1
19	9	2.3	8	1.9
20	10	2.5	4	1.0
21	22	5.5	18	4.3
>21	32	8.0	31	7.4
Mean ± SD	13.4 ± 5.4		13.0 ± 6.0	

Just over half (51.1%) of linezolid patients received 10-15 days of treatment. As noted in the study 39A results, the number of days treated = (stop date-start date) +1. Thus, 15 days in this table is consistent with a prescribed treatment course of 14 days. Results were similar for the clinically evaluable patients, where 56.8% of patients received 10-15 days of treatment.

The following table shows the number of intravenous (IV) doses of study medication. Subjects were given study medication every 6 hours. Four doses of medication correspond to one full day of treatment. In the linezolid treatment arm, two placebo infusions per day were used to maintain the study blind. The mean duration of intravenous treatment was 4.7 (± 3.3) days in the linezolid group and 4.7 (± 3.1) days in the oxacillin group.

Sponsor: Number of Intravenous Doses (ITT)

Duration Assessment	Linezolid		Oxacillin	
Number of Doses	N = 400		N = 419	
<4	34	8.5	41	9.8
4-12	204	51.0	208	49.6
13-20	78	19.5	80	19.1
21-28	40	10.0	46	11.0
29-36	25	6.3	22	5.3
37-44	6	1.5	9	2.1
45-56	6	1.5	9	2.1
>56	7	1.8	4	1.0
Mean ± SD	14.7 ± 13.1		14.6 ± 11.9	

The following table provides the number of oral doses of study medication. The number of doses and oral treatment compliance was assessed using pill counts. Again, the oral treatment was administered every 6 hours and placebo tablets were used in the linezolid group to maintain the study blind. The mean number of oral doses in the linezolid group is roughly twice the number of IV doses. The mean duration of oral treatment was 10.5 (± 4.2) days in the linezolid group and 10.4 (± 4.5) days in the dicloxacillin group.

Sponsor: Number of Oral Doses (ITT)

Duration Assessment	Linezolid		Dicloxacillin	
Number of Doses	N = 400		N = 419	
< 20	29	8.0	41	11.1
20-28	90	24.7	85	23.0
29-40	113	31.0	118	31.9
41-56	82	22.5	79	21.4
57-84	47	12.9	47	12.7
> 84	3	0.8	0	0
Mean ± SD	38.8 ± 17.0		37.8 ± 17.1	

Efficacy Results – As with study 39A, the sponsor provided multiple analyses under the heading of primary efficacy variables in the final study report. These analyses included investigator's assessment of clinical outcome, sponsor-defined clinical outcome (SDCO), sponsor-defined microbiological outcome (SDMO), and sponsor-defined overall outcome (a combination of clinical and microbiologic outcomes). The results of these analyses were consistent with one another.

(M.O. Comment: The medical officer has chosen to present the sponsor-defined clinical and microbiologic outcomes as the primary analyses by the sponsor. The SDCO and SDMO were chosen for the reasons provided in the discussion of study 39A results.)

The sponsor presented clinical outcomes for the modified intent-to-treat (MITT) and clinically evaluable populations in the main body of the final study report. Microbiologic outcomes are presented for the MITT, clinically evaluable (CE) and microbiologically evaluable (ME) populations. The ITT analysis was provided in the appendix. Sponsor's analyses of SDCO for the ITT, MITT, CE, and ME are provided in this review. Sponsor's analyses of SDMO for the MITT and ME populations are also provided here.

(M.O. Comment: The medical officer did not perform analyses of an MITT population and defined an additional ITT-prime population. The reasons for exclusion of a MITT analysis were provided in the discussion of study 39A results. Clinical outcome in the ITT-prime population is treated as the primary FDA analysis for the ITT population. The medical reviewer chose this as the primary analysis, prior to knowing the analysis results, for several reasons. First, although the ITT population best preserves the randomization scheme, the ITT-prime population is the group who meet all baseline inclusion and exclusion criteria. The requirement for systemic inflammatory response represents one of the few criteria that distinguish patients in this trial from subjects with uncomplicated SSSI.)

Clinical Outcome - The tables on the following page provide the sponsor-defined clinical outcome and the FDA analysis of clinical outcome in the ITT population. The test-of-cure assessment was made at the follow-up visit. The sponsor reported clinical cure rates of 85.1% for linezolid and 76.8% for oxacillin/dicloxacillin at follow-up. The clinical cure rates were similar in the sponsor's and reviewer's analyses. The lower bounds of the 95% confidence intervals in the sponsor's and reviewer's analyses were +2.4% and +0.2%, respectively. The numbers of patients with indeterminate or missing outcomes were similar in the two analyses. Missing or indeterminate outcomes were noted in 18.3% of linezolid-treated and 16.9% of oxacillin-treated patients. The number of patients assessed in each of these analyses excluded the patients with missing or indeterminate outcomes. The effect of this missing data is explored in a later section of this document (**Sensitivity Analyses**).

Sponsor: Clinical Outcome at End-of-Therapy and Follow-up (ITT)

		Linezolid N = 400		Oxacillin/ Dicloxacillin N = 419			
Visit	Assessment	n	%	n	%	P-Value	95% CI
EOT	Number of Assessed Patients	376	100.0	390	100.0		
	Success (Cured + Improved)	340	90.4	320	82.1		
	Cured	253	67.3	223	57.2		
	Improved	87	23.1	97	24.9		
	Failed	36	9.6	70	17.9		
	Indeterminate	1	-	1	-		
	Missing	23	-	28	-		
F-U (TOC)	Number of Assessed Patients	328	100.0	354	100.0		
	Cured	279	85.1	272	76.8	0.0064	(2.4, 14.1)
	Failed	49	14.9	82	23.2		
	Indeterminate	55	-	41	-		
	Missing	17	-	24	-		

M. O.: Clinical Outcome at Follow-up (ITT)

		Linezolid		Oxacillin		
Visit	Assessment	N	%	N	%	95% CI
Follow-Up (TOC)	Number of Assessed Patients	327	100	348	100	
	Cured	278	85.0	274	78.7	(0.2, 12.4)
	Failed	49	15.0	74	21.3	
	Indeterminate or Missing	73	-	71	-	

MITT - The following table shows the SDCO results at follow-up for the sponsor's MITT population. These results were comparable to those for the ITT population. The cure rates were slightly lower in the MITT population, but the treatment difference remained about the same.

(M. O. Comment: The results in the ITT and MITT analyses favor linezolid over oxacillin/dicloxacillin, with a 95% confidence interval that does not cross zero. However, the success rates for linezolid and comparator are more comparable in the other populations analyzed.)

Sponsor: Clinical Outcome at Follow-up (MITT)

		Linezolid N=212		Oxacillin N=219		
Visit	Assessment	N	%	N	%	95% CI
Follow-Up (TOC)	Number of Assessed Patients	173	100	184	100	
	Cured	144	83.2	138	75	(-0.1, 16.6)
	Failed	29	16.8	46	25	
	Indeterminate	31	--	22	--	
	Missing	8	--	13	--	

ITT-Prime – The FDA analysis of clinical outcome in the ITT-prime population is provided in the first table on the following page. The sponsor did not provide analyses for a population equivalent to the ITT prime population. The clinical cure rates were

86.2% for linezolid and 82.0% for oxacillin/dicloxacillin. The treatment difference still favors linezolid, though the lower bounds of the 95% confidence interval drops to –2.3%. This reflects both a smaller treatment difference and a smaller population compared to the ITT analysis.

M. O.: Clinical Outcome at Follow-up (ITT-Prime)

Visit	Assessment	Linezolid N	Linezolid %	Oxacillin N	Oxacillin %	95% CI
Follow-Up (TOC)	Number of Assessed Patients	269	100	267	100	
	Cured	232	86.2	219	82.0	(-2.3, 10.8)
	Failed	37	13.8	48	18.0	
	Indeterminate or Missing	47	--	46	--	

Clinically Evaluable -The SDCO in the sponsor's clinically evaluable population is shown in the table below. The clinical cure rates at follow-up were 90.7% for linezolid and 86.3% for oxacillin/dicloxacillin. These cure rates were higher than those reported for the ITT population. The treatment difference was smaller and the lower bound of the 95% confidence interval fell below zero compared to the ITT analysis.

Sponsor: Clinical Outcome at End-of-Therapy and Follow-up (CE)

Visit	Assessment	Linezolid N = 298 n	Linezolid %	Oxacillin N = 302 n	Oxacillin %	95% CI
EOT	Number of Assessed Patients	294	100.0	297	100.0	
	Success (Cured + Improved)	276	93.9	266	89.6	
	Cured	210	71.4	193	65.0	
	Improved	66	22.4	73	24.6	
	Failed	18	6.1	31	10.4	
	Indeterminate	1	-	1	-	
	Missing	3	-	4	-	
F-U (TOC)	Number of Assessed Patients	291	100.0	300	100.0	
	Cured	264	90.7	259	86.3	(-0.7, 9.5)
	Failed	27	9.3	41	13.7	
	Indeterminate	7	-	2	-	

The FDA analysis of clinical outcome at follow-up for the clinically evaluable population is shown in the table on the following page. The clinical cure rates at follow-up were 89.8% for linezolid and 85.1% for oxacillin/dicloxacillin. The number of clinically evaluable subjects was not directly comparable between the sponsor's and FDA's analyses. Clinical cure rates are generally higher in the sponsor's analyses compared to the FDA results, but the treatment difference is roughly the same and favors linezolid. In the FDA analysis, indeterminate outcomes were treated the same as missing data. The patients with indeterminate outcomes in the sponsor's analysis would have been considered non-evaluable in the FDA analysis, unless some other factor led to their inclusion as failures. The lower bounds of the 95% confidence interval were –0.7% in the sponsor's analysis and –1.6% in the FDA analysis.

M. O.: Clinical Outcome at Follow-up (CE)

		Linezolid N=245		Oxacillin N=242		
Visit	**Assessment**	**N**	**%**	**N**	**%**	**95% CI**
Follow-Up	Number of Assessed Patients	245	100	242	100	
(Test-of-Cure)	Cured	220	89.8	206	85.1	(-1.6, 11.0)
	Failed	25	10.2	36	14.9	

Microbiologically Evaluable – There are also large differences in the number of patients considered microbiologically evaluable by the sponsor and FDA. These differences are related to the organisms included as pathogens by the M. O. and the sponsor. The M.O. included patients with *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Enterococcus faecalis*, and *Enterococcus faecium* at baseline in the microbiologically evaluable population. Despite the differences in population analyzed, the results appear fairly similar.

The following table provides the SDCO for the sponsor's microbiologically evaluable population. The clinical cure rates at follow-up were 90.0% for linezolid and 86.1% for oxacillin/dicloxacillin. As with the ITT and CE groups, linezolid had a higher clinical cure rate than oxacillin/dicloxacillin.

Sponsor: Clinical Outcome at EOT and Follow-up (ME)

		Linezolid N = 143		Oxacillin N = 151		
Visit	**Assessment**	**N**	**%**	**n**	**%**	**95% CI**
EOT	Number of Assessed Patients	141	100.0	149	100.0	
	Success (Cured + Improved)	132	93.6	131	87.9	
	Cured	100	70.9	99	66.4	
	Improved	32	22.7	32	21.5	
	Failed	9	6.4	18	12.1	
	Indeterminate	1	-	1	-	
	Missing	1	-	1	-	
F-U	Number of Assessed Patients	140	100.0	151	100.0	
(TOC)	Cured	126	90.0	130	86.1	(-3.5, 11.3)
	Failed	14	10.0	21	13.9	
	Indeterminate	3	-	0	-	

The FDA analysis of clinical outcome at follow-up for the microbiologically evaluable population is shown in the table below. The clinical cure rates at follow-up were 85.1% for linezolid and 82.4% for oxacillin/dicloxacillin. The differences in definition of the ME population make direct comparisons of cures and failures difficult at best. However, a treatment difference (favoring linezolid) was seen in both analyses. The lower bounds of the 95% confidence interval were –3.5% in the sponsor's analysis and –8.2% in the FDA analysis. The wider 95% confidence interval in the FDA analysis reflects the smaller ME population defined by the M. O. and the smaller treatment difference (2.5% versus 3.9%) in the FDA and sponsor's analyses, respectively.

M. O.: Clinical Outcome at Follow-up (ME)

Visit	Assessment	Linezolid N=101 N	%	Oxacillin N=108 N	%	95% CI
Follow-Up	Number of Assessed Patients	101	100	108	100	
(Test-of-Cure)	Cured	86	85.1	89	82.4	(-8.2, 13.7)
	Failed	15	14.9	19	17.6	

A treatment difference of roughly 2-5% (favoring linezolid) was seen in the primary analyses of clinical outcome in the evaluable populations groups, despite differences in the methodology of the FDA and the sponsor and differences in study population. The FDA's ITT-prime analysis also showed a treatment difference in this range (4.2%). A wider treatment difference is reported in the ITT and MITT analyses. Overall, the analyses of clinical outcome are consistent in producing results that are favorable for linezolid.

Microbiological Outcome – The limitations of the assessment of microbiological outcome were outlined in the results section for Study 39A, and apply to this study as well. The following table shows the sponsor's assessment of microbiological outcome for the microbiologically evaluable population. The vast majority of subjects fall into the category of presumed eradication. These results are shown only to demonstrate that microbiological and clinical outcomes determined by the sponsor were similar.

Sponsor: Microbiological Outcome at Follow-Up (ME)

Assessment	Linezolid N = 143 n	%	Oxacillin/ Dicloxacillin N = 151 n	%	95% CI
Number of Assessed Patients	142	100.0	151	100.0	
Microbiological Success	126	88.7	129	85.4	(-4.4, 11.0)
Documented Eradication	15	10.6	16	10.6	
Presumed Eradication	109	76.8	112	74.2	
Colonization	2	1.4	1	0.7	
Microbiological Failure	16	11.3	22	14.6	
Documented Persistence	5	3.5	4	2.6	
Presumed Persistence	11	7.7	18	11.9	
Indeterminate	1	-	0	-	

Patient Overall Outcome – The sponsor also provided tables of patient overall outcome. This analysis involves a combination of the clinical and microbiological outcome data. The results of these analyses are consistent with the clinical and microbiological outcome results already presented. They will not be repeated here, but are available in the sponsor's final study report and appendix tables.

Subgroup Analyses

Pathogen – The following tables show the SDMO and SDCO for selected organisms. The reviewer chose to focus on clinical outcome in these selected pathogens. The results are the same except for one subject in the oxacillin group who was a clinical cure but a microbiological failure.

Sponsor: Microbiological Success Rates at Follow-Up for Selected Pathogens (ME)

	Linezolid		Oxacillin/Dicloxacillin	
Pathogen	**n/N**	**%**	**n/N**	**%**
S aureus	83/93	89.2	87/103	84.5
S epidermidis	19/19	100.0	10/12	83.3
S agalactiae	7/7	100.0	4/6	66.7
S pyogenes	23/29	79.3	27/32	84.4

Sponsor: Clinical Cure Rates at Follow-Up for Selected Pathogens (ME)

	Linezolid		Oxacillin/Dicloxacillin	
Pathogen	**n/N**	**%**	**n/N**	**%**
S aureus	83/93	89.2	88/103	85.4
S epidermidis	19/19	100.0	10/12	83.3
S agalactiae	7/7	100.0	4/6	66.7
S pyogenes	23/29	79.3	27/32	84.4

The sponsor has requested an indication for complicated SSSI that includes *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus agalactiae*, and *Streptococcus pyogenes*.

