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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Zyvox® / Linezolid

PROTOCOL NO.: A5951105

PROTOCOL TITLE: Linezolid vs Vancomycin/Cefazolin in the Treatment of Hemodialysis Patients With Catheter-Related Gram-Positive Bloodstream Infections

Study Centers: A total of 15 centers took part in study and randomized subjects, 6 centers in India, 3 centers in Columbia, and 1 center each in the United States, Israel, Slovinská Republic, Slovakia, Italy, and Poland.

Study Initiation Date and Final Completion Dates: 16 September 2005 to 06 April 2007 (06 April 2007 was the end-of trial notification date). The study was terminated prematurely.

Phase of Development: Phase 3

Study Objectives: Primary Objective:

- Microbiological efficacy of linezolid compared to vancomycin/cefazolin in the treatment of hemodialysis subjects with Gram-positive catheter-related bloodstream infections.

Secondary Objectives:

- Clinical efficacy of linezolid compared to vancomycin/cefazolin.
- Incidence of metastatic sequelae associated with Gram-positive infections in subjects treated with linezolid or vancomycin/cefazolin.
- Pathogen eradication.
- Eradication of *Staphylococcus* (*S*) *aureus* nasal colonization.
- Safety and tolerance.

METHODS

Study Design: This was an open-label, multicenter, randomized (1:1), comparator-controlled study of linezolid versus (vs) vancomycin/cefazolin in the treatment of subjects with known or suspected catheter-related Gram-positive bloodstream infections. Subjects with end-stage renal disease who were 18 years of age or older and weighing 40 kg or more with known or suspected Gram-positive bloodstream infections resulting from tunneled or non-tunneled catheters were eligible for enrollment. Subjects who received

dialysis through a fistula or venous graft were eligible to enroll as long as they had a central vascular catheter that was suspected or known to be the cause of the bloodstream infection. Subjects with acute renal failure undergoing hemodialysis and subjects undergoing peritoneal dialysis were not eligible to enroll in the study.

Prior to receiving the first dose of study medication, Investigators had to obtain one set of blood cultures through the hemodialysis catheter and all other indwelling intravascular catheters. Another set of blood cultures had to be obtained through a peripheral percutaneous site (venous or arterial access). If a catheter had more than 1 port, blood was to be collected from all ports. After obtaining blood for cultures, all intravascular catheters were to be removed. Catheter tips were to be sent to the local laboratory for semiquantitative (Maki method) or quantitative (Brun-Buisson method) cultures. Any exudates present at the catheter access site were to have a qualitative culture by an exit site swab or pus collection. If there was evidence of an abscess, the site was to be aspirated and the aspirate sent for culture to the local laboratory.

A Gram-positive bacterial pathogen had to be cultured from the required baseline blood cultures for the subject to remain eligible to participate in the study. If the Gram-positive isolate was *S aureus*, it was to be cultured from at least 1 culture bottle from either the peripheral set or the catheter set of culture bottles. For all other Gram-positive pathogens (eg, coagulase-negative staphylococci), isolates were to be cultured from at least 2 culture bottles of which one had to be from the peripheral set.

Subjects eligible to remain in the study due to the isolation of a Gram-positive bacterial blood pathogen were required to have peripheral percutaneous blood cultures (venous or arterial access) repeated 24 to 48 hours after the initiation of treatment. If the repeat blood culture was positive (identical Gram-positive pathogen as compared to baseline), the peripheral percutaneous blood culture was to be redrawn within 24 to 48 hours of the culture results being received. If the blood culture remained positive and it was drawn after 96 hours of treatment, the subject was to be considered a treatment failure and withdrawn from the study. Subjects with poor vascular access were permitted to have the repeat blood draws obtained through a newly inserted intravascular catheter or matured fistula. In the absence of repeat peripheral blood culture results, subjects who remained febrile for 96 hours or greater were to be considered treatment failures and withdrawn from the study.

An end-of-treatment (EOT) visit was to occur within 72 hours after the last dose of study medication. A short-term follow-up (STFU) visit for test of cure (TOC) was occurred 2-3 weeks after the last dose of study medication. A long-term follow-up (LTFU) visit was required 6-8 weeks after the last dose of study medication. Schedule of events is summarized in Table 1.

