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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See United States Package Insert (USPI)

NATIONAL CLINICAL TRIAL NO.: NCT00084266

PROTOCOL NO.: A5951001

PROTOCOL TITLE: Linezolid in the Treatment of Subjects with Nosocomial Pneumonia Proven to be due to Methicillin-Resistant *Staphylococcus aureus*

Study Centers: There were 155 centers: 1 center in Argentina, 4 centers in Belgium, 3 centers in Brazil, 3 centers in Chile, 5 centers in Colombia, 4 centers in France, 3 centers in Germany, 4 centers in Greece, 1 center in Hong Kong, 5 centers in Korea, 2 centers in Malaysia, 4 centers in Mexico, 3 centers in Poland, 4 centers in Portugal, 6 centers in Russian Federation, 1 center in Singapore, 3 centers in South Africa, 4 centers in Spain, 4 centers in Taiwan, 1 center in Turkey, 2 centers in the United Kingdom, and 88 centers in the United States. An additional 49 centers including centers in Italy and Venezuela were shipped study drug but did not enroll any subjects.

Study Initiation Date and Completion Dates: 13 October 2004 to 31 March 2010

Phase of Development: Phase 4

Study Objectives: The primary objective of this study was to compare the clinical efficacy of linezolid to vancomycin in the treatment of nosocomial pneumonia due to Methicillin-Resistant *Staphylococcus aureus* (MRSA) in hospitalized adults.

The secondary objective of this study was to compare the bacteriological efficacy and safety and tolerability of linezolid to vancomycin in the treatment of nosocomial pneumonia due to MRSA in hospitalized adults.

For the fecal flora sub-study, the objective was to compare baseline and on-study bacterial counts and susceptibility profiles of aerobic Gram-negative intestinal microflora recovered from subjects receiving either linezolid or vancomycin as the randomized study drug.

METHODS

Study Design: This was a Phase 4, multicenter, double-blind, randomized study with 2 treatment groups, linezolid and vancomycin. Treatment groups were composed of

hospitalized, adult male or females subjects with nosocomial pneumonia (including healthcare-associated pneumonia [HCAP]) proven due to MRSA. Subjects who did not have MRSA isolated were discontinued. Subjects were randomly assigned in a ratio of 1:1 via a centralized randomization system to linezolid 600 mg intravenous (IV) every 12 hours or vancomycin 30 mg/kg/day IV infusion in 2 divided doses, every 12 hours.

Each subject was to initially receive cefepime 1-2 grams every 8-12 hours (or alternative Gram-negative agent[s]) to treat Gram-negative pathogens. If the subject did not have a documented Gram-negative infection, cefepime (or alternative Gram-negative agent[s]) were discontinued at the discretion of the investigator. Study treatment was administered for 7 to 14 days except in subjects with documented bacteremia who could have been treated for up to 21 days at the discretion of the investigator and with prior discussion with the medical monitor.

Subjects had a planned minimum of 4 visits. The maximum and expected duration of participation in this study for an individual subject, including treatment and follow-up, was up to 81 days including the 60-day post-treatment telephone contact. The first follow-up was the end of study (EOS [7-30 days after the last dose of study drug]) and the second follow-up was the telephone contact. The estimated length of time needed to complete the entire study (from enrollment of the first subject to completion of the last subject) was 48 months.

Number of Subjects (Planned and Analyzed): This study had at least 80% power to detect the superiority of linezolid to vancomycin if the linezolid MRSA success rate was 50% or higher. Assuming an evaluability rate of 80% in subjects with documented MRSA, a total of approximately 210 subjects were required per treatment group to achieve the required number of MRSA subjects. Based on an expected MRSA recovery rate of 35%, a total of approximately 1200 subjects were needed to be randomized in this study. The number of subjects analyzed for efficacy and safety is summarized in Table 1.