The review of a random set of case report forms by the M. O. indicated that most isolates of *S. epidermidis* were likely contaminants. The reviewer requested that the sponsor provide a list of subjects in whom actual *S. epidermidis* infection is seen. The sponsor provided a list of 11 linezolid-treated subjects from Study 39A, this study, and Study 33 (a separate study of methicillin-resistant *Staphylococcus* spp. Infections which is the subject of another M. O. review). After reviewing the case report forms for the selected subjects, The M. O. found only one or two subjects whose infections may be due to *S. epidermidis*. Later proposals for product labeling have excluded *Staphylococcus epidermidis* from the complicated SSSI indication.

The FDA analysis of clinical outcome at follow-up by pathogen for the microbiologically evaluable population is shown in the table on the following page. Very few subjects with *Enterococcus faecalis* or *Enterococcus faecium* were part of this trial. None of the enterococci were vancomycin-resistant and most were penicillin-susceptible. The results for *Staphylococcus aureus* were consistent with the clinical cure rates in the primary analyses. There were only three linezolid-treated patients who had MRSA. The experience with linezolid in the treatment of MRSA infections is the subject of another M. O. review.

M. O.: Clinical Cure Rates at Follow-Up for Selected Pathogens (ME)

Pathogen	Clinical Cure Rate			
	Linezolid		Oxacillin/Dicloxacillin	
	n/N	%	N/N	%
E faecalis	0/2	0.0	4/5	80.0
E faecium	1/2	50.0	0/0	--
S aureus	73/83	88.0	72/84	85.7
MRSA	2/3	66.7	0/0	--
S agalactiae	6/6	100	3/6	50.0
S pyogenes	18/26	69.2	21/28	75.0

S. agalactiae is known to cause cases of complicated skin and skin structure infections. The sponsor had a total of 10 subjects in this trial with S. agalactiae at baseline, 8 clinical cures and 2 with indeterminate or missing outcome. Even if both of the latter were clinical failures, the cure rate would still be 8/10 subjects.
(M. O. Comment: These numbers are small, but support the inclusion of *S. agalactiae* in the indication for complicated skin and skin structure infections. Success in 2 cases from Study 39A with *Streptococcus agalactiae* in pure culture provide some additional support.)

Clinical diagnosis – The tables on the following pages provide subgroup analyses of the clinical cure rates by clinical diagnosis produced by the sponsor and the FDA review. The results shown were obtained in the clinically evaluable population. These results were generally consistent between the sponsor and FDA analyses, and also consistent with the primary analyses of clinical outcome. Linezolid showed a lower clinical cure rate than oxacillin in only one of the diagnosis groups, erysipelas.

Sponsor: Clinical Outcome at Follow-Up by Clinical Diagnosis (CE)

		Linezolid N = 298		Oxacillin/Dicloxacillin N = 302	
Diagnosis	**Assessment**	**n**	**%**	**N**	**%**
Infected Wound	Number of Assessed Patients	20	100.0	27	100.0
	Cured	17	85.0	22	81.5
	Failed	3	15.0	5	18.5
	Indeterminate	1	-	0	-
Cellulitis	Number of Assessed Patients	124	100.0	133	100.0
	Cured	116	93.5	118	88.7
	Failed	8	6.5	15	11.3
	Indeterminate	4	-	2	-
Erysipelas	Number of Assessed Patients	32	100.0	33	100.0
	Cured	27	84.4	30	90.9
	Failed	5	15.6	3	9.1
	Indeterminate	1	-	0	-
Skin Ulcer	Number of Assessed Patients	12	100.0	9	100.0
	Cured	11	91.7	8	88.9
	Failed	1	8.3	1	11.1
Skin Abscesses	Number of Assessed Patients	39	100.0	44	100.0
	Cured	36	92.3	36	81.8
	Failed	3	7.7	8	18.2
Infected Bite	Number of Assessed Patients	5	100.0	3	100.0
	Cured	4	80.0	2	66.7
	Failed	1	20.0	1	33.3
Infected Surgical Incision	Number of Assessed Patients	18	100.0	12	100.0
	Cured	15	83.3	8	66.7
	Failed	3	16.7	4	33.3
Other	Number of Assessed Patients	41	100.0	39	100.0
	Cured	38	92.7	35	89.7
	Failed	3	7.3	4	10.3
	Indeterminate	1	-	0	-

M. O.: Clinical Outcome at Follow-Up by Clinical Diagnosis (CE)

Diagnosis	**FDA Clinical Outcome**			
	Linezolid		**Oxacillin/Dicloxacillin**	
	n/N	**%**	**N/N**	**%**
Erysipelas	22/26	84.6	21/23	91.3
Infected surgical incision	15/18	83.3	7/11	63.6
Infected bite	3/4	75.0	2/3	66.7
Infected wound	13/16	81.3	17/21	81.0
Skin abscesses	32/36	88.9	32/40	80.0
Cellulitis	91/97	93.8	87/100	87.0
Skin ulcer	9/10	90.0	7/8	87.5
Other	35/38	92.1	33/36	91.7

Concomitant Use of Aztreonam – Concomitant use of aztreonam was allowed as part of the protocol for coverage of gram-negative pathogens. To investigate the effect of aztreonam on the clinical outcomes for the ITT population, a subgroup analysis was performed. The results are shown in the table on the following page. Roughly 16% of subjects in this trial received aztreonam as concomitant antibiotic therapy for gram-

negative pathogens. Subjects in both treatment arms received aztreonam for a mean of 4.3 days. Although the cure rates dropped for subjects who received aztreonam, and the treatment difference is wider, the treatment difference also favors linezolid in subjects who did not receive gram-negative coverage. Similar results were obtained in the ITT-prime and clinically evaluable population. Aminoglycosides were not allowed or used for gram-negative coverage in this trial.

Effect of Aztreonam use on Clinical Outcome in the ITT population

Aztreonam Used	Linezolid			Oxacillin/Dicloxacillin		
	N	Missing	Cure Rate(%)	N	Missing	Cure Rate(%)
Yes	66	10	75.0	67	6	62.3
No	334	63	87.1	352	65	82.2

Bacteremia – The number of patients with bacteremia in this trial was exceedingly small. Only 2 subjects in the linezolid-treated group were identified by the M. O. with bacteremia due to a pathogen. There were another 13 subjects with blood culture contaminants.

(M. O. Comment: These results of these subgroup analyses do not provide sufficient foundation for the inclusion of concurrent bacteremia as part of the indication for complicated skin and skin structure infections. The M. O. agrees with the inclusion of a statement regarding use of aztreonam as concomitant therapy for suspected gram-negative pathogens.)

Age – The following table provides clinical cure rates in the ITT-prime population, grouped by age. The subjects who are ≥ 65 years show clinical cure rates similar to younger patients. These results do not indicate decreased efficacy of linezolid in older patients.

(M. O. Comment: In the following subgroup analyses of the ITT-prime population, the patients with missing outcomes are excluded from the analyses. A total of 269 linezolid-treated patients and 267 oxacillin-treated patients had non-missing outcomes in the ITT-prime population.)

M. O.: Clinical Cure Rates at Follow-Up by Age Category (ITT)

Age Category	Clinical Cure Rate			
	Linezolid		Oxacillin/Dicloxacillin	
	N	%	N	%
≥ 65 years	38	86.8	62	82.3
< 65 years	231	86.1	205	82.0

Gender – The effect of gender was on efficacy of linezolid was also investigated by looking at clinical cure rates in males and females separately. The following table shows clinical cure rates in the ITT population by gender. As opposed to study 39A, the treatment difference was a bit larger in females compared to males. Again, no gender differences in treatment effect were established.

M. O.: Clinical Cure Rates at Follow-Up by Gender (ITT-Prime)

Gender	Clinical Cure Rate			
	Linezolid		Oxacillin/Dicloxacillin	
	N	%	N	%
Female	98	87.8	93	81.7
Male	171	85.4	174	82.2

Sensitivity Analyses

Effect of Missing Data – The effect of missing data was investigated by looking at changes in clinical cure rates when missing outcomes are changed to failures. The following table shows the clinical cure rates in the ITT-prime population when missing outcome was considered failure. As expected the clinical cure rates decreased, but the treatment difference favoring linezolid was similar to the results of the primary analysis.

M. O.: Clinical Outcome at Follow-up (ITT-Prime)

Visit	Assessment	Linezolid		Oxacillin		95% CI
		N	%	N	%	
Follow-Up (TOC)	Number of Assessed Patients	316	100	313	100	
	Cured	232	73.4	219	70.0	(-2.3, 10.8)
	Failed	84	26.6	94	30.0	

Safety Results – The safety results are excerpted from the sponsor's final study report. The following table provides an overall summary of the treatment emergent adverse events (AE) reported in the ITT population. The number of patients reporting AE was balanced across the two treatment arms, with the exception of drug-related AE resulting in discontinuation of study medication. There were more subjects with study drug discontinuation in the oxacillin arm than in the linezolid arm. The number of subjects with at least one AE was a bit higher in the linezolid arm. A brief description of patient deaths in this study is provided on the following page.

Sponsor: Summary of Adverse Events (ITT)

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

Deaths - There were four deaths in protocol 0055, three of which occurred in linezolid subjects. Patient #5511185 was a 77 year old male with a history of cardiomyopathy, dementia, Parkinson's disease, and contractures who was entered in the study for treatment of decubitus ulcers. The subject was treated with linezolid and gentamicin. The family requested that tube feedings be stopped and only comfort care measures be provided, starting 8 days after the last linezolid dose. He died 11 days after the last dose of study medication.

Patient #5553009 was a 44 year old male in the Czech Republic with a skin ulcer of the left leg. No history of cardiac or pulmonary problems was noted. He died of acute pulmonary edema and cardiac insufficiency on the third day of linezolid treatment. He was in the hospital at the time of the event, but died despite attempts at cardio-pulmonary resuscitation.

Patient #5511733 was a 44-year-old South African diabetic male who was entered into the trial for skin abscess and cellulitis at the penile base. He completed 14 days of linezolid with some improvement of the skin abscess. However, the subject developed a decubitus ulcer during linezolid therapy. The ulcer was debrided during treatment. The patient died on the day after therapy was completed. The investigator reported the cause of death as "sepsis from pressure ulcer". No blood cultures results are reported. Culture swabs from the end of therapy indicated the presence of *Morganella morganii, Klebsiella pneumoniae, Proteus mirabilis, Escherichia coli,* and *Enterococcus faecalis*. The report did not indicate the culture source (pressure ulcer or discharge from penile abscess). *Morganella morganii* and *Staphylococcus aureus* were present at baseline.

Patient #5522012 is a 46 year old male from Brazil with left arm cellulitis. His past history included diabetes and diabetic nephropathy. He failed 7 days of treatment with oxacillin. The patient was treated with vancomycin, ceftriaxone, and metronidazole, but died from sepsis three weeks after the last dose of study medication. No blood culture results were reported.

All Adverse Events - The treatment emergent adverse events occurring in >2% of patients in either treatment arm are shown in the table on the following page. The most common adverse events were nausea, headache, and vomiting. These same events were also common in other studies with linezolid. More subjects in the linezolid treatment arm reported hypertension as an adverse event than was seen with the comparator. This could be related to the use of linezolid. It is possible that monoamine oxidase (MAO) inhibition caused by linezolid resulted in increased reports of hypertension among linezolid patients. A detailed review of linezolid and MAO inhibition is included in the integrated summary of safety.

Sponsor: Study-Emergent AE Occurring in >2% of Patients (ITT)

	Linezolid N = 400		Oxacillin/Dicloxacillin N = 419	
COSTART Body System /MET	**n**	**%**	**n**	**%**
Patients With None	211	52.8	246	58.7
Patients With at Least One	189	47.3	173	41.3
BODY				
Abdominal Pain Localized	8	2.0	5	1.2
Fever	5	1.3	11	2.6
Headache	22	5.5	16	3.8
Localized Pain	11	2.8	3	0.7
CARDIOVASCULAR				
Hypertension	12	3.0	1	0.2
DIGESTIVE				
Constipation	7	1.8	13	3.1
Diarrhea	11	2.8	12	2.9
Dyspepsia	10	2.5	7	1.7
Nausea	23	5.8	24	5.7
Vomiting	13	3.3	8	1.9
NERVOUS				
Dizziness	9	2.3	3	0.7
Insomnia	10	2.5	9	2.1
SKIN				
Pruritus Non-application Site	6	1.5	9	2.1

Drug Related AE – Only two categories of AE were considered drug-related and occurred in >2% of patients in either treatment arm. Drug-related nausea was reported in 14 (3.5%) linezolid patients and 12 (2.9%) clarithromycin patients. Drug-related headache was reported in 10 (2.5%) linezolid patients and 6 (1.4%) clarithromycin patients.

Serious AE – All serious AE noted in this study are listed in the following table. None were considered drug-related by the reporter. Of the serious AE seen in more than one subject, most (cellulitis, abscess, infection, sepsis, peripheral vascular disorder) seem related to the disease under study or effectiveness of the drug. No clear pattern emerged. Non-infectious hepatitis is a known effect of oxacillin.

Sponsor: Study-Emergent Serious Adverse Events (ITT)

COSTART Body System/MET	Linezolid		Oxacillin/Dicloxacillin	
	n	%	n	%
Total Number of Patients Reporting	400	100.0	419	100.0
Patients With None	378	94.5	400	95.5
Patients With at Least One	22	5.5	19	4.5
BODY				
Abdominal Cramp	0	-	1	0.2
Abscess	4	1.0	2	0.5
Cellulitis	1	0.3	3	0.7
Chest Pain	1	0.3	0	-
Drug Fever	0	-	1	0.2
Fever	1	0.3	0	-
Gangrene	0	-	1	0.2
Generalized Edema	0	-	1	0.2
Infection	1	0.3	2	0.5
Infection Superimposed	0	-	1	0.2
Inflammatory Swelling	1	0.3	0	-
Peri-operative Event	0	-	1	0.2
Sepsis	2	0.5	1	0.2
Trauma	1	0.3	0	-
CARDIOVASCULAR				
Cardiac Arrest NEC	1	0.3	0	-
Cardiac Insufficiency	1	0.3	0	-
Deep Vein Thrombosis	0	-	1	0.2
Disorder Peripheral Vascular	2	0.5	0	-
Left Heart Failure NOS	1	0.3	0	-
Myocardial Ischemia	1	0.3	0	-
Thrombosis	0	-	1	0.2
DIGESTIVE				
Carcinoma Esophageal	0	-	1	0.2
Gastrointestinal Bleeding	0	-	1	0.2
Noninfectious Hepatitis	0	-	2	0.5
Nonspecific Hepatitis	0	-	1	0.2
ENDOCRINE				
Diabetes mellitus	0	-	1	0.2

Clinical Summary: Study 55

Subjects with complicated skin and skin structure infections were studied in a randomized, double-blind, comparative trial of linezolid 600 mg IV/PO every 12 hours and oxacillin 2 g IV every 6 hours/ dicloxacillin 500 mg PO every 6 hours. The clinical outcomes in this trial are summarized in the table below. The trials of uncomplicated skin and skin structure infections provide supportive results for this indication. Higher clinical cure rates are seen in the linezolid treatment arm compared to treatment with oxacillin and dicloxacillin. The results provide substantial evidence of effectiveness in complicated SSSI.

Clinical Outcomes (%) and 95% Confidence Intervals for Complicated SSSI

Study Population	Linezolid	Oxacillin/ Dicloxacillin	95% Confidence Interval
Study 55			
ITT	85.0%	78.7%	(+0.2, 12.4)
ITT-Prime	86.2%	82.0%	(-2.3, 10.8)
Clinically Evaluable	89.8%	85.1%	(-1.6, 11.0)

Several subgroup analyses were performed. Clinical outcomes in subgroups identified with specific pathogens at baseline are summarized in the following table. The two major pathogens for this indication, *Staphylococcus aureus* and *Streptococcus pyogenes*, were each identified in more than 10 linezolid-treated subjects with acceptable clinical outcomes. The numbers of microbiologically evaluable patients with *Streptococcus agalactiae* were small, but there were additional subjects in the MITT population with this pathogen. These results support the inclusion of both methicillin-susceptible strains of *S. aureus*, *S. pyogenes*, and *S. agalactiae* within the indication for complicated SSSI.

