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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NCT NO.: NCT00037050

PROTOCOL NO.: M12600080

PROTOCOL TITLE: Linezolid vs Vancomycin/Oxacillin/Dicloxacillin in the Treatment of Catheter-Related Gram-positive Bloodstream Infections

Study Center(s): A total of 101 centers in Argentina (6), Australia (3), Austria (1), Belgium (5), Brazil (1), Chile (2), Colombia (6), Czech Republic (2), Germany (3), Greece (1), Guatemala (2), Hungary (2), India (3), Italy (4), Mexico (4), Pakistan (2), Peru (2), Philippines (2), Russian Federation (7), Slovakia (1), South Africa (2), Spain (8), Thailand (1), Turkey (1), United States (29) and Venezuela (1) enrolled patients into this study.

Study Initiation and Completion Dates: 28 May 2002 to 01 August 2005

Phase of Development: Phase 3

Study Objective(s):
Primary: To demonstrate non-inferiority of linezolid relative to the comparator in the treatment of gram-positive complicated Skin and Skin Structure Infection (cSSSI) related to an indwelling catheter

If, and only if, the latter was confirmed, then the objective was to demonstrate the non-inferiority of linezolid relative to comparator in the treatment of catheter-related blood stream infection (CRBSI) caused by gram-positive pathogens.

Secondary: To compare the clinical efficacy, safety and hospital resource use in linezolid-treated versus comparator-treated patients

METHODS

Study Design: This was an open-label, randomized, comparator-controlled, multinational study in subjects with infection at a catheter entry site and/or generalized infection. Study treatments were with intravenous (IV)/oral (PO) linezolid or vancomycin IV or oxacillin (IV)/dicloxacillin (PO). The study consisted of a baseline visit, a 7- to 28-day treatment phase, an end-of-treatment visit, and a short-term follow-up visit, defined as the test-of cure

(TOC) visit. A long-term follow-up visit was planned to occur, but only for patients with documented baseline *Staphylococcus aureus* infection. Efficacy, other, and safety endpoints were assessed. All death in the study out to 84 days after entry into the study were recorded.

Number of Subjects (Planned and Analyzed):
Planned: 980 subjects (490 subjects per treatment group)

Analyzed: 726 subjects (363 subjects in the linezolid group, 363 in the comparator group)

Diagnosis and Main Criteria for Inclusion: Subjects were males or females who were at least 13 years of age or older (unless restricted to 18 years of age based on local regulatory requirements) and ≥ 40 kg body weight. Subjects also had to have clinical signs and symptoms consistent with infection at a catheter entry site and/or signs and symptoms indicative of generalized infection at enrollment, with microbiological criteria (positive culture results) applied to determine continued study participation and evaluability. Subjects with other endovascular infections, infections resulting in bacteremia or infections that were likely to be cured by catheter removal alone were excluded.

Study Treatment: Study treatments included intravenous/oral (IV/PO) linezolid (600 mg every 12 hours [q12h]) versus comparator: (vancomycin IV [1 g q12h] or oxacillin IV [2 g q6h]/dicloxacillin PO [500 mg q6h]). Linezolid was initially given IV and after at least 1 dose, subjects could, at the investigator's discretion, be switched to PO administration.

Subjects in the comparator arm initially received vancomycin IV until the baseline pathogen was identified and susceptibility to methicillin was determined. If the baseline pathogen was methicillin susceptible, patients could be switched to IV oxacillin and/or PO dicloxacillin. If it was known at enrollment that the baseline gram-positive pathogen was methicillin-susceptible, patients were permitted to begin oxacillin therapy immediately.

Efficacy Evaluations:
Primary: Microbiological outcome, as measured by the eradication rate at the TOC visit

Secondary: Investigator and sponsor assessment of clinical outcome, as measured by cure rate at the TOC visit; pathogen microbiological outcome, as measured by individual (baseline) pathogen eradication rate at the TOC visit; and safety parameters, including mortality

Other Evaluations: The primary outcomes research endpoint was length of stay (LOS). Other endpoints included discharge rates by week, and duration (number of days) of IV and total antibiotic treatment.