Diagnosis and Main Criteria for Inclusion: Eligible subjects were hospitalized (in acute, sub-acute or long-term care facility) males and females aged ≥18 years with clinically documented nosocomial pneumonia or HCAP with at least 2 signs and symptoms present within 24 hours of study enrollment and not treated pre-study for more than 48 hours within the 72 hours prior to enrollment with an antimicrobial with activity against that subject's MRSA isolate. Subjects treated for more than 48 hours with an antimicrobial active against that subject's isolate (other than linezolid or vancomycin) and who had failed treatment could be enrolled. In subjects who had been treated pre-study for 48 hours or less with an antimicrobial with activity against subject's MRSA isolate, symptoms and findings had to have been present within 24 hours prior to that treatment or within 72 hours prior to enrollment (whichever was closer to the time of enrollment). Subjects treated more than 48 hours with an antimicrobial with activity against that subject's MRSA isolate, other than linezolid and vancomycin, and failing treatment could also be enrolled. Subjects with an infection due to organisms known to be resistant to either of the study drug regimens before study entry were excluded from the study.

Study Treatment: Once enrolled, subjects were administered linezolid or vancomycin intravenously every 12 hours. Subjects were treated with linezolid approximately every

12 hours (twice daily) at a dose of 600 mg. Vancomycin was administered approximately every 12 hours (twice daily) at a dose of 30 mg/kg/day in 2 divided doses (15 mg/kg/dose) in subjects with normal renal function. The initial dose of vancomycin was at least 15 mg/kg for subjects with normal renal function. For subjects with renal insufficiency, doses were adjusted according to renal function based on a standard nomogram by the research pharmacist or equivalent. Cefepime or other Gram negative active antimicrobial was administered concomitantly to linezolid-treated and vancomycin-treated subjects every 8-12 hours at a dose of at least 1-2 g IV for the first 2 to 3 days of treatment until culture results were available, at which time the investigator determined if cefepime or other Gram negative antimicrobial was to be continued.

Efficacy Evaluations: The primary efficacy endpoint was clinical response in subjects with baseline MRSA at the EOS visit in the per protocol (PP) population, as assessed by the sponsor. Clinical response at the EOS visit could be cure, failure or unknown, each of which was prospectively defined. The secondary efficacy endpoints were microbiological outcome (documented eradication, presumed eradication, documented persistence, presumed persistence, superinfection, colonization or indeterminate, all prospectively defined) in subjects with baseline MRSA at the EOS and end of treatment (EOT, within 72 hours of the last dose of the study drug) visits as well as the subject clinical response at the EOT visit based on the modified intent-to-treat (mITT) and PP sets. Clinical response at the EOT visit could be cure, improvement, failure or unknown, each of which was also prospectively defined.

Pharmacokinetic and Other Evaluations: Vancomycin trough levels in the PP and mITT populations were summarized. Outcomes research endpoints included duration of hospitalization, duration of intensive care unit (ICU) and non-ICU stays, duration of ventilation, and number of re-admissions. Other efficacy analyses included clinical signs and symptoms, chest X-ray, respiratory cultures, blood cultures and a fecal flora sub-study.

Safety Evaluations: Adverse events (AEs) were monitored throughout the study. Hematology and serum chemistry tests were performed at Screening/Baseline, on-treatment (Days 3 and 9; additional hematology assessments were performed every 7 days if the subject was treated for greater than 14 days), EOT, modified EOS (parameters performed for subjects who discontinued early due to no documented MRSA or resistant pathogens at Baseline), and EOS. For centers conducting additional hematology testing, laboratory tests were also performed on Days 3, 5, 7, 9, 12 and every 3 days up to EOT. Results of any additional hematology tests that subjects required in the course of their care were also to be collected at these centers. Urinalysis was done at Screening/Baseline, modified EOS and EOS. Physical examinations were performed at Screening/Baseline. Vital signs, consisting of temperature, blood pressure, pulse and respiratory rate, were performed at Screening/Baseline, on-treatment, EOT, modified EOS and EOS.

Statistical Methods: The primary analysis for this study was the comparison of clinical outcome at the EOS Visit for the treatment groups. The primary analysis was based on the PP analysis set.