Clinical Outcome by Pathogen for Complicated SSSI

Study/Pathogen	Linezolid	Oxacillin/Dicloxacillin
Study 55		
S. aureus	73/83	72/84
S. pyogenes	18/26	21/28
S. agalactiae	6/6	3/6

Other subgroup analyses were based on age, gender, bacteremia, and clinical diagnosis. In the pivotal trial, no differences in treatment effect based on gender or age over 65 were noted. Results in different clinical diagnoses included were consistent with the overall results. However, patients with diabetic foot ulcers were not included in the trial. Bacteremia was also a rare occurrence in the patients studied.

The safety analyses were generally consistent with results reported in other trials. Headache, nausea, vomiting, and diarrhea were the common AE reported in this trial, as well as other phase 3 studies. Hypertension was reported more frequently as an adverse event in the linezolid group than in the oxacillin group. While this event may be related to MAO inhibition caused by linezolid, similar results were not reported in the other phase 3 comparative trials.

Conclusions: Complicated Skin and Skin Structure infections

The medical officer has concluded that there is sufficient information provided to recommend approval of the indication of complicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible strains), *Streptococcus agalactiae*, or *Streptococcus pyogenes*. Only 3 linezolid-treated subjects in the trial were noted with methicillin-resistant *Staphylococcus aureus* (MRSA). There is not sufficient evidence to approve the use of linezolid for complicated SSSI in subjects with MRSA based on these results. There is insufficient evidence to recommend use of linezolid in patients with concurrent bacteremia. The dosing regimen studied in these trials was 600 mg IV/PO every 12 hours for 10 to 14 days and is the regimen recommended for this indication in the **DOSAGE AND ADMINISTRATION** section of the product label.

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Conclusions of Medical Officer Review

The medical officer recommends approval for the indications of Uncomplicated and Complicated Skin and Skin Structure infections. At this time, the safety and efficacy of linezolid in pediatric patients have not been established. The sponsor should perform further studies to demonstrate the safety of a dosing regimen that provides a similar pharmacokinetic profile to the 600 mg q12 hour regimen in adults.

John Alexander, M. D.

cc:
Original NDA #21-130, #21-131, #21-132
HFD-520
HFD-520/MO/Alexander
HFD-520/MO/Ross
HFD-520/TL/Soreth
HFD-520/PM/Duvall-Miller
HFD-520/DEPDIR/Gavrilovich
HFD-725/Stat/Brittain
HFD-880/Biopharm/Zheng
KEYWORDS:
ADMIN REVIEW
CLASS OXAZOLIDINONE
INDIC OTITIS MEDIA, ACUTE
INDIC PNEUMONIA, CAP
INDIC SSSI, COMP
INDIC SSSI, UNCOMP
POP ADULT
POP PEDIATRICS (0-16 YRS)
STUDY CLIN CONTROL ACTIVE
STUDY CLIN UNCONTROLLED
STUDY PHASE 2
STUDY PHASE 3

Concurrence Only:
HFD-520/DIVDIR/Chikami

APPENDIX: FDA METHODOLOGY

This description of FDA methodology is based on the description given in the statistical review by Erica Brittain Ph.D. The tables below are taken directly from this review. The methodology described below was used for review of the studies of uncomplicated and complicated skin and skin structure infections.

[redacted]

Random Sample Case Review/Data validation

After review of the protocol and amendments for each of the phase 3 trials, the reviewer made an independent assessment of a sample of patients. Random samples of 100 patients from Study 55, 100 patients from Study 39A, and 60 patients from Study 39 were generated by the statistical reviewer. The medical officer remained blinded to treatment for the patients in these random samples. The case report forms were reviewed, and the medical officer recorded evaluability, clinical outcome, and microbiological outcome. Generally, the FDA reviewer agreed with the assessment of outcome made by the investigator. Where there were systematic differences between the FDA assessment and investigator's/sponsor's assessment, changes were incorporated into the FDA algorithm or FDA population definition. (For example, the sponsor-defined ME population included patients with *Staphylococcus epidermidis* and other unlikely pathogens. The medical officer defined the ME population differently.)

Definition of Evaluable Populations

There were no differences in the ITT population between the sponsor and FDA. Any patient who received at least one dose of study medication was included. In Study 55, an ITT-prime population was defined as those patients who met all baseline inclusion and exclusion criteria. In review of the case report forms, the medical officer noted that some patients did not meet certain inclusion criteria, based on available data in the case report forms. Most were subjects who did not have fever or evidence of WBC count elevations specified in the inclusion criteria, though some subjects were excluded from the ITT-prime population for other reasons.

Minor differences in the clinically evaluable populations were present. These changes generally involved the exclusion of subjects with missing outcomes from the FDA CE population, or inclusion of some patients with indeterminate outcomes in the sponsor's analysis, as evaluable treatment failures.

The microbiologically evaluable population differed markedly. The sponsor's approach included all bacterial isolates against which linezolid had some in vitro activity. IN the FDA ME population, the pathogenic potential of certain organisms in the setting of uncomplicated and complicated SSSI was considered. In the final analysis, only *Staphylococcus aureus* and *Streptococcus pyogenes* were included in the FDA ME population for the uncomplicated SSSI studies. This approach excluded a small number of patients whose bacterial isolate may have been pathogenic (e.g., one subject with

Pasteurella multocida). However, it had the advantage of excluding a greater number of patients with organisms that are non-pathogens (e.g., *Staphylococcus epidermidis, Staphylococcus haemolyticus*) in the setting of uncomplicated infection. For the complicated SSSI study, patients with *S. aureus, S. pyogenes, Streptococcus agalactiae, Enterococcus faeciium,* and *Enterococcus faecalis* were included. Most other potential pathogens were isolated in too few numbers to have a significant effect on outcome for the ME population.

Differences in Clinical Outcome Assessment

The tables below provide the most succinct explanation of differences in the FDA's and the sponsor's algorithms. The reader is referred to the statistical review by Erica Brittain, Ph.D. for a more detailed description.

The greatest differences in outcome assessment involved the methods by which deaths were handled in the analyses. Since there were very few deaths in the SSSI trials, these changes had little effect on clinical outcome results. The other differences in the algorithms did result in more failures in the FDA outcome assessments. However, these occurred in only a small portion of the total population, and were roughly even across treatment arms.

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

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

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

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

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

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

Integrated Summary of Safety for Zyvox: NDAs 21-130, 21-131, and 21-132

General information

The safety database comprised data on 431 linezolid-treated patients in Phase I studies, 870 linezolid-treated patients in Phase II studies, and 2046 linezolid-treated patients in Phase III studies. The primary sources for data analysis were electronic datasets supplied by the applicant; these contained data on deaths, adverse events, and laboratory results that had been abstracted from CRFs. Random patient samples were examined to assess the accuracy of abstraction of data from CRFs to the electronic datasets.

The safety analysis was done in collaboration with Dr. Ana Szarfman of the Office of Epidemiology and Biometrics, using interactive graphic techniques developed by her for computer-assisted analysis of safety databases. These techniques allow reviewers to perform independent analyses of mortality, adverse events, and laboratory data contained in regulatory submissions. In two days, Dr. Szarfman implemented and optimized the application of these techniques to this NDA. This work enabled the primary medical reviewer to perform an interactive, independent review of the safety data of this NDA.

Analyses performed by the applicant are presented in regular type and those by the medical reviewer in italics.

Definitions

FDA reviewers used the same definitions and terms for adverse events, drug-related adverse events, serious adverse events (SAEs), and abnormal laboratory values as the applicant.

Mortality analysis

All study reports and CRFs summaries of patient deaths were reviewed. Events were examined for evidence of death due to drug exposure or to lack of drug efficacy. Patients who died before the end of follow-up were considered to have died from the initial infection if either of the following conditions were met:

- the investigator indicated that the initial infection was the cause of death,

or

- the investigator-supplied cause of death directly indicated an ongoing infectious process (e.g., 'septic shock') and clinical observations were consistent with persistence or progression of the original infection. In the case of infections due to VRE, attribution of death to the initial infection also required isolation of the original pathogen from a normally sterile body site or fluid (e.g., blood).

Discontinuations

All cases of discontinuations due to adverse events were reviewed. Events were examined for evidence of relation to study drug, or for evidence of lack of drug efficacy. Discontinuation rates were determined by treatment group for specific subgroups of interest.

Serious adverse events

Serious adverse events were reviewed, including examination of SAEs that might represent lack of drug efficacy. SAE rates were determined by treatment group for specific subgroups of interest.

Laboratory values

Laboratory values were plotted using CrossGraphs 2.0.4 to visualize distributions and compared between treatment groups for specific subgroups of interest. Outliers were identified and reviewed for evidence of a drug-effect relationship.

Phase I studies

Demographics

The Phase I studies enrolled 431subjects who received linezolid; an additional patient was randomized to receive linezolid and aztreonam, but discontinued before linezolid administration. The studies examined linezolid safety and pharmacokinetics in normal volunteers, as well as in a small number of subjects with renal or hepatic impairment. Because of linezolid's capacity to inhibit monoamine oxidase (MAO), the applicant also examined the potential for linezolid to interact with tyramine, phenylpropanolamine, and pseudephedrine. These are all indirect-acting amines that can interact with MAO inhibitors to cause hypertensive crises. Because MAO inhibitors can interact with serotonergic agents to cause serotonin syndrome (characterized by fever, confusion, tremors, and convulsions), the applicant also studied subjects receiving linezolid together with and dextromethorphan, a common ingredient in over-the-counter cold remedies. The results of these studies are described under Drug-drug Interactions.

Subject demographics are shown in Table ISS.1.

Table ISS.1. Phase I subject demographics

		All Linezolid †		Single Linezolid Dose		Multiple Linezolid Dose		Placebo/Other	
		N = 432		N = 256		N = 176		N = 62	
		n	%	n	%	n	%	n	%
Sex	Male	322	74.5	180	70.3	142	80.7	58	93.5
	Female	110	25.5	76	29.7	34	19.3	4	6.5
Race	White	377	87.3	215	84.0	162	92.0	59	95.2
	Black	44	10.2	34	13.3	10	5.7	0	-
	Other	11	2.5	7	2.7	4	2.3	3	4.8
Age	Mean ± SD	30 ± 15		30 ± 18		30 ± 9.1		29 ± 6.9	
	Range	0 to 75		0 to 75		18 to 61		19 to 48	

† Sum of subjects receiving single dose of linezolid plus subjects receiving multiple doses of linezolid. One subject was randomized to receive aztreonam plus linezolid, but discontinued before linezolid administration.

Extent of exposure

The following doses of linezolid were studied as part of Phase I safety, tolerance, and pharmacokinetic studies: Single oral doses of 50 mg to 500 mg; multiple oral doses of 100 mg to 750 mg given every 8 hours for up to 10 days; multiple oral doses of 125 mg to 625 mg given every 12 hours for 14 days; single IV doses of 250 mg to 750 mg; multiple IV doses of 250 mg to 500 mg given every 8 hours for up to 7 days; and, multiple IV doses of 500 mg and 625 mg given every 12 hours for 7 days. The extent of exposure is shown in Table ISS.2, and summary statistics for exposure in multiple-dose studies are shown in Table ISS.3.

Table ISS.2. Extent of exposure in Phase I linezolid studies								
	All Linezolid† N = 432		Single Linezolid Dose N = 256		Multiple Linezolid Dose N = 176		Placebo/Other N = 62	
	n	%	n	%	n	%	n	%
Completed Treatment	415	96.1	246	96.1	169	96.0	59	95.2
Dropout Due to AEs	2	0.5	1	0.4	1	0.6	2	3.2
Dropout Due to Other	15	3.5	9	3.5	6	3.4	1	1.6
† Sum of subjects receiving single dose of linezolid plus subjects receiving multiple doses of linezolid. One subject was randomized to receive aztreonam plus linezolid, but discontinued before linezolid administration.								

Table ISS.3. Extent of exposure in Phase I linezolid multiple dose studies (N=176).		
IV Treatment (days)	Mean ± SD	5.7 ± 3.6
	Median	6
	Range	[redacted]
Oral Treatment (days)	Mean ± SD	3.6 ± 3.0
	Median	1
	Range	[redacted]

Deaths, serious adverse events, and discontinuations

There were no deaths or serious adverse events in Phase I studies. Two subjects (0.5%) discontinued because of adverse events; one patient in a single oral dose study (Study 0001) discontinued for nausea after receiving 50 mg linezolid, while one patient in a multiple oral dose bioavailability study (Study 0008) discontinued for flu-like symptoms during a wash-out period.

Adverse events

Frequencies of all and drug-related adverse events in Phase I studies are shown in Tables ISS.4 and ISS.5. In single dose linezolid studies, 37.3% (95/255) of subjects experienced 1 or more AEs. The only AE that occurred in 5% or more of subjects was headache (11.8%, 30/255). In multiple dose studies, 81.8% (144/176) of subjects experienced 1 or more AEs, and the most commonly occurring AEs (>5%) were headache (31.8%, 56/176), pharyngitis (11.9%, 21/176), rash (20/176, 11.4%), localized pain (5.1%, 9/176), procedural non-surgical event (6.3%, 11/176), diarrhea (7.4%, 13/176), loose stools NEC (6.3%, 11/176), nausea (14.2%, 25/176), tongue discoloration (22.2%, 39/176), and dizziness (10.2%, 18/176).

With oral administration, 61.0% (188/308) of subjects experienced one or more AEs and the most commonly occurring AEs were headache (23.1%, 71/308), nausea (10.1%, 31/308), tongue discoloration (9.7%, 30/308), pharyngitis (6.8%, 21/308), and dizziness (8.1%, 25/308). When linezolid was administered IV, only 41.5% (51/123) subjects experienced 1 or more AEs, and the most common AEs were headache (12.2%, 15/123), tongue discoloration (8.9%, 11/123), and rash (6.5%, 8/123). Drug-related AEs occurred more often in subjects who received multiple doses of linezolid than in subjects who received a single dose of linezolid and drug-related AEs occurred more frequently with oral administration than with IV administration. The most common drug-related AEs in Phase I subjects were headache, rash, diarrhea or loose stools, nausea, and tongue discoloration.

At doses of 625 mg tid, linezolid was associated with frequent nausea and in a significant proportion of patients, with reversible increases in creatinine and alanine aminotransferase, as well as reversible decreases in peripheral leukocyte, erythrocyte, and platelet counts. These findings represented dose-limiting toxicity and led to a decision to discontinue investigations of linezolid at exposures higher than this level (i.e., at 750 mg tid.)

Single-dose studies of oral linezolid were conducted in patients on hemodialysis or with mild to moderate hepatic impairment. Adverse events included dizziness, headache and diarrhea. These studies did not show any significant effects of linezolid on laboratory parameters in these patients.

Table ISS.4. Frequencies of adverse events in Phase I linezolid studies.