Safety Evaluations: Adverse events (AEs), clinical laboratory assessments, vital signs measurements, physical examination findings and concomitant (non-investigational) medication

Statistical Methods: Three analysis populations were identified in this study:

- Intent-to-treat (ITT) Population: All randomized patients who received at least 1 dose of study medication
- Modified Microbiologically Evaluable (MME-1) Population: All microbiologically evaluable patients with a qualifying MME-1 pathogen,
    - Any non-CoNS (coagulase-negative staphylococci) gram-positive species from any valid culture source, OR
    - Any CoNS species for which there was, a) more than one isolate from a valid culture source, at least 2 of which were concordant and, b) at least 1 of the concordant isolates was from a culture source other than the catheter tip
- Microbiologically Evaluable-2 (ME-2) Subjects: All MME-1 subjects for whom the same baseline MME-1 pathogen was isolated from a percutaneous peripheral blood culture and a catheter-related culture (catheter blood, tip or site exudates/aspirates)

Non-inferiority objectives for cSSSI and CRBSI were tested by using a step-down procedure with a non-inferiority margin of 15% and a two-sided 95% confidence interval (CI) for the difference in eradication rates, based on the normal approximation to the binomial distribution. The presumed power of this test is 80%. The non-inferiority of linezolid relative to the comparator in the treatment of cSSSI was tested first. If the latter was confirmed, the non-inferiority of the linezolid relative to the comparator in the treatment of CRBSI was tested using the same non-inferiority margin.

Non-inferiority for either indication was obtained if the lower limit of the 95% CI for the eradication rate of linezolid minus comparator was ≥-15%.

Safety, the primary endpoint for cSSSI and CRBSI were analyzed using the ITT, MME-1, and ME-2 populations, respectively.

RESULTS

Subject Disposition and Demography: A total of 739 subjects were randomized to receive study medication. Four subjects from 1 center were excluded from all analyses due to data inaccuracies and the lack of source documentation. Of the remaining 735 subjects, 9 did not receive study medication. Patient disposition by treatment as well as reason for treatment withdrawal are displayed in Table S1.

Table S1 Subject Disposition by Treatment: ITT Population

	Linezolid n (%[b])	Comparator[a] n (%[b)]
Number of Subjects	363	363
Completed Treatment	193 (53.2)	200 (55.1)
Discontinued During Treatment	170 (46.8)	163 (44.9)
Adverse Event	48 (13.2)	25 (6.9)
Protocol Violation	15 (4.1)	23 (6.3)
Consent Withdrawn	6 (1.7)	4 (1.1)
Lost to Follow-up	6 (1.7)	6 (1.7)
Lack of Efficacy	25 (6.9)	28 (7.7)
Sponsor's Decision[c]	70 (19.3)	77 (21.2)
MME-1 Population	164 (45.2)	151 (41.6)
ME-2 Population	95 (26.2)	74 (20.4)

[a]Comparator = Vancomycin /Oxacillin /Dicloxacillin
[b]Percentages based on total number of subjects in each treatment group
[c]Subjects discontinued due to lack of gram-positive pathogen

For the ITT population, treatment groups were similar with respect to baseline demographics, including age, weight and race. Approximately 60% of the study population was male and approximately 70% was white. The mean age for both treatment groups was approximately 54 years old. The percentage of patients who were ≥ 80 years of age was slightly higher in the linezolid group (23/363, 6.3%) than the comparator group (15/363, 4.1%). The average weight in both treatment groups was approximately 75 kg (165 pounds).

Efficacy Results:

Primary: Results of the primary efficacy endpoint, the patient microbiologic outcome at the TOC visit in subjects with cSSSI or CRBSI are presented in Table S2.

Table S2 Patient Microbiological Outcome at TOC in Patients with cSSSI (MME-1 Population) or CRBSI (ME-2 population)

ALL Gram+ Pathogens	cSSSI (MME-1) N = 315			CRBSI (ME-2) N = 169		
Endpoint/ Number (%) of Patients	Linezolid N = 164 n (%[c])	Comparator[a] N = 151 n (%[c])	95% CI[b]	Linezolid N = 95 n (%[c])	Comparator[a] N = 74 n (%[c])	95% CI[b]
Number of Assessed Patients[d]	163	149		95	74	
Eradication	146 (89.6)	134 (89.9)	(-7.1, 6.4)	82 (86.3)	67 (90.5)	(-13.8, 5.4)
Documented Eradication	122 (74.8)	116 (77.9)		69 (72.6)	57 (77.0)	
Presumed Eradication	24 (14.7)	18 (12.1)		13 (13.7)	10 (13.5)	
Persistence	17 (10.4)	15 (10.1)		13 (13.7)	7 (9.5)	
Documented Persistence	6 (3.7)	2 (1.3)		4 (4.2)	0 (0.0)	
Presumed Persistence	11 (6.7)	13 (8.7)		9 (9.5)	7 (9.5)	
Indeterminate	1	1		0	0	
Missing	0	1		0	0	