Clinical efficacy was assessed at EOT and EOS by comparing the cure rates of the 2 treatment groups. A non-inferiority test based on a two-sided 95% confidence interval (CI) of the linezolid cure rate minus the vancomycin cure rate was constructed. Linezolid was declared non-inferior to vancomycin if the lower bound of this CI was not less than -0.10. Superiority of linezolid to vancomycin was declared if the lower bound was greater than 0.

There was a planned interim analysis to assess baseline assumptions after approximately 50% MRSA enrollment using an O'Brien-Fleming adjustment of the significance level. In order to maintain the overall significance level of the study at 0.05, the significance level used at the interim analysis was 0.005 and at the final analysis was 0.048. The O'Brien-Fleming final boundary was used to test against the primary endpoint. The significance of the key secondary supportive endpoints were tested against the nominal significance level of 0.05 and not adjusted for multiplicity of testing.

AE analysis included summary displays of the number of AEs; the number of subjects with AEs, serious AEs (SAEs), treatment-related AEs, discontinuations due to AEs; as well as a breakdown of AE by body system and severity. Laboratory analysis included summary displays of abnormal laboratory values and median changes in laboratory values. Vital signs were summarized and displayed and presented graphically as appropriate.

RESULTS

Subject Disposition and Demography: Table 1 summarizes the subject disposition and the number of subjects analyzed for efficacy and safety.

Table 1. Subject Disposition

	Linezolid N (%)	Vancomycin N (%)	Total N (%)
Randomized to Treatment	618	607	1225
Received Treatment	597 (100)	587 (100)	1184 (100)
Completed Study	177 (29.6)	184 (31.3)	361 (30.5)
Discontinued Treatment	398 (66.7)	389 (66.3)	787 (66.5)
Subject Died	15 (2.5)	17 (2.9)	32 (2.7)
Related to Study Drug	8 (1.3)	15 (2.6)	23 (1.9)
Adverse Event	5 (0.8)	10 (1.7)	15 (1.3)
Lack of Efficacy	3 (0.5)	5 (0.9)	8 (0.7)
Not Related to Study Drug	375 (62.8)	357 (60.8)	732 (61.8)
Adverse Event	5 (0.8)	4 (0.7)	9 (0.8)
Gram-Negative Pathogen Isolated was not Susceptible to Study Drug	1 (0.2)	2 (0.3)	3 (0.3)
Lost to Follow-up	2 (0.3)	0	2 (0.2)
MRSA Isolate was not Susceptible to Study Medication	0	1 (0.2)	1 (0.1)
Other	139 (23.3)	131 (22.3)	270 (22.8)
Pathogen Isolated was not MRSA	225 (37.7)	213 (36.3)	438 (37.0)
Subject no Longer Willing to Participate in Study	3 (0.5)	6 (1.0)	9 (0.8)
Discontinued Study	420 (70.4)	403 (68.7)	823 (69.5)
Subject Died	42 (7.0)	39 (6.6)	81 (6.8)
Related to Study Drug	7 (1.2)	9 (1.5)	16 (1.4)
Adverse Event	5 (0.8)	5 (0.9)	10 (0.8)
Lack of Efficacy	2 (0.3)	4 (0.7)	6 (0.5)
Not Related to Study Drug	371 (62.1)	355 (60.5)	726 (61.3)
Adverse Event	3 (0.5)	0	3 (0.2)
Lost to Follow-up	5 (0.8)	3 (0.5)	8 (0.7)
Other	360 (60.3)	344 (58.6)	704 (59.5)
Subject no Longer Willing to Participate in Study	3 (0.5)	8 (1.4)	11 (0.9)
Subjects at EOT Visit	242 (40.5)	249 (42.4)	491 (41.5)
Subjects at EOS Visit	534 (89.4)	524 (89.3)	1058 (89.4)
Subjects with 60-day Survival Follow-up	228 (38.2)	243 (41.4)	471 (39.7)
Died (through 60-day Follow-up)	94 (15.7)	100 (17.0)	194 (16.4)
Efficacy Analysis			
mITT	224 (37.5)	224 (38.2)	448 (37.8)
PP			
Clinical EOT	183 (30.7)	188 (32.0)	371 (31.3)
Clinical EOS	172 (28.8)	176 (30.0)	348 (29.4)
Microbiological EOT	183 (30.7)	188 (32.0)	371 (31.3)
Microbiological EOS	172 (28.8)	176 (30.0)	348 (29.4)
Safety Analysis	597 (100.0)	587 (100.0)	1184 (100)