COSTART Body System	Single Dose		Multiple Doses		Oral Only		IV Only	
MET	N = 255		N = 176		N = 308		N = 123	
	n	%	n	%	n	%	n	%
BODY								
Abdominal Cramp	2	0.8	4	2.3	6	1.9	0	-
Abdominal Distention	1	0.4	4	2.3	5	1.6	0	-
Abdominal Pain Generalized	1	0.4	3	1.7	4	1.3	0	-
Abdominal Pain Localized	0	-	7	4.0	6	1.9	1	0.8
Asthenia	4	1.6	5	2.8	8	2.6	1	0.8
Back Pain	3	1.2	2	1.1	4	1.3	1	0.8
Chest Pain	0	-	5	2.8	4	1.3	1	0.8
Chills	0	-	2	1.1	2	0.6	0	-
Headache	30	11.8	56	31.8	71	23.1	15	12.2
Injection Vascular/Catheter Site	2	1.5	0	-	0	-	2	1.6
Hemorrhage								
Injection/Vascular Catheter Site	1	0.4	4	2.3	0	-	5	4.1
Inflammation								
Injection/Vascular Catheter Site Pain	1	0.4	2	1.1	0	-	3	2.4
Localized Pain	4	1.6	9	5.1	7	2.3	6	4.9
Neck – Rigid	0	-	3	1.7	2	0.6	1	0.8
Procedural Non-Surgical Event	1	0.4	11	6.3	9	2.9	3	2.4
Trauma	1	0.4	4	2.3	5	1.6	0	-
Upper Respiratory Infection	1	0.4	5	2.8	5	1.6	1	0.8
CARDIOVASCULAR								
Palpitation	0	-	6	3.4	5	1.6	1	0.8
Vasodilation	0	-	5	2.8	5	1.6	0	-
DIGESTIVE								
Appetite Decreased	1	0.4	3	1.7	2	0.6	2	1.6
Diarrhea	3	1.2	13	7.4	13	4.2	3	2.4
Disorder Tongue	1	0.4	3	1.7	2	0.6	2	1.6
Dry Mouth	2	0.8	4	2.3	5	1.6	1	0.8
Dyspepsia	1	0.4	3	1.7	4	1.3	0	-
Flatulence	1	0.4	4	2.3	5	1.6	0	-
Loose Stools NEC	2	0.8	11	6.3	12	3.9	1	0.8
Nausea	8	3.1	25	14.2	31	10.1	2	1.6
Stomatitis Aphthous	0	-	3	1.7	1	0.3	2	1.6
Throat Dry	0	-	2	1.1	1	0.3	1	0.8
Tongue Discoloration	2	0.8	39	22.2	30	9.7	11	8.9
Ulcer Mouth	0	-	2	1.1	2	0.6	0	-
Vomiting	2	0.8	1	0.6	3	1.0	0	-
HEMIC AND LYMPHATIC								
Ecchymosis/Bruise	2	0.8	1	0.6	3	1.0	0	-

Table ISS.4 (continued)								
COSTART Body System	Single Dose		Multiple Doses		Oral Only		IV Only	
MET	N = 255		N = 176		N = 308		N = 123	
	n	%	n	%	n	%	n	%
METABOLIC AND NUTRITIONAL								
SGOT Increased	0	-	2	1.1	0	-	2	1.6
SGPT Increased	0	-	5	2.8	0	-	5	4.1
NERVOUS								
Agitation	0	-	2	1.1	2	0.6	0	-
Anxiety	0	-	3	1.7	3	1.0	0	-
CNS Stimulation	0	-	3	1.7	0	-	3	2.4
Dizziness	11	4.3	18	10.2	25	8.1	4	3.3
Dysautonomia	0	-	2	1.1	2	0.6	0	-
Insomnia	0	-	3	1.7	3	1.0	0	-
Somnolence	0	-	5	2.8	5	1.6	0	-
RESPIRATORY								
Cough	1	0.4	4	2.3	5	1.6	0	-
Epistaxis	0	-	2	1.1	2	0.6	0	-
Pharyngitis	5	2.0	21	11.9	21	6.8	5	4.1
Rhinitis	2	0.8	7	4.0	8	2.6	1	0.8
Sinusitis	1	0.4	2	1.1	2	0.6	1	0.8
SKIN								
Dermatitis Fungal	1	0.4	6	3.4	7	2.3	0	-
Erythema	0	-	2	1.1	1	0.3	1	0.8
Folliculitis	0	-	4	2.3	3	1.0	1	0.8
Herpes Simplex Derm	2	0.8	2	1.1	3	1.0	1	0.8
Moniliasis – Skin	0	-	2	1.1	2	0.6	0	-
Pruritus Non-Application Site	0	-	6	3.4	5	1.6	1	0.8
Rash	3	1.2	20	11.4	15	4.9	8	6.5
Rash – Vesiculobullous	0	-	2	1.1	2	0.6	0	-
Skin Irritation – Nonapplication Site	0	-	3	1.7	3	1.0	0	-
SPECIAL SENSES								
Ear Pain	1	0.4	3	1.7	4	1.3	0	-
Taste Perversion	2	0.8	7	4.0	7	2.3	2	1.6
UROGENITAL								
Disorder Vulvovaginal	0	-	3	1.7	3	1.0	0	-
Dysuria	0	-	2	1.1	1	0.3	1	0.8
Vaginal Discharge NOS	0	-	4	2.3	4	1.3	0	-

Table ISS.5. Frequencies of drug-related adverse events in Phase I linezolid studies								
COSTART Body System	Single Dose		Multiple Doses		Oral Only		IV Only	
MET	N = 255		N = 176		N = 308		N = 123	
	n	%	n	%	n	%	n	%
BODY								
Abdominal Cramp	1	0.4	2	1.1	3	1.0	0	-
Abdominal Distention	0	-	4	2.3	4	1.3	0	-
Abdominal Pain Localized	0	-	4	2.3	4	1.3	0	-
Asthenia	0	-	2	1.1	2	0.6	0	-
Headache	6	2.4	17	9.7	20	6.5	3	2.4
Injection/Vascular Catheter Site	1	0.4	4	2.3	0	-	5	4.1
Inflammation								
Injection/Vascular Catheter Site Pain	1	0.4	2	1.1	0	-	3	2.4
Localized Pain	1	0.4	2	1.1	2	0.6	1	0.8

Table ISS.5 (continued)									
COSTART Body System		Single Dose		Multiple Doses		Oral Only		IV Only	
MET		N = 255		N = 176		N = 308		N = 123	
		n	%	n	%	n	%	n	%
CARDIOVASCULAR									
Vasodilation		0	-	3	1.7	3	1.0	0	-
DIGESTIVE									
Appetite Decreased		0	-	3	1.7	1	0.3	2	1.6
Diarrhea		2	0.8	11	6.3	10	3.2	3	2.4
Dry Mouth		2	0.8	2	1.1	4	1.3	0	-
Dyspepsia		1	0.4	2	1.1	3	1.0	0	-
Flatulence		0	-	4	2.3	4	1.3	0	-
Loose Stools NEC		2	0.8	9	5.1	10	3.2	1	0.8
Nausea		6	2.4	17	9.7	22	7.1	1	0.8
Tongue Discoloration		2	0.8	29	16.5	20	6.5	11	8.9
Tongue Disorder		1	0.4	2	1.1	1	0.3	2	1.6
Vomiting		2	0.8	1	0.6	3	1.0	0	-
METABOLIC AND NUTRITIONAL									
SGOT Increased		0	-	2	1.1	0	-	2	1.6
SGPT Increased		0	-	5	2.8	0	-	5	4.1
NERVOUS									
Anxiety		0	-	2	1.1	2	0.6	0	-
CNS Stimulation		0	-	3	1.7	0	-	3	2.4
Dizziness		1	0.4	4	2.3	5	1.6	0	-
Insomnia		0	-	2	1.1	2	0.6	0	-
Somnolence		0	-	4	2.3	4	1.3	0	-
RESPIRATORY									
Pharyngitis		0	-	7	4.0	4	1.3	3	2.4
SKIN									
Dermatitis Fungal		1	0.4	5	2.8	6	1.9	0	-
Erythema		0	-	2	1.1	1	0.3	1	0.8
Folliculitis		0	-	2	1.1	2	0.6	0	-
Moniliasis – Skin		0	-	2	1.1	2	0.6	0	-
Pruritus Non-Application Site		0	-	5	2.8	4	1.3	1	0.8
Rash		1	0.4	17	9.7	11	3.6	7	5.7
SPECIAL SENSES									
Ear Pain		0	-	3	1.7	3	1.0	0	-
Taste Perversion		2	0.8	7	4.0	7	2.3	2	1.6
UROGENITAL									
Disorder Vulvovaginal	0	-		3	1.7	3	1.0	0	-
Dysuria	0	-		2	1.1	1	0.3	1	0.8
Vaginal Discharge NOS	0	-		3	1.7	3	1.0	0	-
Vaginitis/VAG Infection	0	-		1	0.6	1	0.3	0	-

Laboratory tests

Laboratory test results were pooled from 151 patients in Phase I studies. The results are shown in Table ISS.6. For analytic purposes, patients were classified as receiving low dose (<1 g/d) or high-dose (≥ 1 g/d) linezolid. Patients receiving 750 mg tid were considered to have received high-dose linezolid. According to the applicant, abnormal laboratory values promptly returned to normal after linezolid dosing was stopped. In a few subjects, the analyses were still abnormal at follow-up but were approaching normal.

Table ISS.6. Frequencies of substantially abnormal laboratory test results in Phase I linezolid studies								
	Low-Dose	High-Dose		Race			Sex	
	(< 1 g/d)	(≥ 1 g/d)†	White	Black	Other	Male		Female
Hematology	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)		n/N (%)
Hemoglobin	0/79	0/41	0/115	0/4	0/1	0/113		0/7
Hematocrit	0/79	1/41 (2.4)	1/115 (0.9)	0/4	0/1	0/113		1/7 (14.3)
RBC	0/79	1/41 (2.4)	1/115 (0.9)	0/4	0/1	0/113		1/7 (14.3)
Platelets	0/79	1/41 (2.4)	1/115 (0.9)	0/4	0/1	1/113 (0.9)		0/7
WBC	0/79	0/41	0/115	0/4	0/1	0/113		0/7
Neutrophil	0/6	0/23	0/26	0/3	0/0	0/22		0/7
Chemistry								
AST	1/79 (1.3)	0/41	1/115 (0.9)	0/4	0/1	1/113 (0.9)		0/7
ALT	2/79 (2.5)	4/41 (9.8)	6/115 (5.2)	0/4	0/1	6/113 (5.3)		0/7
Creatinine	0/79	0/41	0/115	0/4	0/1	0/113		0/7
Amylase	0/79	0/41	0/115	0/4	0/1	0/113		0/7
† High-dose group includes subjects who received 750 mg TID.								

Medical Officer's Comment

These data show the expected adverse events to be expected with linezolid to include nausea, vomiting, diarrhea, and headache. The incidence of adverse events was higher in multiple dose studies compared to single dose studies, consistent with an exposure-response effect. The dose-limiting toxicities appeared to be nausea and laboratory changes in hepatic, renal, and hematologic parameters. These studies, in combination with the information on pharmacokinetics and pharmacodynamics of linezolid, provided the basis for proceeding to Phase II trials involving pneumonia, bacteremia, and skin/skin structure infections.

Phase II studies

Demographics

Four Phase II studies were conducted using various TID and BID dosage regimens of linezolid. These enrolled a total of 870 patients who received linezolid. Of these, 471 received ≥1 g/d of linezolid; 399 received < 1 g/d of linezolid. Demographics for these patients are shown in Table ISS.7. One patient in the low-dose group did not have adverse event information recorded, and is therefore excluded from analyses of AEs.

Table ISS.7. Phase II patient demographics						
	All Linezolid		High-Dose (>1 g/d)		Low-Dose (<1 g/d)	
	N = 870		N = 471		N = 399	
Parameter	**n**	**%†**	**n**	**%†**	**n**	**%†**
Age (years)						
<18	0	-	0	-	0	-
18 to 44	332	38.2	164	34.8	168	42.1
45 to 64	280	32.2	162	34.4	118	29.6
≥65	258	29.7	145	30.8	113	28.3
Sex						
Male	523	60.1	286	60.7	237	59.4
Female	347	39.9	185	39.3	162	40.6
Race						
White	625	71.8	309	65.6	316	79.2
Black	154	17.7	103	21.9	51	12.8
Asian or Pacific Islander	4	0.5	1	0.2	3	0.8
Other‡	87	10.0	58	12.3	29	7.3
† Percentages are based on the total number of patients in each group. Percentages may not add to 100 due to rounding.						
‡ The "Other" race category includes "Not allowed to ask," "Mixed, and "Missing" responses.						

Extent of exposure

The extent of exposure in Phase II studies is shown in Table ISS.8. Study 9 enrolled 178 patients with pneumonia who were treated with linezolid at doses of 750 mg/day (62 patients) or 1125 to 1250 mg/day (116 patients). Study 10 enrolled 339 patients with uncomplicated or complicated skin infections who were treated with 750 mg/day (148 patients) or 1125 to 1250 mg/day (191 patients). Study 11 enrolled 164 patients with bacteremia who were treated with 600 mg BID. These three studies were not randomized and, in the two studies using multiple dosage regimens, patients were assigned to the low or high dose treatment groups sequentially, rather than in parallel. Study 26 enrolled 189 patients with skin infections who were randomized to treatment with either 100 mg BID (103 patients) or 200 mg BID (86 patients). The range of doses used in these studies resulted in the selection of 600 mg BID for treatment of patients with pneumonia or complicated skin infections, while doses of 400 mg BID were chosen for patients with uncomplicated skin infections.

Table ISS.8. Extent of exposure by daily linezolid dose in Phase II patients.			
	All Linezolid	High-Dose (>1 g/d)	Low-Dose (<1 g/d)
	N = 870	N = 471	N = 399
Parameter	**n**	**n**	**n**
Days on IV Treatment			
Total Reporting	692	471	221
Mean ± SD	4.9 ± 2.8	5.1 ± 3.1	4.5 ± 1.9
Range	[redacted]		
Days on Oral Treatment			
Total Reporting	726	366	360
Mean ± SD	8.1 ± 4.0	7.6 ± 4.0	8.6 ± 3.8
Range	[redacted]		

Table ISS.8 (continued)			
	All Linezolid	High-Dose (>1 g/d)	Low-Dose (<1 g/d)
	N = 870	N = 471	N = 399
Parameter	**n**	**n**	**n**
Total Days on Treatment			
Total Reporting	865	471	394
Mean ± SD	10.3 ± 4.7	10.5 ± 5.1	10.0 ± 4.1
Range	[redacted]		

Patients in Studies 9, 10, and 11 received IV therapy at the beginning of the study period; patients could be switched over to oral therapy if they showed clinical improvement. Patients in Study 26 could initiate therapy by either the IV or oral routes. Table ISS.9 shows exposure by route of administration.

Table ISS.9. Extent of exposure in Phase II patients by route of administration			
	IV to Oral Switch	IV Only	Oral Only
	N = 553	N = 139	N = 177
Parameter	**n**	**n**	**n**
Days on IV Treatment			
Total Reporting	553	139	0
Mean ± SD	4.7 ± 2.2	5.7 ± 4.4	-
Range	[redacted]		
Days on Oral Treatment			
Total Reporting	553	0	173
Mean ± SD	7.5 ± 3.9	-	9.9 ± 3.6
Range	[redacted]		
Total Days on Treatment			
Total Reporting	553	139	173
Mean ± SD	11.5 ± 4.3	5.7 ± 4.4	9.9 ± 3.6
Range	[redacted]		

The compassionate use of linezolid was evaluated in Study 25. An interim report was provided for 230 patients for whom data were available as of the cutoff date of 30 June 1999. Patients are treated with 600 mg linezolid using any combination of the intravenous solution, oral tablets, or oral suspension. Patients less than 13 years old or who weighed less than 40 kg were treated with a dose of 10 mg/kg oral suspension twice daily (up to 600 mg BID).