Table 1. Schedule of Events

Protocol Activities and Forms to be Completed		Treatment Day				End of Treatment[a]	STFU [b]	LTFU[c]
	Baseline	3	7	14	21			
Informed consent	X							
Review of eligibility criteria	X							
MPM II	X							
Pitt bacteremia score	X							
Medical history & demographics	X							
Physical examination	X					X	X	X
12-lead ECG	X							
Hematology[d]	X	X	X	X	X	X	X	X
Serum chemistry[d]	X	X	X	X	X	X	X	X
Pregnancy test[e]	X						X	
Vital signs[f]	X	X	X	X	X	X	X	X
Culture & susceptibility[g]								
Peripheral blood[h]	X	X-as required				X	X	X
Catheter blood[i]	X							
Site exudate	X-if obtain-able							
Aspirate of abcess	X-if obtain-able							
Catheter tip[j]	X							
Nasal swab[k]	X		X		X	X	X	X
Signs & symptoms of catheter- related infection	X	X	X	X	X	X	X	X
Echocardiogram[l]	X					X-if clinically indicated	X-if clinically indicated	X-if clinically indicated
Study medication record						X		
Clinical response evaluation						X	X	X
Record concomitant medications	7 days prior to Baseline through the final visit							
Adverse events		As needed						
Serious adverse events		As needed						

Table 1. Schedule of Events

Protocol Activities and Forms to be Completed		Treatment Day				End of Treatment[a]	STFU [b]	LTFU[c]
	Baseline	3	7	14	21			
End of study report		To be completed at end of subject participation in study						

ECG = electrocardiogram; EOT = end of treatment; LTFU = long term follow-up; MPM = mortality probability model; STFU = short term follow-up; *S* = *Staphylococcus*; TOC = test of cure.

a. An EOT visit must had occurred within 72 hours after last dose of study medication.
b. A STFU visit for TOC was occurred 2-3 weeks after the last dose of study medication.
c. A LTFU visit was required 6-8 weeks after the last dose of study medication.
d. To be performed by the central laboratory.
e. For females of child-bearing potential. Performed at Baseline visit by the local laboratory to determine subject enrollment eligibility. Performed by the central laboratory at Baseline and STFU visit.
f. Record vital signs (blood pressure, pulse, respiratory rate, body temperature) at baseline, on Days 3, 7, 14, 21, EOT, STFU and LTFU (body temperature was recorded at time of highest daily temperature). On days 2, 4, 5, and 6 only record the highest daily temperature.
g. Local laboratory were culture the microbiology samples and conduct identification and antibiotic susceptibility testing for linezolid and the comparator agents. The local laboratory send (in a timely manner) a viable pathogenic isolate to the central laboratory.
h. Required at baseline and then collected 24 to 48 hours after the start of treatment. If positive (identical Gram-positive pathogen as compared to baseline), blood must be retaken in 24 to 48 hours of culture results being received. If the blood culture is again positive and it was drawn after 96 hours of treatment, the subject were discontinued from the study. Required by all subjects at the EOT, STFU and LTFU visits.
i. Required at baseline. Must have drawn through the hemodialysis catheter and all other indwelling intravascular catheters.
j. The local laboratory cultured the catheter tips from the pulled hemodialysis catheter and all other indwelling intravascular catheters using either the Brun-Buisson method or the Maki method.
k. Required at baseline, Days 7 and 21, EOT, STFU and LTFU visits. The local laboratory was qualitatively culture a swab specimen that was taken at least 1 cm inside the nares. The membrane sampled by rotating the swab and leaving it in place for 10-15 seconds.
l. Subjects with clinically suspected endocarditis or subjects with baseline *S aureus* bacteremia had an echocardiogram at baseline. All subjects should have had an echocardiogram performed at the EOT and F-U visits as clinically indicated. Testing occurred using the transesophageal method. Sites may only use the transthoracic method when the transesophageal method were not available.

Number of Subjects (Planned and Analyzed): One hundred and sixty six (166) subjects per treatment group were planned; 61 subjects received treatment and were analyzed.