N = total number of subjects, MRSA = Methicillin-resistant *Staphylococcus aureus*, EOT = end of treatment, EOS = end of study

Table 2 summarizes the subject demographics for the ITT population. The 2 treatment groups were evenly distributed with respect to age, gender, and race.

Table 2. Subject Demographics – ITT

	Linezolid (N=597)	Vancomycin (N=587)
Age (years)		
Mean (SD)	60.5 (18.4)	60.5 (18.4)
Range	18-98	18-93
Race		
White	405 (67.8)	392 (66.8)
Black	63 (10.6)	62 (10.6)
Asian	86 (14.4)	85 (14.5)
Other	43 (7.2)	48 (8.2)
Weight (kg)		
n	596	586
Mean (SD)	76.7 (20.8)	77.3 (21.4)
Range	35-215	31.8-182
Smoking Status		
Current Smoker	141 (23.6)	142 (24.2)
Ex-Smoker	169 (28.3)	182 (31.0)
Non-Smoker	285 (47.7)	262 (44.6)
Unspecified	2 (0.3)	1 (0.2)

ITT = intent-to-treat, N = total number of subjects, SD = standard deviation, n = number of subject evaluated for the criterion

Efficacy Results:

Primary Evaluation

Table 3 displays the sponsor-assessed clinical success rates based on the PP population. The clinical success rates for linezolid and vancomycin at EOS were 95/165 (57.6%) and 81/174 (46.6%), respectively. Using the CI and Chi-square methods as described to assess non-inferiority and nested superiority, linezolid was shown to be non-inferior to vancomycin (95% CI: 0.5%, 21.6%) and statistically superior (p-value: 0.042). This significance level was compared against the final O'Brien-Fleming boundary of 0.048 as specified in statistical methods section.

Table 3. Sponsor's Assessment of Clinical Outcome at End of Study (EOS)– Per Protocol (PP)

	Linezolid N (%)	Vancomycin N (%)	P-value	95% CI
End of Study (EOS)				
Subjects in Analysis	165 (100.0)	174 (100.0)		
Success	95 (57.6)	81 (46.6)	0.042	(0.5, 21.6)
Cure	95	81		
Failure	70 (42.4)	93 (53.4)		
Unknown (excluded from analysis)	7	2		

N = total number of subjects, CI = confidence intervals

Secondary Evaluations

Linezolid was also non-inferior and statistically superior to vancomycin in sponsor-assessed clinical outcome at EOT (Table 4) and microbiological outcome at EOT and EOS (Table 5) in the PP population.

The results of the sponsor-assessed clinical outcome in the PP population showed non-inferiority and statistical superiority at EOT, 83.3% success rate for linezolid compared to 69.9% for vancomycin (95% CI: 4.9%, 22.0%; P-value = 0.002) (Table 4).

Table 4. Sponsor's Assessment of Clinical Outcome at End of Treatment (EOT)– Per Protocol (PP)

	Linezolid N (%)	Vancomycin N (%)	P-value	95% CI
End of Treatment (EOT)				
Subjects in Analysis	180 (100.0)	186 (100.0)		
Success	150 (83.3)	130 (69.9)	0.002	(4.9, 22.0)
Cure	76	70		
Improvement	74	60		
Failure	30 (16.7)	56 (30.1)		
Unknown (excluded from analysis)	3	2		

N = total number of subjects, CI = confidence intervals

The results of the microbiological outcome in the PP population showed non-inferiority and statistical superiority at EOT, 81.9% success rate for linezolid compared to 60.6% for vancomycin (95% CI: 12.3%, 30.2%; P-value <0.001). The results of the microbiological outcome in the PP population showed non-inferiority and statistical superiority at EOS, 58.1% success rate for linezolid compared to 47.1% for vancomycin (95% CI: 0.4%, 21.5%; P-value = 0.043) (Table 5).