Medical Officer's Comment

The applicant also conducted Phase II studies on eradication of Staphyloccocus aureus *and enterococcal carriage (Studies 29 and 30), as well as pediatric studies (Studies 45 and 49). The safety analysis presented here will focus on Studies 9, 10, 11, 25, and 26 since these involve patients rather than asymptomatic subjects.*

Discontinuations

Primary reasons for discontinuation from treatment in Studies 9, 10, 11, and 26 are shown in Table ISS.10 by daily dose and in Table ISS.11 by route of administration.

Table ISS.10. Reasons for discontinuation by dose in Studies 9, 10, 11, and 26						
	All Linezolid		High-Dose (>1 g/d)		Low-Dose (<1 g/d)	
	N = 870		N = 471		N = 399	
Parameter	**n**	**%**	**n**	**%**	**n**	**%**
Discontinued Patients	170	19.5	102	21.7	68	17.0
Lack of Efficacy	49	5.6	29	6.2	20	5.0
Death	6	0.7	5	1.1	1	0.3
Adverse Event (Serious)	13	1.5	12	2.5	1	0.3
Adverse Event (Nonserious)	31	3.6	13	2.8	18	4.5
Ineligible but Started Study Medication	21	2.4	16	3.4	5	1.3
Protocol Noncompliance	7	0.8	4	0.8	3	0.8
Subject's Personal Request	11	1.3	4	0.8	7	1.8
Lost to Follow-Up	16	1.8	8	1.7	8	2.0
Other	16	1.8	11	2.3	5	1.3

Table ISS.11. Reasons for discontinuation by route of administration in Studies 9, 10, 11, and 26						
	IV to Oral Switch		IV Only		Oral Only	
	N = 553		N = 139		N = 177	
Parameter	**n**	**%**	**n**	**%**	**n**	**%**
Discontinued Patients	40	7.2	105	75.5	24	13.6
Lack of Efficacy	7	1.3	36	25.9	6	3.4
Death	1	0.2	5	3.6	0	-
Adverse Event (Serious)	3	0.5	10	7.2	0	-
Adverse Event (Nonserious)	11	2.0	12	8.6	8	4.5
Ineligible but Started Study Medication	1	0.2	20	14.4	0	-
Protocol Noncompliance	3	0.5	2	1.4	2	1.1
Subject's Personal Request	5	0.9	2	1.4	4	2.3
Lost to Follow-Up	6	1.1	5	3.6	4	2.3
Other	3	0.5	13	9.4	0	-

Medical Officer's Comment

Discontinuations were somewhat more common in the high-dose group. The most common reason for discontinuation was lack of efficacy. The proportion of patients discontinued was much higher in the IV-only group, and the most common reason was again lack of efficacy; these patients were predominantly in Studies 9, 10, and 11, and represented a sicker patient population with an anticipated worse prognosis. In addition, a substantial number of patients in Studies 9, 10, and 11 were started empirically on linezolid but then found to be ineligible based on culture results.

The incidence of discontinuations due to any adverse event (serious or nonserious) was similar in the high-dose and low-dose groups. The incidence of discontinuations due to either serious or nonserious events was substantially higher in the IV-only group than in patients who received oral therapy at any point in their course.

In Study 25 (compassionate use), thirty-seven (16.1%) of the 230 enrolled patients had AEs that resulted in discontinuation of study medication either during the treatment or follow-up period due to an AE. Most of the AEs that led to discontinuation from the trial were related to the underlying illnesses. Only 9 (3.9%) of the 230 enrolled patients discontinued from the trial due to AEs that the investigator judged to be related to the

administration of linezolid. The primary drug-related AE that led to the discontinuation of linezolid was thrombocytopenia (2.2%, 5/230).

Medical Officer's Comment

The high incidence of AEs in Study 25 may have been due in part to the nature of the patient population; however, these patients also received linezolid for a prolonged period, which could have contributed to the high AE rate. The frequency of discontinuation for thrombocytopenia is noteworthy, given the results from Phase I and Phase III studies; however, since a substantial number of these patients had hematologic malignancies, this result should be interpreted cautiously.

Deaths

A total of 19 deaths were reported in Phase II Studies 09, 10, 11, and 26 with 16 deaths in the high-dose group and 3 deaths in the low-dose group. Reasons for deaths are shown in Table ISS.12. The applicant concluded that these deaths were not related to administration of linezolid.

Table ISS.12. Reasons for death in Phase II studies 9, 10, 11, and 26

COSTART Body System	All Linezolid		High-Dose		Low-Dose	
MET			>1 g/day		<1 g/day	
	N =869		N=471		N=398	
	n	%	n	%	n	%
Patients with non-fatal outcome	850	97.8	455	96.6	395	99.2
Patients who died	19	2.2	16	3.4	3	0.8
BODY						
Septic Shock	3	0.4	3	0.6	0	-
Sepsis	1	0.1	0	-	1	0.3
CARDIOVASCULAR						
Hypotension	1	0.1	1	0.2	0	-
Myocardial infarction	2	0.2	1	0.2	1	0.3
Cardiac arrest NEC	1	0.1	1	0.2	0	-
Cardiac rhythm abnormal	1	0.1	1	0.2	0	-
DIGESTIVE						
Gastrointestinal bleeding	1	0.1	1	0.2	0	-
Intestinal obstruction	1	0.1	1	0.2	0	-
NERVOUS						
Status Epilepticus	1	0.1	0	-	1	0.3
RESPIRATORY						
Respiratory Failure	5	0.6	5	1.1	0	-
Respiratory Arrest	1	0.1	1	0.2	0	-
Bronchospasm	1	0.1	1	0.2	0	-

Medical Officer's Comment

Of the high-dose patients who died in Studies 9, 10, 11, and 26, 13/169 were in Study 11, a trial of linezolid in the treatment of bacteremia. These patients were generally seriously ill; the medical reviewer agrees with the lack of evidence for a relationship between use of linezolid and mortality in these patients.

One patient death was attributed by the investigator to linezolid. All of the other deaths were attributed to the illnesses of the patients and not to the study medication.

The one patient whose death was attributed to linezolid was a 37-year-old man who was being treated with linezolid for SSTI at a dose of 750 mg/day for 6 days. On post-

treatment day 4, he experienced severe status epilepticus, which lasted 15 days. Treatment with study medication was completed prior to the start of the event. At the time of the event, he was taking furosemide, phenytoin sodium, levothyroxine sodium, phenobarbital, calcium carbonate, and docusate sodium with casanthranol. The patient's medical history revealed that the patient had a pineal tumor at 19 years old. Following surgery (including a ventricular shunt) and radiation treatment, he had resided in a nursing home. He was not ambulatory, spoke some, and fed himself. Apparently he had a seizure disorder related to the tumor and/or the treatments, which had been well controlled with phenytoin and phenobarbital, with no seizures in the year before enrollment into study. He had developed cellulitis of the right thigh and was enrolled in this study. After 6 days of treatment the cellulitis had resolved and he was recorded as a Clinical Cure. At STFU he was doing well and again recorded as a Clinical Cure. Two days later, he developed status epilepticus. He apparently developed aspiration pneumonia at the same time, which was treated with a cephalosporin antibiotic. The pneumonia became serious 2 days later. He died on 22 November 96. No autopsy was performed. Cause of death was reported as 1) status epilepticus, 2) aspiration pneumonia. The investigator judged these events to be related to treatment with study medication, based on the fact that the admission phenylhydantoin level was 19 µg/mL and the level at the time of the seizure was 11 µg/mL (still a therapeutic level) and felt that a pharmacokinetic interaction between linezolid and phenylhydantoin might have occurred.

Ninety-eight (42.6%) of the 230 patients enrolled in the compassionate use study (Study 25) died either during the treatment or follow-up period. All of the deaths were attributed to complications of the underlying life-threatening illnesses of the patients with most deaths due to sepsis (13.0%, 30/230) or multisystem organ failure (9.1%, 21/230).

Medical Officer's Comment

The case described above is not clear-cut; it would be helpful to know what the phenylhydantoin concentrations had been when the patient had previously had had seizures. The likelihood that linezolid played a causal role in this death is lessened by in vitro *findings that linezolid does not appear to interact with cytochrome P450 isoforms (see below Drug-drug interactions). However, this may represent a signal event that should be monitored in post-marketing surveillance.*

The high mortality rate in Study 25 was to be expected, given that many of the patients in this study had multiple co-morbidities and were enrolled in the study because of the lack of therapeutic options for resistant pathogens. Deaths in Study 25 were reviewed by the medical officer. There was no case in this study in which linezolid appeared to directly contribute to the patient's death. However, the high mortality rate also confounded the determination of treatment effect in this uncontrolled trial; thus, Study 25 provides only limited support for the efficacy of linezolid in the treatment of VRE infection.

Serious adverse events

A total of 14.0% (66/471) of patients in the high-dose group experienced one or more SAEs versus 4.8% (19/398) of patients in the low-dose group. The only SAEs that occurred at a percentage of 1% or greater were sepsis (1.1%, 5/471) and pneumonia (1.3%, 6/471) in the high-dose group. The only events that had a frequency of greater than 2 were related to the underlying infection (cellulitis, sepsis, septic shock, pneumonia, and respiratory failure). There was no dose-related pattern for any single serious adverse event.

There were a total of 199 SAEs reported in 135 (58.7%) of the 230 patients who were enrolled in this compassionate use study; in general, the SAEs were deemed to be related to the underlying diseases of the severely ill patients who were enrolled in this trial.

Medical Officer's Comment

The medical officer concurs that SAEs that occurred at greater frequency did not appear, in general, to be related to administration of linezolid. It is not possible to exclude a relation between linezolid and SAEs related to laboratory abnormalities (e.g., elevations in transaminase concentrations), although there were generally few such cases.

Adverse events and Drug-related Adverse Events

The incidences of all adverse events in Phase II studies are shown in Table ISS.13. The most common AEs experienced by patients in Studies 9, 10, 11, and 26 were diarrhea (12.7%, 60/471), headache (10.8%, 51/471), and nausea (9.8%, 46/471) in the high-dose group, and headache (16.8%, 67/398), diarrhea (10.3%, 41/398), nausea (10.3%, 41/398), and localized pain (6.8%, 27/398) in the low-dose group.

Table ISS.13. Frequencies of adverse events in Phase II linezolid studies

COSTART Body System	All Linezolid		High-Dose (>1 g/d)		Low-Dose (<1 g/d)	
MET	N=869		N=471		N=398	
	n	%†	n	%†	n	%†
Patients With None	226	26.0	125	26.5	101	25.4
Patients With at Least One	643	74.0	346	73.5	297	74.6
BODY						
Abdominal Cramp	9	1.0	4	0.8	5	1.3
Abdominal Pain Generalized	17	2.0	12	2.5	5	1.3
Abdominal Pain Localized	13	1.5	6	1.3	7	1.8
Abscess	9	1.0	5	1.1	4	1.0
Asthenia	11	1.3	3	0.6	8	2.0
Back Pain	23	2.6	13	2.8	10	2.5
Cellulitis	7	0.8	2	0.4	5	1.3
Chest Pain	23	2.6	13	2.8	10	2.5
Chills	8	0.9	3	0.6	5	1.3
Fatigue	14	1.6	7	1.5	7	1.8
Fever	34	3.9	17	3.6	17	4.3
Generalized Pain	12	1.4	6	1.3	6	1.5
Headache	118	13.6	51	10.8	67	16.8
Injection/Vascular Catheter Site Pain	17	2.0	11	2.3	6	1.5
Injection/Vascular Catheter Site	6	0.7	5	1.1	1	0.3
Phlebitis/Thrombosis						
Injection/Vascular Catheter Site	14	1.6	12	2.5	2	0.5
Reaction						
Localized Edema	22	2.5	14	3.0	8	2.0
Localized Pain	48	5.5	21	4.5	27	6.8
Malaise	8	0.9	4	0.8	4	1.0
Sepsis	7	0.8	6	1.3	1	0.3
Trauma	14	1.6	8	1.7	6	1.5
Upper Respiratory Infection	19	2.2	6	1.3	13	3.3
CARDIOVASCULAR						
Atrial Fibrillation	9	1.0	7	1.5	2	0.5
Congestive Heart Failure	10	1.2	6	1.3	4	1.0
Hypertension	30	3.5	20	4.2	10	2.5
Hypotension	21	2.4	15	3.2	6	1.5

Table ISS.13 (continued)						
COSTART Body System	All Linezolid		High-Dose (>1 g/d)		Low-Dose (<1 g/d)	
MET	N=869		N=471		N=398	
	n	%†	n	%†	n	%†
CARDIOVASCULAR						
Tachycardia	8	0.9	4	0.8	4	1.0
DIGESTIVE						
Anorexia	7	0.8	1	0.2	6	1.5
Appetite Decreased	11	1.3	7	1.5	4	1.0
Constipation	29	3.3	15	3.2	14	3.5
Diarrhea	101	11.6	60	12.7	41	10.3
Disorder Rectal	6	0.7	5	1.1	1	0.3
Disorder Tongue	10	1.2	7	1.5	3	0.8
Dry Mouth	22	2.5	11	2.3	11	2.8
Dyspepsia	32	3.7	13	2.8	19	4.8
Liver Function Tests Abnormal NOS	9	1.0	3	0.6	6	1.5
Loose Stools NEC	5	0.6	5	1.1	0	-
Monilia Oral	17	2.0	12	2.5	5	1.3
Nausea	87	10.0	46	9.8	41	10.3
Noninfectious Hepatitis	7	0.8	5	1.1	2	0.5
Tongue Discoloration	19	2.2	16	3.4	3	0.8
Vomiting	34	3.9	23	4.9	11	2.8
HEMIC AND LYMPHATIC						
Anemia	14	1.6	12	2.5	2	0.5
METABOLIC AND NUTRITIONAL						
Amylase Increased	14	1.6	14	3.0	0	-
Gamma Glutamyl Transpeptidase Increased	10	1.2	4	0.8	6	1.5
Gout	4	0.5	0	-	4	1.0
Hyperglycemia	8	0.9	3	0.6	5	1.3
Hypoalbuminemia	9	1.0	5	1.1	4	1.0
Hypokalemia	12	1.4	6	1.3	6	1.5
Lipase High	18	2.1	14	3.0	4	1.0
Peripheral Edema	16	1.8	10	2.1	6	1.5
Phosphatase Alkaline Increased	6	0.7	5	1.1	1	0.3
SGOT Increased	9	1.0	5	1.1	4	1.0
SGPT Increased	13	1.5	8	1.7	5	1.3
NERVOUS						
Agitation	7	0.8	5	1.1	2	0.5
Anxiety	15	1.7	8	1.7	7	1.8
Confusion	10	1.2	9	1.9	1	0.3
Depressive Symptoms	7	0.8	3	0.6	4	1.0
Dizziness	28	3.2	11	2.3	17	4.3
Hypertonia	8	0.9	6	1.3	2	0.5
Insomnia	34	3.9	18	3.8	16	4.0
Paresthesia	8	0.9	4	0.8	4	1.0
Somnolence	10	1.2	4	0.8	6	1.5
RESPIRATORY						
Cough	13	1.5	7	1.5	6	1.5
Dyspnea	17	2.0	11	2.3	6	1.5
Effusion Pleural	9	1.0	7	1.5	2	0.5
Epistaxis	7	0.8	6	1.3	1	0.3
Pharyngitis	21	2.4	9	1.9	12	3.0
Pneumonia	14	1.6	10	2.1	4	1.0

Table ISS.13 (continued)						
COSTART Body System	**All Linezolid**		**High-Dose (>1 g/d)**		**Low-Dose (<1 g/d)**	
MET	**N=869**		**N=471**		**N=398**	
	n	**%†**	**n**	**%†**	**n**	**%†**
RESPIRATORY						
Rhinitis	8	0.9	3	0.6	5	1.3
Sinusitis	10	1.2	6	1.3	4	1.0
SKIN						
Dermatitis Fungal	9	1.0	5	1.1	4	1.0
Diaphoretic	11	1.3	5	1.1	6	1.5
Disorder Skin NEC	5	0.6	1	0.2	4	1.0
Erythema	15	1.7	10	2.1	5	1.3
Herpes Simplex Derm	14	1.6	7	1.5	7	1.8
Moniliasis Skin	9	1.0	5	1.1	4	1.0
Pressure Sore	6	0.7	5	1.1	1	0.3
Pruritus Non-Application Site	24	2.8	9	1.9	15	3.8
Rash	34	3.9	20	4.2	14	3.5
Rash Vesiculobullous	6	0.7	2	0.4	4	1.0
Skin Infection	10	1.2	4	0.8	6	1.5
Ulcer Skin	10	1.2	6	1.3	4	1.0
SPECIAL SENSES						
Blurred Vision	6	0.7	5	1.1	1	0.3
Taste Perversion	17	2.0	8	1.7	9	2.3
UROGENITAL						
Disorder Vulvovaginal	13	1.5	8	1.7	5	1.3
Incontinence Urinary	5	0.6	5	1.1	0	-
Infection Urinary Tract	13	1.5	6	1.3	7	1.8
Moniliasis Vaginal	10	1.2	4	0.8	6	1.5
† Percentages are based on the total number of patients reporting. Patients are counted once per COSTART MET.						