Diagnosis and Main Criteria for Inclusion: Subjects were to be males and females, 18 years of age or older, weighing 40 kg or more with end-stage renal disease. Subjects were to be on hemodialysis and had: 1) signs and symptoms of a localized catheter-related infection (eg, tenderness and/or pain, erythema, swelling, purulent exudates within 2 cm of entry site); 2) a body temperature of 38^{o} C or higher or less than 36^{o} C (oral equivalent); or 3) a blood culture positive for a Gram-positive pathogen. If the Gram-positive isolate was *S aureus*, it had to be cultured from at least 1 culture bottle from either the peripheral set or the catheter set of culture bottles. For all other Gram-positive pathogens (eg, coagulase-negative staphylococci), isolates were to be cultured from at least 2 culture bottles, of which 1 had to be from the peripheral set. There was to be no other obvious source of the bacteremia. Subjects were to have at least one of the following systemic signs of infection

(obtained up to 24 hours prior to baseline): 1) hypotension, defined as systolic blood pressure of 90 mm Hg or lower or its reduction by 40 mm Hg or greater from the subject's baseline, in the absence of other causes for hypotension; 2) tachycardia defined as a pulse rate greater than 100 beats per minute; 3) tachypnea defined as a respiratory rate >20 breaths per minute or partial pressure of carbon dioxide ($PACO_2$) <32 torr; or 4) a white blood count greater than 10,000 cells/mm^3 or less than 4,000 cells/mm^3, or with a differential count showing greater than 10% band neutrophil forms. Hemodialysis subjects were to have tunneled or non-tunneled catheters, including antibiotic-coated catheters. Subjects could have more than 1 concurrent catheter.

Study Treatment: Subjects in the linezolid arm received empiric treatment of intravenous (IV) or oral (PO) linezolid (600 mg) every 12 hours along with IV gentamicin (2 mg/kg body weight loading dose and subsequent doses targeted to keep serum peak levels between 6-8 μg/mL and trough levels less than 1 μg/mL). Once it was known that the baseline pathogen was Gram-positive, gentamicin therapy was discontinued, and subjects were to continue with either IV or PO linezolid (600 mg every 12 hours) alone.

Subjects in the comparator-treatment arm received empiric treatment of IV vancomycin (15 mg/kg body weight loading dose and subsequent doses targeted to keep serum trough levels between 10-15 μg/mL) along with IV gentamicin (2 mg/kg body weight loading dose and subsequent doses targeted to keep serum peak levels between 6-8 μg/mL and trough levels less than 1 μg/mL). Once it was known that the baseline pathogen was Gram-positive, gentamicin therapy was to be stopped. Subjects with a methicillin-resistant Gram-positive pathogen were to continue with IV vancomycin alone and subjects with a methicillin-susceptible Gram-positive pathogen and not allergic to penicillin could be switched to IV cefazolin (1 g every 24 hours) alone.

If the identification of the Gram-positive pathogen was known at study enrollment, subjects were initiated on linezolid or vancomycin without gentamicin. Also, a subject randomized to the comparator arm could be initiated on IV cefazolin without gentamicin if it was known at study enrollment that the pathogen was methicillin-susceptible and the subject was not allergic to penicillin. Sites could use aztreonam instead of gentamicin for the initial empiric Gram-negative coverage for catheter-related bloodstream infections if there was a high likelihood of gentamicin resistant Gram-negative bacteria at the site.

Both treatment groups could use aztreonam (supplied by the investigative site) to treat Gram-negative bacterial infections that developed after the Baseline visit. If a scheduled antibiotic treatment occurred close to a hemodialysis treatment session, antibiotic therapy was to be given after the hemodialysis treatment session. Subjects could be treated on an inpatient basis at the discretion of the Investigator based on the subjects' medical condition. Subjects with bacteremia were to receive a minimum of 7 days of therapy up to a maximum of 28 days of therapy. Twenty one (21) days of therapy were recommended.

Linezolid (IV and PO), vancomycin (IV), cefazolin (IV), and gentamicin (IV) were supplied by the Sponsor as open-label supplies. Ancillary supplies (0.9% sodium chloride for injection, 5% dextrose for injection, and sterile water for injection) were supplied by the study sites. Aztreonam could be used for coverage of concomitant Gram-negative infections that developed during the study. In such cases, the drug was provided by the study site.