[a]Comparator = Vancomycin/Oxacillin/Dicloxacillin
[b]95% Confidence Interval for the difference (linezolid minus comparator) in eradication rates (expressed as percentage)
[c]Percentage based on number of "Assessed Patients"
[d]Excludes patients with Indeterminate or Missing outcomes.

Secondary: A summary of Sponsor's Assessment of Clinical Outcome (SACO), Investigator Assessment of Clinical Outcome (IACO) and PMO by baseline pathogen is presented in Table S3, below.

Table S3 Overview of Efficacy Results at the Test of Cure Visit by Indication

Endpoint/ Number (%) of Patients	cSSSI (MME-1), N = 315			CRBSI (ME-2), N = 169		
	Linezolid N = 164	Comparator[a] N = 151	95% CI	Linezolid N = 95	Comparator[a] N = 74	95% CI
	n (%)	n (%)		n (%)	n (%)	
SACO[b]						
N[c]	158	145		93	73	
Cured	123 (77.8)	113 (77.9)	(-9.4, 9.3)	70 (75.3)	59 (80.8)	(-18.1, 7.0)
Failed	35 (22.2)	32 (22.1)		23 (24.7)	14 (19.2)	
IACO[b]						
N[c]	143	128		82	62	
Cured	140 (97.9)	120 (93.8)		81 (98.8)	61 (98.4)	(-10.4, 9.6)
Failed	3 (2.1)	8 (6.3)		1 (1.2)	1 (1.6)	
PMO by Pathogen, N (%) of Patients						
S. aureus						
Eradication	75 (86.2)	58 (85.3)	(-10.2, 12.0)	46 (82.1)	35 (83.3)	(-16.3, 13.9)
Persistence	12 (13.8)	10 (14.7)		10 (17.9)	7 (16.7)	
MRSA						
Eradication	42 (87.5)	34 (87.2)	(-13.7, 14.4)	21 (80.8)	18 (85.7)	
Persistence	6 (12.5)	5 (12.8)		5 (19.2)	3 (14.3)	
MSSA						
Eradication	34 (85.0)	25 (83.3)		26 (83.9)	18 (81.8)	
Persistence	6 (15.0)	5 (16.7)		5 (16.1)	4 (18.2)	
CoNS						
Eradication	50 (96.2)	62 (92.5)		30 (96.8)	25 (100.0)	
Persistence	2 (3.8)	5 (7.5)		1 (3.2)	0 (0.0)	
MR-CoNS						
Eradication	38 (97.4)	53 (94.6)		24 (100.0)	22 (100.0)	
Persistence	1 (2.6)	3 (5.4)		0 (0.0)	0 (0.0)	
MS-CoNS						
Eradication	17 (94.4)	10 (83.3)		10 (90.9)	3 (100.0)	
Persistence	1 (5.6)	2 (16.7)		1 (9.1)	0 (0.0)	
MR-CoNS/*S. epidermidis*						
Eradication	30 (100.0)	36 (97.3)		19 (100.0)	19 (100.0)	
Persistence	0 (0.0)	1 (2.7)		0 (0.0)	0 (0.0)	
MS-CoNS/*S. epidermidis*						
Eradication	14 (93.3)	8 (80.0)		8 (88.9)	3 (100.0)	
Persistence	1 (6.7)	2 (20.0)		1 (11.1)	0 (0.0)	
Enterococci						
Eradication	17 (77.3)	22 (84.6)		4 (80.0)	8 (88.9)	
Persistence	5 (22.7)	4 (15.4)		1 (20.0)	1 (11.1)	
Enterococcus faecalis						
Eradication	13 (76.5)	12 (75.0)		4 (80.0)	5 (83.3)	
Persistence	4 (23.5)	4 (25.0)		1 (20.0)	1 (16.7)	