The incidences of drug-related adverse events in Phase II studies are shown in Table ISS.14. The most common drug-related AEs experienced by high-dose patients in Phase II Studies 9, 10, 11, and 26 were nausea (5.1%), diarrhea (4.9%), tongue discoloration (3.4%), headache (2.3%), oral moniliasis (2.3%), and increased amylase and lipase (1.9% each). For low-dose patients, the most common drug-related AEs were diarrhea (4.4%), nausea (4.3%), headache (4.3%), taste perversion (2.3%), dry mouth (2.0%), and dyspepsia (2.0%).

Table ISS.14. Frequencies of drug-related adverse events in Phase II linezolid studies						
COSTART Body System	**All**		**High-Dose**		**Low-Dose**	
MET	**Linezolid**		**>1 g/day**		**<1 g/day**	
	N=869		**N=471**		**N=398**	
	n	**%†**	**n**	**%†**	**n**	**%†**
Patients With None	584	67.2	307	65.2	277	69.6
Patients With At Least One	285	32.8	164	34.8	121	30.4
BODY						
Headache	28	3.2	11	2.3	17	4.3
Injection/Vascular Catheter Site Pain	10	1.2	6	1.3	4	1.0
CARDIOVASCULAR						
Hypertension	8	0.9	7	1.5	1	0.3
DIGESTIVE						
Diarrhea	41	4.7	23	4.9	18	4.5
Disorder Tongue	9	1.0	6	1.3	3	0.8
Dry Mouth	14	1.6	6	1.3	8	2.0
Dyspepsia	12	1.4	4	0.8	8	2.0
Liver Function Tests Abnormal NOS	8	0.9	3	0.6	5	1.3

Table ISS.14 (continued)						
	All Linezolid		High-Dose >1 g/day		Low-Dose <1 g/day	
COSTART Body System	N=869		N=471		N=398	
MET	n	%†	n	%†	n	%†
DIGESTIVE						
Monilia Oral	15	1.7	11	2.3	4	1.0
Nausea	41	4.7	24	5.1	17	4.3
Tongue Discoloration	19	2.2	16	3.4	3	0.8
Vomiting	10	1.2	5	1.1	5	1.3
METABOLIC AND NUTRITIONAL						
Amylase Increased	9	1.0	9	1.9	0	-
Gamma Glutamyl Transpeptidase Increased	8	0.9	3	0.6	5	1.3
Lipase High	13	1.5	9	1.9	4	1.0
SGOT Increased	6	0.7	2	0.4	4	1.0
SGPT Increased	8	0.9	3	0.6	5	1.3
NERVOUS						
Dizziness	6	0.7	1	0.2	5	1.3
Insomnia	4	0.5	0	-	4	1.0
SKIN						
Rash	10	1.2	4	0.8	6	1.5
SPECIAL SENSES						
Taste perversion	16	1.8	7	1.5	9	2.3
UROGENITAL						
Disorder Vulvovaginal	10	1.2	5	1.1	5	1.3
Moniliasis Vaginal	9	1.0	3	0.6	6	1.5
† Percentages are based on the number of patients reporting. Patients are counted once per COSTART MET.						

Medical Officer's Comment

The pattern of adverse events appears similar to that seen in Phase I studies. The incidences of drug-related AEs did not, in general, appear to be dose-dependent; however, the increased incidence of linezolid-associated hypertension in the high-dose group is noteworthy, given linezolid's inhibition of MAO activity. However, this result is difficult to interpret, given that these patients were in general sicker and had more comorbidities.

Laboratory findings

Medical Officer's Comment

The applicant pooled Phase II and Phase III laboratory data for analysis purposes; because the populations and doses studied differed between Phase II and Phase III, the medical reviewer analyzed the Phase II laboratory data separately, using the interactive graphic techniques developed by Dr. Szarfman.

With respect to hematology data, there was a higher incidence of thrombocytopenia in patients with normal platelet counts at baseline in the high-dose treatment group compared to the low-dose group (13/467 (2.8%) vs. 7/394 (1.8%)). The highest incidence of thrombocytopenia was in Study 11, a study of high-dose linezolid in bacteremic patients; in that study, approximately 6% of patients with normal platelet counts at baseline developed thrombocytopenia. Two patients in the high-dose group had decreases in platelet counts to less than 50,000/mm^3; none of these patients had associated clinical adverse events. In patients with laboratory follow-up, thrombocytopenia generally resolved.

There was also a higher incidence of leukopenia (38/471 (8.1%) v. 25/394 (6.3%)) in the high-dose arm. Although there was a similar incidence of neutropenia in both arms,

there was a higher incidence of grade III neutropenia (ANC< 1000) among high-dose patients who had a baseline ANC > 1000/mm^3 (5/471 (1.1%) vs. 2/397 (0.5%). There were no clinical adverse events related to these changes. There was also a higher incidence of decreases in hemoglobin concentration to less that 10 g/dL in high-dose patients above this level at baseline (26/453 (5.7%) vs. 8/392 (2.0%)).

With respect to chemistry tests, there was no evidence in either arm of significant increases in hepatic, renal, or pancreatic parameters.

In the linezolid compassionate use trial (Study 25), there was also a substantial number of patients who developed thrombocytopenia, some of whom had clinically related adverse events. While the role of linezolid in causing thrombocytopenia in these patients cannot be excluded, it is important to recognize that most of these patients had underlying illnesses predisposing to thrombocytopenia (e.g., acute myelogenous leukemia) or were receiving medications (e.g., heparin, systemic glucocorticosteroids) that are known to be associated with hemorrhagic events.

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Phase III Studies

Demographics

These trials comprised seven comparator-controlled studies. A dose-comparison study, 54A, examining the use of linezolid in the treatment of VRE infection, was also conducted by the applicant. Because that study had a unique design and enrolled a considerably different patient population than the other Phase III studies, it was not pooled for safety analysis. The reader is referred to the medical review of Study 54A for the safety analysis of that study.

There were 2046 linezolid-treated patients and 2001 comparator-treated patients in the Phase III trials. Of the linezolid-treated patients, 1498 received linezolid 600 mg bid and 548 received linezolid 400 mg bid. The comparators included ceftriaxone, cefpodoxime, clarithromycin, oxacillin, dicloxacillin, and vancomycin. Demographics of patients in these studies are shown in Table ISS.15.

Table ISS.15. Phase III patient demographics

	All Linezolid N = 2046		All Comparators N = 2001	
Parameter	**n**	**%**	**n**	**%**
Age (years)				
<18	10	0.5	8	0.4
18 to 44	816	39.9	814	40.7
45 to 64	631	30.8	602	30.1
>65	589	28.8	577	28.8
Sex				
Male	1212	59.2	1152	57.6
Female	834	40.8	849	42.4
Race				
White	1453	71.0	1421	71.0
Black	207	10.1	223	11.1
Asian or Pacific Islander	125	6.1	136	6.8
Other‡	261	12.8	221	11.0
Indication				
Pneumonia	908	44.4	874	43.7
Skin/Soft Tissue	1070	52.3	1064	53.2
Other	68	3.3	63	3.1
Region				
North America	933	45.6	926	46.3
Latin America	343	16.8	321	16.0
Europe	652	31.9	635	31.7
Other	118	5.8	119	5.9

Medical Officer's Comment

The demographics of the linezolid and comparator groups are comparable. The size of the linezolid safety population allows detection with reasonable confidence of adverse events occurring at a frequency of 0.1% or greater. The size of the safety population 65 years of age or older allows detection with reasonable confidence of adverse events occurring at a frequency of 0.5% or greater.

Extent of exposure

The extent of exposure for patients in Phase III studies is shown in Table ISS.16.

Table ISS.16. Extent of exposure in Phase III studies		
	All Linezolid	All Comparators
Parameter	**N = 2046**	**N = 2001**
Days on IV Treatment		
Total Reporting	1224	1198
Mean ± SD	5.8 ± 4.1	6.7 ± 4.9
Range	[redacted]	
Days on Oral Treatment		
Total Reporting	1646	1451
Mean ± SD	10.4 ± 4.1	10.7 ± 3.9
Range	[redacted]	
Total Days on Treatment		
Total Reporting	2031	1985
Mean ± SD	11.6 ± 4.9	11.6 ± 4.8
Range	[redacted]	

Medical Officer's Comment

These exposures are comparable with those that would be seen with the intended use of this drug.

Deaths

The causes of death in patients in Phase 3 studies are shown in Table ISS.17. The frequencies of deaths for the patient populations in Phase III comparator-controlled studies were similar between treatment groups: 4.8% (98/2046) of patients in the linezolid group died versus 4.9% (99/2001) of patients in the all comparators group.

Table ISS.17. Causes of death in patients in Phase III studies				
COSTART Body System MET	**All Linezolid N=2046**		**All Comparators N=2001**	
	n	**%†**	**n**	**%†**
Patients with non-fatal outcome	1948	95.2	1902	95.1
Patients with fatal outcome	98	4.8	99	4.9
BODY				
Cardiogenic Shock	2	<0.1	1	<0.1
Cardiovascular Shock	1	<0.1	1	<0.1
Hypovolemic Shock	0	-	1	<0.1
Infection Superimposed	0	-	1	<0.1
Pneumoperitoneum	1	<0.1	0	-
Sepsis	6	0.3	12	0.6
Septic Shock	5	0.2	8	0.4
Shock	2	<0.1	0	-
Sudden Death	0	-	1	<0.1
Trauma	1	<0.1	1	<0.1
CARDIOVASCULAR				
Atrial Fibrillation	0	-	1	<0.1
Atrioventricular Block	1	<0.1	0	-
Cardiac Arrest NEC	4	0.2	6	0.3
Cardiac Rhythm Abnormal	1	<0.1	0	-
Cardiopulmonary Arrest	6	0.3	3	0.1
Congestive Heart Failure	7	0.3	3	0.1
Coronary Artery Disease	1	<0.1	1	<0.1
Embolism Pulmonary	4	0.2	4	0.2
Myocardial Infarction	3	0.1	3	0.1

Table ISS.17 (continued)				
COSTART Body System MET	All Linezolid N=2046		All Comparators N=2001	
	n	%†	n	%†
CARDIOVASCULAR				
Occlusion Mesenteric	1	<0.1	0	-
Right Heart Failure NEC	0	-	2	<0.1
Sinus Bradycardia	1	<0.1	0	-
Ventricular Fibrillation	1	<0.1	3	0.1
DIGESTIVE				
Carcinoma Colorectal	1	<0.1	0	-
Carcinoma Stomach	1	<0.1	0	-
Gastrointestinal Bleeding	0	-	1	<0.1
Intestinal Obstruction	1	<0.1	0	-
Intestinal Perforation	1	<0.1	0	-
Multiple Organ Failure	7	0.3	6	0.3
Neoplasm Pancreas Malignant	0	-	1	<0.1
Pancreatitis Necrotizing	1	<0.1	0	-
Peritonitis	2	<0.1	1	<0.1
METABOLIC AND NUTRITIONAL				
Alcohol Intoxication	1	<0.1	0	-
MUSCULO-SKELETAL				
Fasciitis	1	<0.1	0	-
NERVOUS				
Brainstem Infarct	1	<0.1	0	-
Cerebral Infarction	4	0.2	3	0.1
Edema Brain	0	-	1	<0.1
Encephalopathy	3	0.1	1	<0.1
Hemorrhage Cerebral	2	<0.1	3	0.1
Neoplasm CNS	0	-	1	<0.1
RESPIRATORY				
Arrest Respiratory	1	<0.1	3	0.1
Aspiration	1	<0.1	1	<0.1
Aspiration Pneumonia	3	0.1	1	<0.1
Dyspnea	2	<0.1	1	<0.1
Edema Lung	1	<0.1	0	-
Infarction Pulmonary	1	<0.1	0	-
Lung Disease Obstructive	1	<0.1	0	-
Pneumonia	2	<0.1	11	0.5
Respiratory Distress Syndrome	1	<0.1	1	<0.1
Respiratory Failure	10	0.5	9	0.4
UROGENITAL				
Carcinoma Bladder	0	-	1	<0.1
Hydronephrosis	1	<0.1	0	-
Kidney Failure	0	-	1	<0.1

† Percentages are based on the number of patients reporting. Patients are counted once per COSTART MET. Only the primary cause of death is recorded for each patient.

Medical Officer's Comment

The medical officer reviewed all patient deaths. None of the deaths appeared to be directly related to linezolid or comparator. In the two comparator-controlled studies with significant numbers of deaths, the mortality rates differed between arms. In study 48A (HAP), the mortality rate was lower in the linezolid arm (17.7% for linezolid vs. 25.4% for vancomycin), while in Study 31 (MRSS), the mortality rate was higher in the linezolid arm

(16.7% for linezolid vs. 13.6% for vancomycin). The higher mortality rate in linezolid-treated patients in Study 31 did not appear to reflect decreased efficacy in this population.

Serious adverse events

SAEs occurred at similar rates in the two treatment groups: 233/2046 (11.4%) in the linezolid population and 212/2001 (10.6%) in the comparator population. There were no major differences between treatment groups in the occurrence of SAEs by body system. The only SAE which occurred at a proportion >1% was pneumonia (linezolid 1.3%, 26/2046; comparators 1.2%, 24/2001).

SAEs analyzed by route of linezolid administration are shown in Table ISS.18. When SAEs were evaluated based on the route of administration for linezolid, the results were comparable to those for all AEs. The highest occurrence of SAEs was in the IV-only group (31.9%, 123/385). Patients who only received oral study medication had the lowest occurrence of SAEs (4.0%, 33/822).