Table 5. Microbiological Outcome at End of Treatment (EOT) and End of Study (EOS)– Per Protocol (PP)

	Linezolid N (%)	Vancomycin N (%)	P-value	95% CI
End of Treatment (EOT)				
Subjects in Analysis	182 (100.0)	188 (100.0)		
Success	149 (81.9)	114 (60.6)	<0.001	(12.3, 30.2)
MRSA Eradication	76	59		
With Other Acquired Organisms	49	27		
Without Other Acquired Organisms	27	32		
Presumed MRSA Eradication	73	55		
Failure	33 (18.1)	74 (39.4)		
MRSA Persistence	16	50		
With Other Acquired Organisms	9	13		
Without Other Acquired Organisms	7	37		
Presumed MRSA Persistence	17	24		
Indeterminate (Excluded from Analysis)	1	0		
End of Study (EOS)				
Subjects in Analysis	167 (100.0)	174 (100.0)		
Success	97 (58.1)	82 (47.1)	0.043	(0.4, 21.5)
MRSA Eradication	35	26		
With Other Acquired Organisms	20	11		
Without Other Acquired Organisms	15	15		
Presumed MRSA Eradication	62	56		
Failure	70 (41.9)	92 (52.9)		
MRSA Persistence	7	15		
With Other Acquired Organisms	1	4		
Without Other Acquired Organisms	6	11		
MRSA Recurrence	15	11		
With Other Acquired Organisms	10	4		
Without Other Acquired Organisms	5	7		
Presumed MRSA Persistence	48	66		
Indeterminate (Excluded from Analysis)	5	2		

N = total number of subjects, CI = confidence intervals, MRSA = Methicillin-resistant *Staphylococcus aureus*

The results of the analyses based on the mITT population were similar to the PP population (Table 6 and Table 7). In all cases, linezolid success rates were higher than vancomycin success rates, and the differences showed non-inferiority and statistical superiority at $p \leq 0.050$.

The results of the sponsor-assessed clinical outcome in the mITT population showed non-inferiority and statistical superiority at EOT, 80.1% success rate for linezolid compared to 67.8% for vancomycin (95% CI: 4.0%, 20.7%; P-value = 0.004). The results of the sponsor-assessed clinical outcome in the mITT population showed non-inferiority and statistical superiority at EOS, 54.8% success rate for linezolid compared to 44.9% for vancomycin (95% CI: 0.1%, 19.8%; P-value = 0.049) (Table 6).

Table 6. Sponsor-Assessed Clinical Outcome at End of Treatment (EOT) and End of Study (EOS) – Modified Intent-to-Treat (mITT)

	Linezolid N (%)	Vancomycin N (%)	P-value	95% CI
End of Treatment (EOT)				
Subjects in Analysis	201 (100.0)	214 (100.0)		
Success	161 (80.1)	145 (67.8)	0.004	(4.0, 20.7)
Cure	81	77		
Improvement	80	68		
Failure	40 (19.9)	69 (32.2)		
Unknown/Missing (excluded from analysis)	23	10		
End of Study (EOS)				
Subjects in Analysis	186 (100.0)	205 (100.0)		
Success	102 (54.8)	92 (44.9)	0.049	(0.1, 19.8)
Cure	102	92		
Failure	84 (45.2)	113 (55.1)		
Unknown/Missing (excluded from analysis)	38	19		

N = total number of subjects, CI = confidence intervals

The results of the microbiological outcome in the mITT population showed non-inferiority and statistical superiority at EOT, 79.3% success rate for linezolid compared to 58.3% for vancomycin (95% CI: 12.5%, 29.7%; P-value <0.001). The results of the microbiological outcome in the mITT population showed non-inferiority and statistical superiority at EOS, 56.9% success rate for linezolid compared to 45.9% for vancomycin (95% CI: 1.3%, 20.7%; P-value = 0.027) (Table 7).