[a]Comparator = Vancomycin/Oxacillin/Dicloxacillin.
[b]Results for all gram-Positive Pathogens. Methicillin resistant/susceptible pathogens are a subset of the specific species.
[c]Excludes patients with indeterminate or missing outcomes.
CoNS= Coagulase-negative staphylococci, CRBSI= Catheter-Related Bloodstream Infection, cSSSI= Complicated Skin and Skin Structure Infection, IACO= Investigator Assessment of Clinical Outcome, MT= Methicillin-resistant, MRSA= Methicillin-resistant *Staphylococcus aureus,* MS= Methicillin-susceptible, MSSA= Methicillin-susceptible *Staphylococcus aureus,* PMO= Patient Microbiologic Outcome, SACO= Sponsor's Assessment of Clinical Outcome

Three comparator-treated patients died between Study Day 1 and the TOC visit (1 to 2 weeks following the end of therapy). One linezolid-treated patient with cSSSI died at the end of therapy. None of the deaths were related to study therapy

Other Evaluations: Outcomes Research: Analysis of the health outcomes data suggested linezolid did not reduce duration of hospitalization of patients, as reflected in statistically nonsignificant difference in length of stay in the two treatment groups. However, linezolid did significantly reduce the duration of IV therapy across subgroups, with the largest difference of 4.6 days in the ME-2 subgroup. Economic analyses of health care resource utilization were not presented in this report.

Safety Results: Table S4 summarizes all categories of study-emergent AEs for both treatment groups.

Table S4 Overview of Adverse Events – ITT Population

Adverse Event Category	Linezolid N = 363	Comparator[a] N = 363
	n (%)[b]	n (%)
Total Patients Reported	363	363
Patients with ≥1 AE	244 (67.2)	230 (63.4)
Patients with ≥1 drug-related AE	36 (9.9)	29 (8.0)
Patients with ≥1 AE leading to discontinuation	30 (8.3)	17 (4.7)
Patients with ≥1 drug-related AE leading to discontinuation	6 (1.7)	4 (1.1)
Patients with ≥1 serious AE	122 (33.6)	94 (25.9)
Patients with ≥1 drug-related serious AE	6 (1.7)	1 (0.3)
Total number of deaths	78 (21.5)	58 (16.0)
Total number of deaths up to test of cure visit	45 (12.4)	33 (9.0)

[a]Comparator = Vancomycin/Oxacillin/Dicloxacillin.
[b]All percentages are based on number of patients reporting.
AE = Adverse event

Study-emergent AEs occurring in ≥ 2.0% of patients in either treatment group are presented in Table S5.

Table S5 Study Emergent Adverse Events Occurring in ≥ 2.0% of Patients: ITT Population

	Linezolid		Comparator[a]	
Adverse Event (Medically Equivalent Term)	**n**	**%[b]**	**n**	**%**
Total Reporting	**363**		**363**	
Patients with at least 1 adverse event	**244**	**67.2**	**230**	**63.4**
Diarrhea	42	11.6	30	8.3
Nausea	38	10.5	22	6.1
Sepsis	36	9.9	26	7.2
Fever	28	7.7	30	8.3
Vomiting	26	7.2	21	5.8
Anemia	20	5.5	25	6.9
Hypokalemia	19	5.2	16	4.4
Abdominal Pain Generalized	16	4.4	13	3.6
Constipation	16	4.4	22	6.1
Reaction Unevaluable	15	4.1	9	2.5
Infection Urinary Tract	14	3.9	13	3.6
Pneumonia	14	3.9	12	3.3
Localized Pain	13	3.6	9	2.5
Headache	12	3.3	14	3.9
Insomnia	11	3.0	9	2.5
Back Pain	10	2.8	9	2.5
Cardiac Arrest NEC	10	2.8	8	2.2
Dyspnea	10	2.8	6	1.7
Hypertension	10	2.8	11	3.0
Pruritus Non-Application Site	10	2.8	8	2.2
Septic Shock	10	2.8	8	2.2
Bradycardia NOS	8	2.2	6	1.7
Effusion Pleural	8	2.2	9	2.5
Hypotension	8	2.2	15	4.1
Injection/Vascular Catheter-Site Hemorrhage	8	2.2	2	0.6
Localized Edema	8	2.2	7	1.9
Chest Pain	4	1.1	11	3.0
Confusion	4	1.1	9	2.5
Deep Vein Thrombosis	3	0.8	8	2.2
Failure Kidney Acute	3	0.8	9	2.5
Generalized Edema	3	0.8	10	2.8
Hyperglycemia	2	0.6	11	3.0