Table ISS.18. SAEs in linezolid-treated patients in Phase III studies

COSTART Body System	IV to Oral Switch		IV Only		Oral Only	
MET	N=839		N=385		N=822	
	n	%	n	%	n	%
Patients With None	762	90.8	262	68.1	789	96.0
Patients With at Least One	77	9.2	123	31.9	33	4.0
BODY						
Fever	0	-	4	1.0	0	-
Sepsis	7	0.8	12	3.1	0	-
Septic shock	2	0.2	7	1.8	0	-
CARDIOVASCULAR						
Cardiac arrest NEC	2	0.2	5	1.3	0	-
Cardiopulmonary arrest	0	-	5	1.3	1	0.1
Congestive heart failure	2	0.2	9	2.3	0	-
Hypotension	0	-	4	1.0	0	-
Myocardial infarction	2	0.2	4	1.0	1	0.1
DIGESTIVE						
Gastrointestinal bleeding	1	0.1	4	1.0	0	-
Multiple organ failure	1	0.1	9	2.3	0	-
RESPIRATORY						
Dyspnea	3	0.4	6	1.6	1	0.1
Pneumonia	4	0.5	10	2.6	12	1.5
Respiratory failure	1	0.1	17	4.4	0	-

Medical Officer's Comment

SAEs generally appeared to be related to the patient' s underlying illness and not to linezolid administration, as evidenced by pneumonia being the most common SAE. There was no apparent association between use of potential interacting medications and SAEs (see below).

Adverse events and Drug-related adverse events

Adverse events and drug-related adverse events occurring in at least 1% of patients in Phase III studies are shown in Tables ISS.19 and ISS.20.

Table ISS.19. Adverse Events occurring in >1% of Phase III Patients				
COSTART Body System	**All Linezolid**		**All Comparators**	
MET	**N=2046**		**N=2001**	
	n	**%**	**N**	**%**
Patients With at Least One	1137	55.6	988	49.4
BODY				
Abdominal Pain Generalized	23	1.1	17	0.8
Abdominal Pain Localized	25	1.2	15	0.7
Chest Pain	23	1.1	30	1.5
Fever	33	1.6	42	2.1
Headache	134	6.5	110	5.5
Localized Pain	38	1.9	25	1.2
Sepsis	28	1.4	25	1.2
Trauma	43	2.1	36	1.8
Upper Respiratory Infection	16	0.8	20	1.0
CARDIOVASCULAR				
Hypertension	34	1.7	9	0.4
Hypotension	19	0.9	20	1.0
DIGESTIVE				
Constipation	44	2.2	42	2.1
Diarrhea	170	8.3	126	6.3
Dyspepsia	39	1.9	25	1.2
Liver Function Tests Abnormal NOS	26	1.3	12	0.6
Monilia Oral	28	1.4	15	0.7
Nausea	127	6.2	92	4.6
Vomiting	75	3.7	41	2.0
HEMIC AND LYMPHATIC				
Anemia	34	1.7	20	1.0
NERVOUS				
Dizziness	41	2.0	38	1.9
Insomnia	52	2.5	35	1.7
RESPIRATORY				
Cough	18	0.9	26	1.3
Dyspnea	31	1.5	29	1.4
Pharyngitis	20	1.0	28	1.4
Pneumonia	38	1.9	38	1.9
Respiratory Failure	25	1.2	22	1.1
SKIN				
Pruritus Non-Application Site	23	1.1	23	1.1
Rash	40	2.0	44	2.2
SPECIAL SENSES				
Taste Perversion	25	1.2	15	0.7
UROGENITAL				
Infection Urinary Tract	43	2.1	27	1.3
Moniliasis Vaginal	26	1.3	14	0.7

Table ISS.20. Phase III Drug-related Adverse Events Occurring in >1% of Patients				
COSTART Body System	**All Linezolid**		**All Comparators**	
MET	**N=2046**		**N=2001**	
	n	**%**	**n**	**%**
Patients With at Least One	444	21.7	314	15.7
BODY				
Headache	44	2.2	27	1.3
DIGESTIVE				
Diarrhea	89	4.3	65	3.2
Liver function tests abnormal NOS	21	1.0	7	0.3
Nausea	69	3.4	46	2.3
Vomiting	23	1.1	8	0.4
SPECIAL SENSES				
Taste perversion	24	1.2	14	0.7
UROGENITAL				
Moniliasis vaginal	24	1.2	13	0.6

Medical Officer's Comment

The increased incidence of digestive system AEs (nausea, vomiting, and diarrhea) in linezolid-treated patients relative to comparator-treated patients is notable. The relative frequency of adverse events and their significance varied widely among studies; for example, thrombocytopenia was very common in Study 31 (MRSA), but not in Study 51 (outpatient CAP). However, it seems fairly clear that nausea, vomiting and diarrhea can be expected in a substantial number of patients treated with linezolid; this may affect the suitability of its use for indications where other effective and less toxic alternatives are available. The increased incidence of hypertension in linezolid-treated patients relative to comparator-treated patients is noteworthy, given the MAO inhibitory activity of linezolid. Although a causal relationship cannot be proven, this finding and the increased incidence of drug-associated hypertension in Phase II patients receiving high-dose linezolid suggest that MAO inhibition by linezolid may be clinically relevant and should be addressed in product labeling.

The increased incidence of liver function test abnormalities was examined for evidence of chemical hepatitis; in addition, pancreatic lab parameters were examined by the reviewer given the incidence of nausea, vomiting and abdominal pain as well as the occurrence of drug-related increases in amylase and lipase in Phase II studies (see below).

Discontinuations

The proportions of AEs that resulted in discontinuation of study drug in the Phase III comparator-controlled studies were similar between treatment groups: 5.8% (118/2046) for the linezolid group and 5.2% (105/2001) for the comparator group. The most common AEs resulting in discontinuation were nausea (0.5%), pneumonia (0.5%), headache (0.4%), vomiting (0.3%), and diarrhea (0.3%). There were no AEs occurring in >1% of the patients that resulted in the discontinuation of study medication.

The proportions of AEs that led to the discontinuation of study medication were analyzed by the linezolid route of administration. IV-only patients had the highest rate of discontinuation (10.1%, 39/385); oral-only patients had an intermediate rate of discontinuation (7.3%, 60/822); and patients who began with IV administration and switched

to the oral route had the lowest percentage of discontinuation (2.3%, 19/839). The AEs occurring with a proportion >1% that resulted in the discontinuation of study medication were fever (1.3%) in the IV-only group and pneumonia (1.0%) in the oral-only group.

The proportions of drug-related AEs that resulted in discontinuation of study drug in the Phase III comparator-controlled studies were similar for both treatment groups: 2.4% (50/2046) of patients in the linezolid group and 1.9% (38/2001) of patients in the comparator group experienced drug-related AEs that resulted in the discontinuation of study medication. The most common drug-related AEs resulting in discontinuation were nausea (0.5%), headache (0.4%), vomiting (0.3%), and diarrhea (0.3%). There were no drug-related AEs that occurred in >1% of the patients that resulted in the discontinuation of study medication.

Medical Officer's Comment

As would be expected from the Phase I and II studies, digestive system AEs (particularly nausea and diarrhea) were the most common reason for linezolid discontinuation. The applicant suggested that the higher rate of discontinuations in the IV linezolid treatment group was due to the enrollment of sicker patients in that population. While this is possible, these patients also received higher doses of linezolid and had a longer duration of therapy. The data are most consistent with a higher incidence of drug-related discontinuations in the IV treatment group.

Laboratory findings

Hematology

The applicant provided a separate analysis of Phase III laboratory results. Analysis of mean values for hematologic parameters over time revealed that mean platelet counts were lower in linezolid-treated patients during therapy than in comparator-treated patients; there was also a lower mean hemoglobin concentration in linezolid-treated patients, but this did not appear clinically significant.

The applicant 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 ISS.21.

Table ISS.21. Substantially Abnormal Hematology Values in Phase III patients

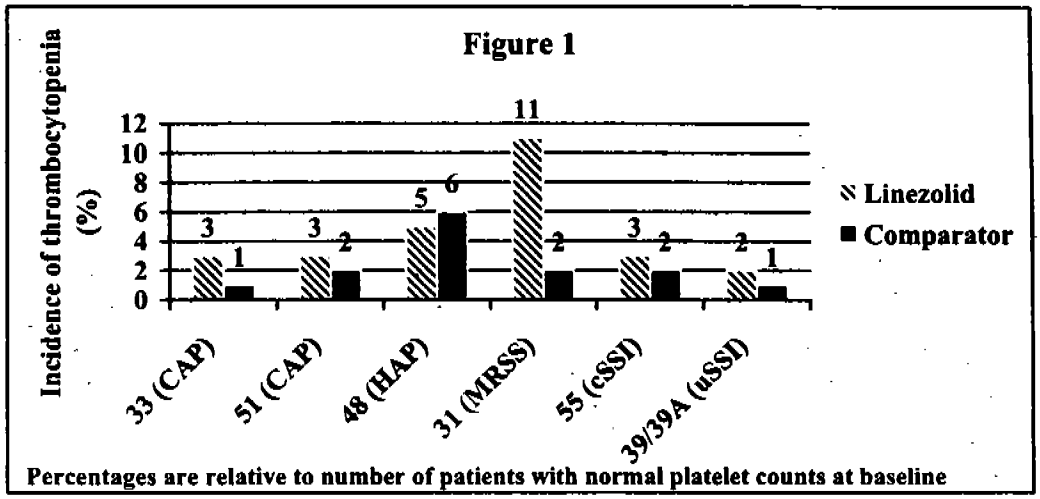
		Linezolid		All Comparators	
Laboratory Assay	**Criteria**	**n/N**	**%**	**n/N**	**%**
Hemoglobin	<75% of LLN	110/1997	5.5	95/1952	4.9
Hematocrit	<75% of LLN	78/1993	3.9	65/1951	3.3
Platelet Count	<75% of LLN	48/1987	2.4	30/1944	1.5
WBC	<75% of LLN	33/1997	1.7	21/1952	1.1
Neutrophils	<0.5 LLN	15/1931	0.8	16/1887	0.8
Eosinophils	>10%	107/1992	5.4	102/1947	5.2
Reticulocyte Count	>2 x ULN	2/1983	0.1	10/1935	0.5

Medical Officer's Comment

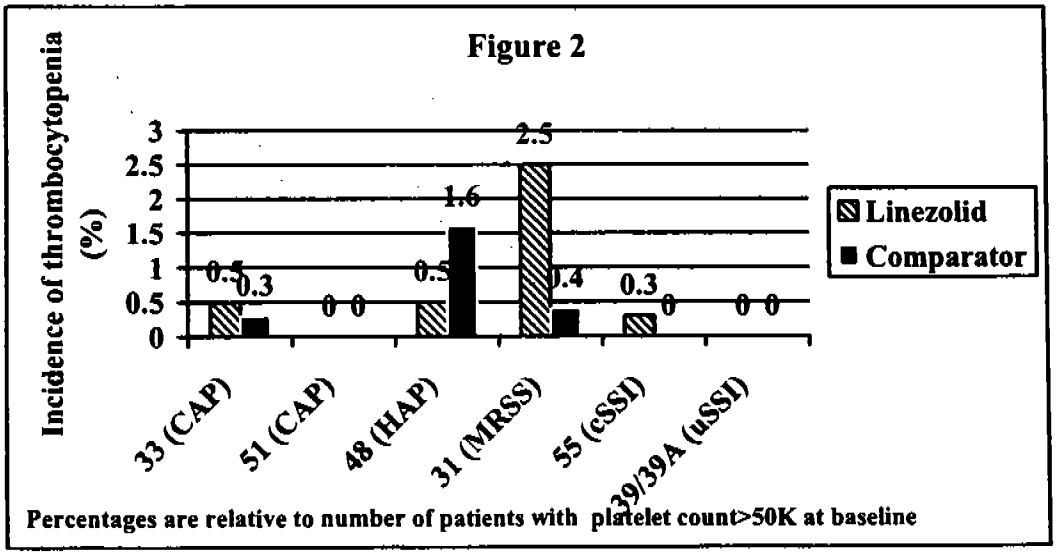
As mentioned above, the medical officer separated Phase II and Phase III trials for purposes of laboratory analysis, and analyzed the patient population with normal values at baseline. There was a higher incidence of thrombocytopenia in linezolid-treated Phase III patients who were normal at baseline than comparator-treated patients (5% vs 3%), as well as leukopenia (5% vs. 4%). The differences between the medical reviewer's percentages and

the applicant's are due to the exclusion of patients with mild thrombocytopenia from the applicant's analysis of substantially abnormal values, as well as the exclusion of patients with abnormal baseline values from the medical reviewer's analysis. There did not appear to be significant differences in the incidence of neutropenia or anemia in the medical reviewer's analysis. No clinically related adverse events were found in association with thrombocytopenia.

The medical officer also analyzed thrombocytopenia by study, as shown in Figure 1. The incidence of thrombocytopenia ranged from [redacted] *with the highest incidence in the MRSS study (Study 31). The incidence of thrombocytopenia in comparator-treated patients ranged from* [redacted]



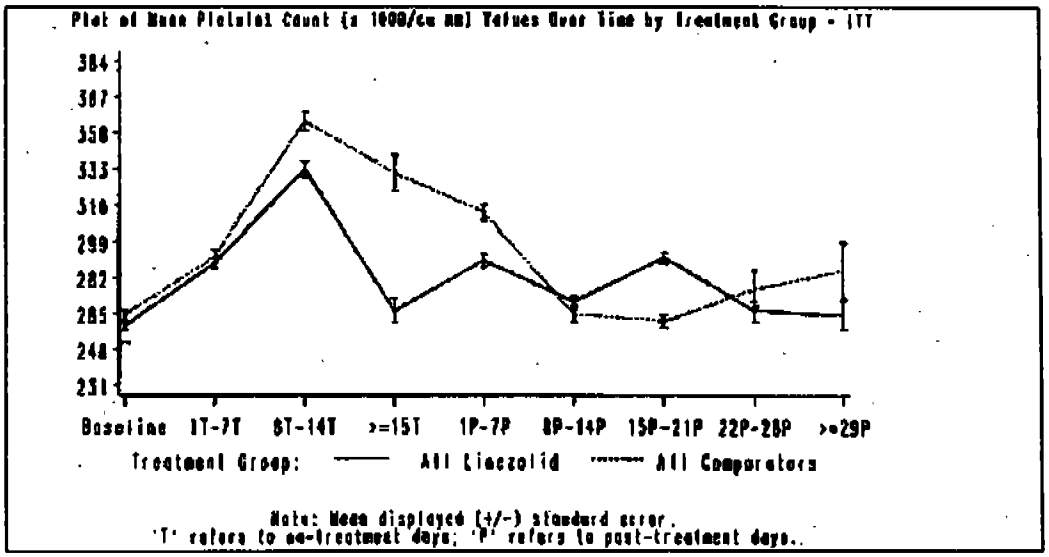
The medical officer also analyzed the incidence of grade III thrombocytopenia (platelet count <5·10⁴/μL) by study, as shown in Figure 2. The incidence of grade III



thrombocytopenia ranged from [redacted] for comparators, the range was [redacted]

A comparison of thrombocytopenia incidences between patients in Phase II and Phase III studies receiving >1 g/d of linezolid with those receiving <1 g/d suggested that thrombocytopenia was dose-dependent, with the possibility that sicker patient populations were more likely to become thrombocytopenic on linezolid therapy. An analysis by the sponsor of the kinetics of platelet count changes in linezolid-treated patients showed a difference in mean platelet counts between linezolid and comparator-treated patients by the second week of therapy, with the maximum difference after two weeks of therapy (Figure 3). Patients with laboratory follow-up appeared to show resolution of thrombocytopenia.

Figure 3



These results suggest that linezolid is associated with thrombocytopenia that may reach clinical significant levels; that the occurrence of thrombocytopenia is dose- and duration-dependent; and that the effect is reversible. Although these effects were not seen for other cell lines, given the toxicology results, it is reasonable to predict that anemia and leukopenia may also be seen in post-marketing surveillance. Product labeling should reflect the possibility of thrombocytopenia occurring in patients at increased risk for this effect.

The applicant performed a similar analysis for chemistry tests. The results are shown in Table ISS.22.