Table 7. Microbiological Outcome at End of Treatment (EOT) and End of Study (EOS)– Modified Intent-to-Treat (mITT)

	Linezolid N (%)	Vancomycin N (%)	P-value	95% CI
End of Treatment (EOT)				
Subjects in Analysis	203 (100.0)	218 (100.0)		
Success	161 (79.3)	127 (58.3)	<0.001	(12.5, 29.7)
MRSA Eradication	84	65		
With Other Acquired Organisms	54	28		
Without Other Acquired Organisms	30	37		
Presumed MRSA Eradication	77	62		
Failure	42 (20.7)	91 (41.7)		
MRSA Persistence	19	60		
With Other Acquired Organisms	11	18		
Without Other Acquired Organisms	8	42		
Presumed MRSA Persistence	23	31		
Missing/Indeterminate (Excluded from Analysis)	21	6		
End of Study (EOS)				
Subjects in Analysis	195 (100.0)	209 (100.0)		
Success	111 (56.9)	96 (45.9)	0.027	(1.3, 20.7)
MRSA Eradication	46	35		
With Other Acquired Organisms	26	17		
Without Other Acquired Organisms	20	18		
Presumed MRSA Eradication	65	61		
Failure	84 (43.1)	113 (54.1)		
MRSA Persistence	9	22		
With Other Acquired Organisms	1	9		
Without Other Acquired Organisms	8	13		
MRSA Recurrence	16	12		
With Other Acquired Organisms	10	5		
Without Other Acquired Organisms	6	7		
Presumed MRSA Persistence	59	79		
Missing/Indeterminate (Excluded from Analysis)	29	15		

N = total number of subjects, CI = confidence intervals, MRSA = Methicillin-resistant *Staphylococcus aureus*

Fecal Flora Sub-Study Results

The administration of antibiotics to subjects in an intensive care unit setting affects both the number and susceptibility profile of Gram negative bacilli. In this sub-study, linezolid had a greater impact on Gram negative fecal flora compared to vancomycin, with isolation of more resistant *Enterobacteriaceae* and non-fermenters from the linezolid subjects, however, the role of pre-study Gram negative agents on gut microflora must be considered. The administration of Gram negative active agents prior to the study period, which was more common in linezolid subjects, was likely to have contributed to the noted changes in fecal flora.

Outcomes Research

There were 5 subjects in the mITT population (4 linezolid, 1 vancomycin) and 3 subjects at EOS in the PP population (2 linezolid, 1 vancomycin) whose duration of hospitalization was zero days since their locations were not considered as "hospital".

Minimum, maximum, median, mean and standard deviations of these outcomes research endpoints were compared for each study medication arm. These unadjusted analyses did not show any statistically significant differences between study arms.

Pharmacokinetic Results: The overall median plasma concentrations were comparable for the mITT and PP populations. It was not until Day 6, however that the median vancomycin plasma trough concentrations in both these populations were close to the recommended lower limit of 15 μg/mL for the trough.

Safety Results: One hundred and ninety four (194) deaths were recorded in the project (clinical study) database for subjects on study, ie, up through the 60-day follow-up, 94 (15.7%) in the linezolid group and 100 (17.0%) in the vancomycin group. A total of 233 subjects died per the sponsor's corporate safety database (Table 8). Occasional differences in data could exist between the corporate safety database and the clinical study database.