Patients are counted only once for each medically equivalent term.
[a]Comparator = Vancomycin/Oxacillin/Dicloxacillin
[b]All percentages are based on number of patients reporting.
NEC = Not Elsewhere Classified, NOS = Not Otherwise Specified

Serious adverse events (SAEs) resulting in or contributing to death occurred in 78/363 (21.5%) patients in the linezolid-treated group and 58/363 (16.0%) patients in the comparator group. A table of all SAEs with an outcome of death (reported up to 84 days after study entry) is presented in Table S6 below.

Table S6 Patients With Serious Adverse Events With an Outcome of Death[a]: ITT Population

	Linezolid	Comparator[b]
Serious Adverse Event (MET) with an Outcome of Death	**n (%)**	**n (%)**
Total Reporting	**363 (100.0)**	**363 (100.0)**
Patients with at least 1 adverse event with an Outcome of Death	78 (21.5)	58 (16.0)
Sepsis	11 (3.0)	7 (1.9)
Cardiac Arrest NEC	9 (2.5)	5 (1.4)
Septic Shock	8 (2.2)	4 (1.1)
Multiple Organ Failure	6 (1.7)	1 (0.3)
Pneumonia	5 (1.4)	2 (0.6)
Respiratory Failure	5 (1.4)	2 (0.6)
Cardiogenic Shock	3 (0.8)	1 (0.3)
Cerebral Infarction	2 (0.6)	0
Coma Hepatic	2 (0.6)	0
Congestive Heart Failure	2 (0.6)	4 (1.1)
Embolism Pulmonary	2 (0.6)	1 (0.3)
Hypoxia	2 (0.6)	1 (0.3)
Kidney Failure	2 (0.6)	0
Respiratory Distress Syndrome	2 (0.6)	1 (0.3)
Sinus Arrhythmia	2 (0.6)	1 (0.3)
Advancing metastatic cancer	1 (0.3)	0
Arrest Respiratory	1 (0.3)	0
Arthritis Single and Multiple Joint	1 (0.3)	0
Aspiration	1 (0.3)	0
Bleeding Esophageal varices	1 (0.3)	0
Cardiac Rhythm Abnormal	1 (0.3)	1 (0.3)
Cardiorespiratory arrest	1 (0.3)	0
Cardiovascular Shock	1 (0.3)	0
Cholecystitis	1 (0.3)	0
Coma	1 (0.3)	0
Disorder Brain Stem	1 (0.3)	0
Dyspnea	1 (0.3)	0
Edema Brain	1 (0.3)	0
Edema Lung	1 (0.3)	0
Effusion Pleural	1 (0.3)	0
Failure Kidney Acute	1 (0.3)	2 (0.6)
Fever	1 (0.3)	0
Function Kidney Abnormal	1 (0.3)	0
Gastrointestinal Bleeding	1 (0.3)	0
Generalized Edema	1 (0.3)	0
Hemorrhage	1 (0.3)	0
Hemorrhage Cerebral	1 (0.3)	1 (0.3)
Hemorrhage Lung	1 (0.3)	0
Hemorrhage Retroperitoneal	1 (0.3)	0
Hypertension Intracranial	1 (0.3)	1 (0.3)
Injection/Vas Cath Site Infection	1 (0.3)	0
Liver Failure	1 (0.3)	0
Lupus Erythematosis Syndrome	1 (0.3)	0
Mediastinitis	1 (0.3)	0
Mesenteric Ischemia	1 (0.3)	0
Occulsion Mesenteric	1 (0.3)	0
Pancreatitis	1 (0.3)	0
Paralytic Ileus	1 (0.3)	0
Peritonitis	1 (0.3)	2 (0.6)
Reaction Unevaluable	1 (0.3)	1 (0.3)
Thromboembolism	1 (0.3)	0
Acute Pulmonary Thromboembolism	0	1 (0.3)