Linezolid for IV use was provided as a ready-to-use sterile solution containing 600 mg of active medication. IV infusion bags of 300 mL each contained 2 mg of active medication for every 1 mL of diluent (2 mg/mL), plus dextrose, sodium citrate, citric acid, and water for injection (final pH adjusted at time of manufacturing using 10% hydrochloric acid or 10% sodium hydroxide). Linezolid tablets for oral administration were provided as 600 mg film-coated compressed tablets. Vancomycin (sterile vancomycin hydrochloride United States Pharmacopeia [USP]) was supplied in vials containing 500 mg or 1 g of active ingredient. Cefazolin (sterile cefazolin sodium USP) was supplied in vials containing 1 g of active ingredient. Gentamicin (sterile gentamicin sulfate USP) was supplied in 1 mL vials containing 20 mg/mL or 2 mL vials containing 40 mg/mL of active ingredient.

Efficacy and Safety Endpoints:

Primary Endpoint:

- To assess the primary objective was subject microbiologic outcome at the Test of Cure (TOC) visit.

Secondary Endpoints:

- Clinical efficacy was measured by clinical outcome of treatment.
- Incidence of complications during the study, such as metastatic infection, was measured at the LTFU.
- Pathogen eradication was measured by eradication rates of individual pathogens at the TOC visit.
- Eradication of *S aureus* nasal colonization was measured by nasal carriage rate at the follow-up visits.
- Safety and tolerance was measured by laboratory assay results and adverse event (AE) findings, including mortality.

Safety Evaluations: Safety assessments were to be based on the disposition of subjects with regards to AEs, vital signs, safety laboratory assessments, physical examinations, incidence of metastatic infections, and concomitant (non-investigational) medication.

Statistical Methods: Microbiologically evaluable (ME) subjects were a subset of intent-to-treat (ITT) subjects, where ITT subjects were those who received one or more doses of active study medication. All ITT subjects who had a gram-positive pathogen recovered from a peripheral or catheter blood culture in baseline ITT analysis window were defined as

modified intent-to-treat (MITT) subjects. The sample size was determined using a two-sided α=0.05, power of 80%, equivalence between treatments to within 20%, and assuming that each treatment group would yield a 70% microbiological success rate, the number of microbiologically evaluable subjects required per treatment group was 83. Assuming a microbiological evaluability rate of 50%, this translated to a requirement of 166 enrolled subjects per treatment group.

Analyses of primary and secondary efficacy variables were to be done separately using ME, modified-microbiologically evaluable (MME), and MITT subjects. Comparability of treatment groups at the TOC visit with respect to clinical and microbiological outcomes was to be assessed using 95% confidence intervals on the differences in cure/eradication rates (based on the normal approximation to the binomial distribution) and chi-square tests for homogeneity of proportions. Due to the expected small number of evaluable subjects at each center, terms for Investigator effect and treatment group-by-Investigator interaction were not to be included in the statistical models used for analysis. However, consistency of treatment effects across centers was to be investigated for those centers with appreciable numbers of subjects by pooling all centers within a country. Safety variables were to be analyzed using the ITT population. All statistical tests were two-sided. A p-value of 0.05 or less was considered statistically significant.

RESULTS: Enrollment in the study was suspended as a precautionary measure in light of the mortality imbalance observed in a similar study of catheter-related bloodstream infections. Less than one-third of intended subjects had been enrolled since study initiation. A decision was taken to terminate the study due to factors affecting the timeline to completion, such as the slow enrollment and the inclusion of sufficient evaluable subjects.

Subject Disposition and Demography: Of the 65 subjects screened for the study, 61 received study treatment (30 from the linezolid group and 31 from the comparator group). Nine subjects (30%) from the linezolid group completed the study compared to 14 subjects (45%) from the comparator group. Most of the subjects in both treatment groups discontinued the study due to non-treatment-related reasons categorized as "Other". These were mostly due to either no pathogen isolated at baseline, pathogen isolated from a source other than peripheral blood, or pathogen isolated concomitantly with *Pseudomonas aeruginosa*, a Gram-negative bacillus. Three subjects from the linezolid group died while receiving active treatment. The cause of death was reported as being unrelated to study drug treatment (ie, cardiopulmonary failure, endocarditis, and myocardial infarction). One subject was discontinued on Day 9 due to persistently sterile cultures after enrollment and died on Day 15. Table 2 summarizes the subject disposition.