Table ISS.22. Substantially Abnormal Chemistry Values in Phase III patients

		Linezolid		All Comparators	
Laboratory Assay	**Criteria**	**n/N**	**%**	**n/N**	**%**
Total Bilirubin (mg/dL)	>2 x ULN	14/1998	0.7	16/1959	0.8
Total Protein (g/dL)	<0.75 x LLN	37/2004	1.8	21/1963	1.1
	>1.5 x ULN	0/2004	-	1/1963	<0.1
Albumin (g/dL)	<0.75 x LLN	64/1996	3.2	54/1959	2.8
AST (U/L)	>2 x ULN	80/1936	4.1	102/1898	5.4
ALT (U/L)	>2 x ULN	145/1936	7.5	139/1897	7.3

Table ISS.22 (continued)

		Linezolid		All Comparators	
Laboratory Assay	Criteria	n/N	%	n/N	%
LDH (U/L)	>2 x ULN	28/1995	1.4	22/1958	1.1
Alkaline Phosphatase (U/L)	>2 x ULN	53/2000	2.7	46/1963	2.3
BUN (mg/dL)	>2 x ULN	31/2004	1.5	22/1963	1.1
Creatinine (mg/dL)	>2 x ULN	4/2003	0.2	9/1965	0.5
Sodium (mEq/L)	<0.95 x LLN	34/2002	1.7	25/1963	1.3
	>1.05 x ULN	4/2002	0.2	7/1963	0.4
Potassium (mEq/L)	<0.9 x LLN	24/1994	1.2	27/1962	1.4
	>1.1 x ULN	20/1994	1.0	15/1962	0.8
Chloride (mEq/L)	<0.9 x LLN	4/2002	0.2	8/1962	0.4
	>1.1 x ULN	0/2002	-	2/1962	0.1
Bicarbonate (mEq/L)	<0.9 x LLN	62/1993	3.1	76/1955	3.9
	>1.1 x ULN	27/1993	1.4	30/1955	1.5
Calcium (mg/dL)	<0.9 x LLN	68/2004	3.4	65/1963	3.3
	>1.1 x ULN	3/2004	0.1	2/1963	0.1
Nonfasting Glucose (mg/dL)	<0.6 x LLN	13/1993	0.7	8/1956	0.4
	>1.4 x ULN	158/1993	7.9	158/1956	8.1
Creatine Kinase (U/L)	>2 x ULN	103/1994	5.2	64/1954	3.3
Lipase (U/L)	>2 x ULN	79/1995	4.0	74/1954	3.8
Amylase (U/L)	>2 x ULN	35/2001	1.7	30/1961	1.5

Medical Officer's Comment

The applicant concluded that there were no significant differences between treatment groups with respect to chemistry parameters. The medical reviewer reached similar conclusions with respect to the comparability of the treatment groups. However, there was a substantial incidence of elevated lipase concentrations in both arms, probably reflecting the number of ill patients at risk for pancreatitis. It should be kept in mind that in some studies (e.g., Study 33), there were sporadic cases of linezolid-treated patients with clinical pancreatitis and elevated serum concentrations of lipase. Thus, pancreatitis is an event that should be monitored in post-marketing surveillance.

Drug-demographic interactions

The applicant analyzed adverse event data by age. Frequencies of adverse events were generally comparable for linezolid-treated patients younger than 65 years and those older than 65 years (nausea 3.4% vs. 3.2%; vomiting 1.0% vs. 1.5%; diarrhea 4.0% vs. 5.3%; headache 2.7% vs. 0.8%). Adverse event frequencies were also comparable when analyzed between men and women, although women generally showed slightly higher incidences for the most common adverse events (nausea 2.5% vs. 4.7%; vomiting 1.0% vs. 1.3%; diarrhea 3.5% vs. 5.5%; headache 1.6% vs. 3.0%). Analysis of AEs by race also appeared to show comparability between subgroups; however, because the vast majority of Phase III subjects were white, no firm conclusions can be drawn.

The applicant also analyzed laboratory data by age and sex, as shown in Tables ISS.23 and ISS.24. These analyses showed that differences in laboratory parameters between younger and older patients, and between men and women, were comparable between linezolid-treated and comparator-treated patients.

Table ISS.23. Substantially abnormal laboratory values in Phase III patients by age									
		All Linezolid				All Comparator			
Laboratory		<65 years		>65 years		<65 years		>65 years	
Assay	Criteria	n/N	%	n/N	%	n/N	%	n/N	%
Hematology									
WBC	<75% of LLN	44/2082	2.1	9/906	1.0	15/1385	1.1	6/567	1.1
Neutrophils	<0.5 LLN	21/2025	1.0	5/896	0.6	9/1329	0.7	7/558	1.3
Platelets	<75% of LLN	38/2071	1.8	37/903	4.1	14/1383	1.0	16/561	2.9
Hemoglobin	<75% of LLN	91/2082	4.4	81/906	8.9	52/1385	3.8	43/567	7.6
Hematocrit	<75% of LLN	68/2079	3.3	66/904	7.3	40/1384	2.9	25/567	4.4
Chemistry									
ALT	>2 x ULN	179/2022	8.9	74/901	8.2	101/1335	7.6	38/562	6.8
AST	>2 x ULN	94/2021	4.7	49/902	5.4	78/1337	5.8	24/561	4.3
Amylase	>2 x ULN	35/2079	1.7	24/910	2.6	20/1391	1.4	10/570	1.8

Table ISS.24. Substantially abnormal laboratory values in Phase III patients by sex									
		All Linezolid				All Comparator			
Laboratory		Male		Female		Male		Female	
Assay	Criteria	n/N	%	n/N	%	n/N	%	n/N	%
Hematology									
WBC	<75% of LLN	31/1752	1.8	22/1236	1.8	11/1126	1.0	10/826	1.1
Neutrophils	<0.5 LLN	14/1705	0.8	12/1216	1.0	7/1082	0.6	9/805	1.1
Platelets	<75% of LLN	51/1742	2.9	24/1232	1.9	17/1119	1.5	13/825	1.6
Hemoglobin	<75% of LLN	113/1752	6.4	59/1236	4.8	75/1126	6.7	20/826	2.4
Hematocrit	<75% of LLN	95/1747	5.4	39/1236	3.2	51/1126	4.5	14/825	1.7
Chemistry									
ALT	>2 x ULN	181/1706	10.6	72/1217	5.9	95/1089	8.7	44/808	5.4
AST	>2 x ULN	98/1705	5.7	45/1218	3.7	59/1088	5.4	43/810	5.3
Amylase	>2 x ULN	37/1755	2.1	22/1234	1.8	21/1130	1.9	9/831	1.1

Drug-disease interactions

Two Phase I studies were conducted by the applicant to examine the safety and pharmacokinetics of linezolid in patients with renal or hepatic impairment. A brief summary of the applicant's results and conclusions is presented from the NDA; the reader is referred to the Biopharmaceutics review by Dr. Jenny Zheng for more details.

Phase I, Study 21 – Pharmacokinetics in Patients with Impaired Renal Function.

This single-dose, open-label, parallel-group study was conducted in 25 adult volunteers. Subjects were divided into 4 groups based on degree of renal function and each subject received one 600 mg linezolid film-coated tablet except for those subjects maintained on hemodialysis, who received linezolid during two treatment periods (once on a dialysis day and once between dialytic periods) and were tested during both the intra-dialysis and inter-dialysis periods. Plasma and urine were assayed for linezolid using validated chromatographic methods and results showed that linezolid clearance was independent of renal function. Four of the 25 subjects experienced AEs that were mild to moderate in intensity, resolved with no residual effects, and were not considered to be related to study medication. No SAEs were reported. The only notable changes in safety laboratory examinations were small drops in hemoglobin, hematocrit and/or red blood cell count, which could be attributed to the volume of blood taken during phlebotomy.

Phase I, Study 47 – Pharmacokinetics in Patients with Impaired Hepatic Function

This single-dose, open-label study was conducted in 8 patients with liver impairment and 8 healthy subjects given a single linezolid 600 mg dose to determine the effect of hepatic disease on linezolid metabolism. Blood and urine samples were collected up to 48 hours for both groups. Volunteers remained in the clinic for 48 hours after dosing. Plasma and urine samples were assayed for linezolid. No difference in clearance was found between the two groups. One out of these 16 subjects experienced a nonserious AE of toothache, which was mild in intensity and resolved with no residual effects.

Medical Officer's Comment

The applicant also submitted an analysis of 48 linezolid-treated patients with serum creatinine concentrations greater than 2.5 mg/dL. There was a higher incidence of drug-related adverse events in these patients relative to comparator-treated patients (see Table ISS.25); however, given the small sample size, these results should be interpreted with caution.

Table ISS.25. Adverse events in Phase III patients with serum creatinine concentrations > 2.5 mg/dL

	Linezolid (N=48)		Comparator (N=44)	
Mean days of therapy	9.6 ± 6.7		10.3 ± 7.1	
	n	%		
≥ 1 AE	38	79.2	32	72.7
≥ 1 drug-related AE	6	12.5	3	6.8
≥ 1 SAE	19	39.6	21	47.7
≥ 1 AE leading to discontinuation	7	14.6	5	11.4
≥ 1 drug-related AE leading to discontinuation	1	2.1	0	0.0
Deaths	10	20.8	13	29.5

Although these data in combination with the Phase I data support the use of linezolid in these populations, these studies are limited in size and cannot address a wide spectrum of clinical scenarios. No information is available on the toxicity or pharmacokinetics of linezolid in patients undergoing continuous ambulatory peritoneal dialysis or patients with concomitant renal and hepatic failure. In addition, metabolites of linezolid accumulate in the presence of renal failure (see Dr. Zheng's review for more details); potential toxicities from these metabolites have not been studied.

Drug-drug interactions

The applicant conducted single-dose cross-over studies of linezolid in combination with gentamicin or aztreonam. Concomitant administration of either of these drugs with linezolid did not appear to affect the adverse event profile of linezolid.

The applicant also conducted an enzyme induction study in patients treated concomitantly with linezolid and warfarin; the latter drug is a substrate for CYP2C9. There was no evidence for alteration in coagulation parameters or linezolid pharmacokinetics when warfarin and linezolid were administered together. *In vitro* studies showed that linezolid is neither a substrate for, nor an inhibitor of, any of the major human cytochrome P-450 isoforms (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4).

Because of the MAO inhibitory activity of linezolid, the applicant conducted Phase I studies examining potential clinical interactions between linezolid and indirect-acting amines (e.g., phenylpropanolamine), as well as between linezolid and serotonergic agents (e.g.,

dextromethorphan) at usual doses of the latter. Please see the Biopharmaceutics review by Dr. Jenny Zheng for full details.

These studies demonstrated a transient pressor response when linezolid was co-administered with phenylpropanolamine or pseudephedrine, or with tyramine. For this reasons, Phase III studies were designed to monitor patients for signs and symptoms of MAO inhibitor-associated AEs, to capture data on concomitant medications that might interact with linezolid, and to exclude patients who might be at increased risk of hypertensive crisis (e.g., patients with pheochromocytoma).

In Phase III studies, 30.9% (632/2046) of patients treated with linezolid also received medications that potentially interact with MAO. In comparison, 30.3% (605/1999) patients treated with comparator drugs were also on MAO-interacting agents.

In both linezolid and comparator groups, the incidence of potential MAOI-related AEs were generally higher in those that also took MAO-interacting drugs compared to those that did not. Among patients who did not receive MAO-interacting drugs, the incidence of AEs were comparable between linezolid and the comparator groups except for hypertension which occurred with a slightly greater incidence in the linezolid group (1.6% in linezolid vs. 0.3% in the comparator group).

Among the patient population that received MAO-interacting drugs, the overall incidence of AEs was relatively low and none resulted in the discontinuation of study medication. In general, the incidence of potential MAOI-related events was similar between patients in the linezolid group as compared with patients in the comparator group. AEs potentially related to MAOI effect were generally of mild to moderate intensity. Hypertension was observed more often in patients treated with linezolid and MAO-interacting drugs than with the comparator plus MAO interacting drugs (2.1% vs 0.8%).

Medical Officer's Comment

The medical reviewer performed an independent analysis of the occurrence of MAOI-associated events in linezolid-treated and comparator-treated patients. There was no evidence for the occurrence of cases of hypertensive crisis or serotonin syndrome. Analysis of potentially related events did reveal slightly higher frequencies in the linezolid-treated patients receiving sympathomimetic bronchodilators, but the numbers involved are so low that no conclusions can be drawn. For example, of patients developing ventricular tachycardia, 4/5 linezolid-treated patients received concomitant bronchodilators vs. 1/2 comparator-treated patients. Examination of clinical courses of these individual patients suggested that these adverse events were more likely related to pre-existing disease, although exacerbation of such conditions by linezolid cannot be excluded.

The increased incidence of hypertension in patients receiving linezolid and MAO-interacting drugs is of concern. While this could be a chance effect given the small numbers of patients involved, it would be prudent to regard this as a possible manifestation of drug interactions that should be addressed in labeling and monitored in post-marketing surveillance.

Use in pregnancy

Women of childbearing potential were allowed to participate in most of the linezolid studies if they were not pregnant and were not at risk of becoming pregnant. Despite this, 5 patients were found to be pregnant after enrolling. Two patients in Study 39 in the

comparator arm became pregnant during the study. One patient was lost to follow-up and the other patient remains pregnant with an estimated date of delivery of November 1999. Three patients treated with linezolid became pregnant during the study. Two patients had spontaneous abortions and recovered. One patient delivered a healthy infant on September 22, 1999.

Medical Officer's Comment

Since a substantial number of pregnancies result in spontaneous abortion, these data do not prove or exclude the possibility that linezolid is a teratogen or that it can induce spontaneous abortion. Given this, linezolid should be used in pregnant women only if the potential benefit outweighs the potential risk to the fetus.

Final conclusions

The applicant has provided safety data from 430 Phase I subjects, 871 Phase II patients, and 2048 Phase III patients from comparator-controlled trials, as well as safety data from 145 patients in the VRE dose-response trial (Study 54A). The safety database is large enough to demonstrate adverse events occurring at frequencies of 0.1% or greater. These data show the most common toxicities of linezolid to be gastrointestinal (nausea, vomiting, and diarrhea), headache, and insomnia. These adverse events generally occurred at somewhat higher frequencies in linezolid-treated patients than in those receiving comparator agents, but the differences were not substantial enough to alter the risk-benefit balance for linezolid for the indications for which efficacy was demonstrated. Deaths and serious adverse events did not, in general, appear to be causally associated with use of linezolid.

The pharmacokinetics and risk profile of linezolid appears similar in special populations (the elderly and those with renal or hepatic impairment) to the general population. However, because of the limited size of these populations in the safety database, the safety profile in such populations may not be fully characterized, and post-marketing surveillance may provide additional information.

Two particular safety issues need to be addressed in labeling. First, linezolid is an MAO inhibitor. Although the safety database did not show clinical events representing adrenergic or serotonergic drug interactions with linezolid, such events are possible. Therefore, product labeling should advise prescribers about the possibility of such interactions, and inform patients of the need to avoid foods with a high tyramine content.

Second, linezolid is associated with development of thrombocytopenia. Although clinical sequelae of thrombocytopenia were not identified in the NDA safety database, such consequences are predictable given the patient population that is likely to receive this drug. Thus, prescribers should be advised about this issue in product labeling, with information about potential risk factors. The applicant should also be asked to investigate the mechanism(s) of and risk factors for linezolid-associated thrombocytopenia as a Phase IV commitment. Given results in animal toxicology studies, linezolid may show effects on other hematopoetic cell lines in humans; post-marketing surveillance should be monitored in regard to this issue.

In summary, the applicant has demonstrated an acceptable safety profile for linezolid for indications for which efficacy has been demonstrated; the profile is adequate to support approval.