Serious Adverse Event (MET) with an Outcome of Death	Linezolid n (%)	Comparator[b] n (%)
Asystolia	0	1 (0.3)
Atelectasis	0	1 (0.3)
Bradycardia	0	1 (0.3)
Carcinoma	0	2 (0.6)
Carcinoma Breast	0	1 (0.3)
Cardiac arrest	0	1 (0.3)
Cardiomyopathy Worsening	0	1 (0.3)
Cardiopulmonary arrest	0	2 (0.6)
Cognitive Impairment	0	1 (0.3)
Complications of Blunt Closed Head Trauma	0	1 (0.3)
Convulsion	0	1 (0.3)
Deterioration of General Condition	0	1 (0.3)
Disorder coagulation	0	1 (0.3)
Encephalopathy	0	1 (0.3)
Endocarditis	0	1 (0.3)
Esophageal Adenocarcinoma	0	1 (0.3)
Gram Negative Bacteremia	0	2 (0.6)
Heart Disorder NOS	0	1 (0.3)
Hemorrhage Subarachnoid	0	1 (0.3)
Hydrocephalus	0	1 (0.3)
Hypotension	0	1 (0.3)
Ischemic Bowel	0	1 (0.3)
Pneumothorax	0	1 (0.3)
Presumed Disseminated Candidiasis	0	1 (0.3)
Progression of Cancer (Bladder)	0	1 (0.3)
Pulmonary Hemorrhage	0	1 (0.3)
Purpura Thrombopenic Thrombotic	0	1 (0.3)
Sigmoid Colon Perforation	0	1 (0.3)
Thrombocytopenia	0	1 (0.3)
Thrombosis	0	1 (0.3)
Ventricular Tachycardia & Fibrillation	0	1 (0.3)
Wound Infection	0	1 (0.3)

[a]Reported up to 84 days after study entry.
[b]Comparator = Vancomycin/Oxacillin/Dicloxacillin
MET = Medically equivalent term, NEC = Not elsewhere classified, NOS = Not otherwise specified,

Table S7 shows the frequency of study-emergent SAEs that occurred in more than 1 patient in either treatment group.

Table S7 Study-Emergent Serious Adverse Events Occurring in >1 Patient: ITT Population

	Linezolid		Comparator [a]	
Adverse Event (MET)	**n**	**%[b]**	**n**	**%[b]**
Patients With at Least 1 SAE	**122**	**33.6**	**94**	**25.9**
Sepsis	18	5.0	15	4.1
Septic Shock	10	2.8	8	2.2
Cardiac Arrest NEC	9	2.5	8	2.2
Fever	6	1.7	5	1.4
Multiple Organ Failure	6	1.7	1	0.3
Pneumonia	6	1.7	3	0.8
Reaction Unevaluable[c]	5	1.4	4	1.1
Respiratory Failure	5	1.4	4	1.1
Congestive Heart Failure	4	1.1	4	1.1
Dyspnea	4	1.1	1	0.3
Gastrointestinal Bleeding	4	1.1	2	0.6
Cardiogenic Shock	3	0.8	1	0.3
Hemorrhage	3	0.8	1	0.3
Kidney Failure	3	0.8	1	0.3
Peritonitis	3	0.8	1	0.3
Abdominal Pain Generalized	2	0.6	2	0.6
Abscess	2	0.6	1	0.3
Angina Pectoris	2	0.6	2	0.6
Arthritis Single and Multiple Joint	2	0.6	0	0.0
Cardiopulmonary Arrest	2	0.6	2	0.6
Cardiovascular Shock	2	0.6	0	0.0
Cerebral Infarction	2	0.6	0	0.0
Coma	2	0.6	0	0.0
Coma hepatic	2	0.6	0	0.0
Convulsion	2	0.6	1	0.3
Embolism Pulmonary	2	0.6	3	0.8
Endocarditis	2	0.6	1	0.3
Generalized Edema	2	0.6	0	0.0
Hypoxia	2	0.6	1	0.3
Injection/Vascular Catheter-Site Infection	2	0.6	0	0.0
Liver Cirrhosis	2	0.6	0	0.0
Pancreatitis	2	0.6	1	0.3
Pleurisy	2	0.6	0	0.0
Sinus Arrhythmia	2	0.6	1	0.3
Bradycardia NOS	1	0.3	2	0.6
Failure Kidney Acute	1	0.3	3	0.8
Infection Urinary Tract	1	0.3	2	0.6
Pneumothorax	1	0.3	2	0.6
Carcinoma	0	0.0	2	0.6
Infection Bacterial NOS	0	0.0	2	0.6