Table 2. Subject Disposition

Disposition		Linezolid N=30	Comparator N=31
Number of subjects screened	65		
Assigned to study treatment		30	31
Treated		30	31
Completed		9 (30.0)	14 (45.2)
Discontinued		21 (70.0)	17 (54.8)
Reason for discontinuation			
Related to study drug			
Lack of efficacy		1 (3.3)	2 (6.5)
Not related to study drug			
Death		3 (10.0)	0 (0.0)
Adverse event		3 (10.0)	1 (3.2)
Other		14 (46.7)	14 (45.2)
Analyzed for safety			
Adverse events		30 (100)	31 (100)
Laboratory data		30 (100)	29 (93.5)

N = total number of subjects.

Both treatment groups were comparable with respect to baseline demographics. Subjects ranged in age from 22 to 89 years with a mean age of 54 and 50 years in the linezolid and comparator groups, respectively. There was a higher proportion of subjects 45 years of age or older in the linezolid group (80%) vs the comparator group (52%). The majority of the subjects enrolled in each group were males (57% and 58% in the linezolid and comparator groups, respectively). Both groups were comparable with respect to race. Demographics are summarized in Table 3.

Table 3. Subject Demographics

Variables	Linezolid			Comparator		
	Male	Female	Total	Male	Female	Total
Number of subjects	17	13	30	18	13	31
Age (years)						
18-44	4 (23.5)	2 (15.4)	6 (20.0)	8 (44.4)	7 (53.8)	15 (48.4)
45-64	7 (41.2)	7 (53.8)	14 (46.7)	6 (33.3)	3 (23.1)	9 (29.0)
≥65	6 (35.3)	4 (30.8)	10 (33.3)	4 (22.2)	3 (23.1)	7 (22.6)
Mean	53.6	55.5	54.4	50.5	48.6	49.7
SD	18.8	16.8	17.7	16.5	14.2	15.4
Range	22-89	24-82	22-89	26-82	22-70	22-82
Race						
White	4 (23.5)	6 (46.2)	10 (33.3)	4 (22.2)	4 (30.8)	8 (25.8)
Asian	9 (52.9)	2 (15.4)	11 (36.7)	9 (50.0)	3 (23.1)	12 (38.7)
Other	4 (23.5)	5 (38.5)	9 (30.0)	5 (27.8)	6 (46.2)	11 (35.5)
Weight (kg)						
Mean	61.2	70.0	65.0	63.7	59.5	62.0
SD	14.3	22.9	18.7	15.8	12.5	14.5
Range	42.6-85.4	50.0-118.6	42.6-118.6	45.0-103.5	41.3-86.2	41.3-103.5
Height (cm)						
Mean	161.8	160.6[a]	161.3[b]	168.2	159.1	164.4
SD	14.3	8.7	12.1	9.6	5.1	9.1
Range	115.0-180.0	143.0-176.0	115.0-180.0	157.0-196.0	147.0-165.0	147.0-196.0

N = total number of subjects; SD = standard deviation.
a. Based on N=12.
b. Based on N=29.

Efficacy Results: Due to the early termination of this study, there were not enough subjects available to perform a meaningful efficacy analysis.

Safety Results: Table 4 summarizes treatment emergent AEs by system organ class and preferred term. Vomiting occurred more frequently in the linezolid group compared to the comparator group (6 vs 1 subjects).

Table 4. Treatment-Emergent Non Serious Adverse Events by System Class and Preferred Term (All Causalities)

System Organ Class and MedDRA Preferred Term	Linezolid n (%)	Vancomycin/Cefazolin n (%)
Number (%) of subjects: evaluable for AEs	30	31
Number (%) of subjects: with AEs	12 (40.0)	9 (29.0)
Cardiac disorders	1 (3.3)	0
Supraventricular tachycardia	1 (3.3)	0
Gastrointestinal disorders	8 (26.7)	2 (6.5)
Abdominal pain upper	1 (3.3)	0
Dyspepsia	1 (3.3)	1 (3.2)
Gastric ulcer	1 (3.3)	0
Gastritis	1 (3.3)	0
Nausea	2 (6.7)	1 (3.2)
Oesophagitis	1 (3.3)	0
Vomiting	6 (20.0)	1 (3.2)
General disorders and administration site conditions	2 (6.7)	4 (12.9)
Asthenia	0	1 (3.2)
Pyrexia	2 (6.7)	3 (9.7)
Infections and infestations	2 (6.7)	3 (9.7)
Candidiasis	1 (3.3)	0
Endocarditis	0	1 (3.2)
Psoas abscess	0	1 (3.2)
Sepsis	1 (3.3)	0
Viral infection	0	1 (3.2)
Investigations	0	1 (3.2)
Aspartate aminotransferase increased	0	1 (3.2)
Metabolism and nutrition disorders	0	1 (3.2)
Hypoglycaemia	0	1 (3.2)
Musculoskeletal and connective tissue disorders	0	1 (3.2)
Back pain	0	1 (3.2)
Nervous system disorders	1 (3.3)	0
Grand mal convulsion	1 (3.3)	0
Psychiatric disorders	1 (3.3)	1 (3.2)
Agitation	1 (3.3)	0
Anxiety	0	1 (3.2)
Renal and urinary disorders	0	1 (3.2)
Bladder outlet obstruction	0	1 (3.2)
Respiratory, thoracic and mediastinal disorders	1 (3.3)	0
Pneumonitis	1 (3.3)	0

Table 4. Treatment-Emergent Non Serious Adverse Events by System Class and Preferred Term (All Causalities)

System Organ Class and MedDRA Preferred Term	Linezolid n (%)	Vancomycin/Cefazolin n (%)
Skin and subcutaneous tissue disorders	1 (3.3)	1 (3.2)
Erythema	1 (3.3)	0
Rash	0	1 (3.2)
Vascular disorders	1 (3.3)	1 (3.2)
Hypotension	1 (3.3)	0
Jugular vein thrombosis	0	1 (3.2)
Subclavian vein thrombosis	0	1 (3.2)

Subjects are only counted once per treatment for each row.
Includes data up to 30 days after last dose of study drug.
MedDRA (v14.1) coding dictionary applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects.

Treatment related AEs are summarized in Table 5.

Table 5. Treatment-Emergent Adverse Events by System Organ Class (Treatment Related) Intent to Treat Subjects

Number of Subjects With AEs by System Organ Class:	Linezolid n (%)	Vancomycin/Cefazolin n (%)
Number (%) of subjects: assessed for AEs	30	31
Number (%) of subjects: with AEs	3 (10.0)	2 (6.5)
Discontinued due to adverse events	0	0
Gastrointestinal disorders	3 (10.0)	0
General disorders and administration site conditions	0	1 (3.2)
Skin and subcutaneous tissue disorders	0	1 (3.2)

Subjects are only counted once per treatment for each row.
Includes data up to 30 days after last dose of study drug.
MedDRA (v10.0) coding dictionary applied.
AEs and SAEs are not separated out in this table.
AEs = adverse events; MedDRA = medical dictionary for regulatory activities; n = number of subjects; SAEs = serious adverse events.

Treatment emergent serious adverse events (SAEs) are summarized in Table 6.

Table 6. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

System Organ Class and MedDRA Preferred Term	Linezolid n (%)	Vancomycin/Cefazolin n (%)
Number (%) of subjects: evaluable for AEs	30	31
Number (%) of subjects: with AEs	7 (23.3)	3 (9.7)
Cardiac disorders	2 (6.7)	0
Cardiopulmonary failure	1 (3.3)	0
Myocardial infarction	1 (3.3)	0
Gastrointestinal disorders	2 (6.7)	1 (3.2)
Diarrhoea	0	1 (3.2)
Duodenal ulcer	1 (3.3)	0
Vomiting	1 (3.3)	0
General disorders and administration site conditions	2 (6.7)	2 (6.5)
Chills	1 (3.3)	0
Death	0	1 (3.2)
Pyrexia	1 (3.3)	1 (3.2)
Infections and infestations	2 (6.7)	0
Bronchopneumonia	1 (3.3)	0
Endocarditis	1 (3.3)	0
Metabolism and nutrition disorders	1 (3.3)	0
Fluid overload	1 (3.3)	0
Vascular disorders	2 (6.7)	1 (3.2)
Hypertension	0	1 (3.2)
Hypertensive crisis	1 (3.3)	0
Hypotension	1 (3.3)	0

Subjects are only counted once per treatment for each row.
Includes data up to 30 days after last dose of study drug.
MedDRA (v14.1) coding dictionary applied.
AE = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects.