[a]Comparator = Vancomycin/Oxacillin/Dicloxacillin.
[b]Percentages are based on number of patients reporting.
[c]Investigator terms coding to Reaction Unevaluable included mental status changes with hospitalization, endoangitis, drug ineffective, gastroesophagus pacemaker malfunction, evisceration for linezolid and superior mesenteric artery syndrome, evisceration, emergency dialysis and obstruction of colostomy for comparator
MET = Medically equivalent term, NEC = Not elsewhere classified, NOS = Not otherwise specified, SAE = Serious adverse event

Table S8 shows the frequency of study emergent AEs that led to study discontinuation in >1 patient in either treatment group. The most frequent AEs leading to discontinuation were associated with the signs and symptoms of infection: sepsis and septic shock for the linezolid group and sepsis and fever for the comparator group.

Table S8 Study Emergent Adverse Events Resulting in Discontinuation of Study Medication in >1 Patient: ITT Population

Adverse Event (MET)	Linezolid	Comparator[a]
Total Reporting	**n (%)[b]**	**n (%)**
Patients with at least 1 event	30 (8.3)	17 (4.7)
Fever	1 (0.3)	3 (0.8)
Sepsis	5 (1.4)	5 (1.4)
Septic Shock	4 (1.1)	0 (0.0)

AE = Adverse event, MET = Medically equivalent term.
[a]Comparator = Vancomycin/Oxacillin/Dicloxacillin
[b]All percentages are based on number of patients reporting.

A greater percentage of linezolid-treated patients had abnormal platelet counts (< 75% of lower limit of normal) than patients in the comparator group: 13.1% linezolid versus 7.4% comparator. The majority of the abnormal platelet counts were classified as 1- or 2- toxicity grade shifts for both treatment groups. A 4-grade shift was reported for a single linezolid-treated patient. Patients with a platelet count below 50,000/mm^3 at anytime after baseline included 9.8% of linezolid-treated and 8.3% of comparator-treated patients. Among these patients, 12/33 linezolid-treated and 10/29 comparator-treated patients experienced bleeding related AEs (eg, epistaxis and anemia).

The linezolid group also experienced a greater percentage of patients with abnormal WBC and neutrophils values than the comparator group, although the magnitude of difference was less than what was observed for the platelet values. Among patients who experienced a categorical shift to a higher toxicity grade in ANC, the majority of cases were classified as 1- or 2-grade shifts for both treatment groups. Linezolid-treated patients had fewer 3-grade shifts and the same proportion of 4-grade shifts as comparator-treated patients.

A greater percentage of linezolid-treated patients had abnormal amylase values (5.1%) than patients in the comparator group (2.8%). The linezolid group also experienced a greater percentage of patients with abnormal sodium, chloride and bicarbonate values than the comparator group. The comparator group experienced a greater percentage of patients with abnormal AST, ALT, creatinine, BUN, total bilirubin, GGT, and potassium values than the linezolid group.

No statistically significant difference between groups was observed for any vital sign category.

The frequencies of selected study emergent AEs, categorized by the use of monoamine oxidase inhibitors (MAOIs) and concomitant non-investigational medications (NIMs) known to interact with MAOIs, were examined. There appeared to be an association between study-emergent AEs and the use of concomitant MAOI-interacting NIMs in the linezolid group.

The frequency of patients with at least 1 AE while on a MAOI-interacting drug was higher in the linezolid group (34 of 163 patients, 20.9%) than that of the comparator group (16 of 148 patients, 10.8%), and higher than that of the linezolid group not receiving a MAOI-interacting drug (18 of 199 patients, 9.0%).

CONCLUSION(S):

Results of this study demonstrated that linezolid was as effective as standard therapy for the treatment of gram-positive, catheter-related infections, specifically treatment of cSSSI related to indwelling catheters, and for the treatment of CRBSI. The incidence of SAEs and deaths were higher in the linezolid than the comparator group.