Eight subjects from the linezolid group and 3 subjects from the comparator group had 1 or more SAEs. None of the SAEs were related to study treatment. Four subjects (3 linezolid, 1 comparator) died; the 1 death in the comparator group occurred 6 days after the subject was discontinued from the study due to a persistently sterile culture following enrollment. Table 7 summarizes the SAEs and deaths.

Table 7. Summary of Serious Adverse Events and Deaths

Serial Number	SAE MedDRA Preferred Term	Action Taken	Outcome	Investigator Causality
Linezolid				
1	Cardiopulmonary failure	None (Post therapy)	Death	Other illness
2	Endocarditis	None (Post therapy)	Death	Other
	Pyrexia	--	--	--
3	Bronchopneumonia	Discontinued	Recovered	Other illness
	Pyrexia	--	--	--
4	Myocardial infarction	None (Post therapy)	Death	Other illness
5[a]	Metabolic encephalopathy	None (Post therapy)	Recovered	Other
6	Chills	None	Recovered	Other illness
	Vomiting	--	--	--
	Hypotension	--	--	--
	Fluid overload	None (Post therapy)	Recovered	Other illness
7	Duodenal ulcer	Discontinued	Recovering	Other
8	Hypertensive crisis	None	Recovered	Other illness
Comparator				
1[b]	Death	None	Death	Other
2	Hypertension	None	Recovered	Other illness
3	Pyrexia	None	Recovered	Other illness
	Diarrhea	None	Recovered	Other illness

MedDRA = Medical Dictionary for Regulatory Activities (V10.0), SAE = serious adverse event.

a. One subject stopped therapy on Day 7 and had the SAE post therapy (Day 26). This event was not captured in the project database as an SAE and therefore was not included in the table.

b. Subject was discontinued on Day 9 due to persistently sterile cultures after enrollment and died on Day 15. Her death was not captured in the project database as a death and therefore was not included in table.

Discontinuation: Four subjects (3 in the linezolid group and 1 in the comparator group) discontinued the study due to non-treatment-related AEs. These events included bronchopneumonia, endocarditis, and duodenal ulcer in the linezolid group, and sepsis in the comparator group. The Investigator considered the bronchopneumonia and duodenal ulcer to be SAEs (Table 7).

Majority of subjects across both treatment arms had Gram-positive infections. Gram-negative infections occurred at a similar rate in both treatment arms. During active treatment, 3 deaths occurred on the linezolid arm while no deaths were observed on the comparator arm (Table 8). Of the 3 subjects who died, all 3 had Gram positive-only infections (*S hominis*, *S aureus*, and/or *S pyogenes*).

Table 8. Deaths by Treatment and Baseline Organisms From Any Culture Source - ITT

Variables	Linezolid N=30			Comparator N=31		
	Subjects who Survived	Subjects who Died	Total	Subjects who Survived	Subjects who Died[a]	Total
Gram- infection only	3 (10.0)	0	3 (10.0)	2 (6.5)	0	2 (6.5)
Gram+ infection only	19 (63.3)	3 (10.0)	21 (70.0)	20 (64.5)	0	20 (64.5)
Mixed infection (Gram+/Gram-)	6 (20.0)	0 (0)	6 (20.0)	4 (12.9)	0	4 (12.9)
No organisms at baseline	0	0	0	5 (16.1)	0	5 (16.1)
Total	27	3	30	31	0	31

The following pathogen categories are mutually exclusive: Gram-negative infection only, Gram-positive infection only, mixed infection, and no organisms at baseline.
ITT = intent to treat; N= number of subjects.

a. One subject discontinued on Day 9 due to persistently sterile cultures after enrollment and died on Day 15. Her death was not captured in the project database as a death and therefore was not included in this table.

Other Safety Parameters: Changes in safety laboratory values were similar between the linezolid and comparator groups and generally consisted of elevations in blood urea nitrogen (BUN) and creatinine and decreases in hemoglobin, hematocrit, and red blood cell counts. These findings were consistent with a population of subjects having impaired renal function and bloodstream infections.

CONCLUSION: There were no new or unexpected safety findings following administration of the study drugs.