Table 8. Deaths

Page 1 of 5		
Sex/Age (years)	**Causality of Death (MedDRA Preferred Term)**	**Day of Death[a]**
Treatment at Death: Linezolid		
M/81	Cardiac arrest	11
M/64	Sepsis	29
M/74	Respiratory failure	42
F/89	Respiratory failure	23
F/85	Cardiac failure congestive	7
M/79	Death	35
M/73	Respiratory failure	72
M/82	Pneumonia	12
F/79	Multi-organ failure	15
M/90	Pleural effusion	25
M/41	Sepsis	3
M/38	Acute respiratory distress syndrome	5
F/81	Respiratory failure	14
M/82	Renal failure acute	50
F/78	Sepsis	37
M/62	Cardio-respiratory arrest, Brain hypoxia	8
M/62	Chronic hepatic failure	57
M/76	Multi-organ failure	12
M/72	Myocardial infarction	4
M/61	Systemic candida	16
F/59	Renal impairment, Sepsis	13
F/82	Multi-organ failure	38
F/40	Cardio-respiratory arrest	27
M/73	Septic shock	7
F/81	Sepsis	21
F/29	Respiratory failure	6
F/24	Pneumonia	14
F/57	Cardiac arrest	5
F/73	Septic shock	6
F/63	Aortic dissection	7
M/88	Respiratory failure	10
M/60	Septic shock	36
M/42	Abdominal sepsis[b]	24
F/83	Not available	3
M/31	Mesenteric vein thrombosis	28
M/24	Multi-organ failure	9
M/43	Respiratory failure	22
F/68	Shock	3
M/76	Not available	14
M/77	Lung infection pseudomonal	29
M/55	Brain edema	25
F/70	Cerebrovascular accident	22
M/83	Multi-organ failure	23
M/56	Brain edema	13
M/73	Renal cancer metastatic	11

MedDRA (v13.0) coding dictionary applied.
Abbreviations: M = male, F = female, MedDRA = Medical Dictionary for Regulatory Activities
[a] Day of death relative to start of study.
[b]MedDRA (v13.1) coding dictionary applied.

Table 8. Deaths

Page 2 of 5		
Sex/Age (years)	**Causality of Death (MedDRA Preferred Term)**	**Day of Death[a]**
M/55	Neoplasm recurrence	9
M/76	Intestinal ischemia	10
F/88	Pneumonia	13
F/78	Myocardial infarction	10
F/28	Pneumonia staphylococcal, Acute respiratory distress syndrome	20
M/27	Cardio-respiratory arrest	14
F/72	Not available	31
M/67	Pneumonia	27
M/84	Respiratory arrest	13
M/63	Pneumonia	14
M/98	Lung disorder	19
M/81	Pneumonia	2
F/82	Respiratory failure	11
M/79	Depressed level of consciousness	13
M/76	Cardiopulmonary failure	16
M/76	Cardiopulmonary failure	11
F/54	Cardiopulmonary failure	10
M/77	Cardiac arrest	26
M/45	Cardio-respiratory arrest	2
M/57	Cardio-respiratory arrest	2
M/86	Cardio-respiratory arrest	6
M/41	Brain death	14
F/80	Cerebrovascular accident	4
M/72	Neuroendocrine tumor	31
F/40	Injury, Respiratory failure	9
F/69	Cardiac arrest	8
F/77	Death	21
F/40	Cardiac arrest	21
F/75	Respiratory failure	7
F/57	Cardiac arrest	8
M/39	Cardiac arrest	17
M/87	Cardiac arrest	19
M/58	Renal failure acute	19
M/50	Respiratory distress	16
M/71	Cardiac arrest	14
F/86	Respiratory failure	10
M/52	Hemorrhage intracranial	33
M/46	Septic shock	17
M/21	Brain compression	23
F/78	Pneumonia aspiration	24
M/73	Multi-organ failure	11
M/75	Septic shock	7
F/61	Respiratory failure	32
F/82	Sepsis	18
M/92	Sepsis	16
M/86	Pneumonia	12
M/63	Death	16

MedDRA (v13.0) coding dictionary applied.
Abbreviations: M = male, F = female, MedDRA = Medical Dictionary for Regulatory Activities
[a] Day of death relative to start of study.

Table 8. Deaths

Page 3 of 5		
Sex/Age (years)	**Causality of Death (MedDRA Preferred Term)**	**Day of Death[a]**
F/55	Cardio-respiratory arrest	11
M/76	Cardiomyopathy	7
M/81	Chronic obstructive pulmonary disease, Cardio-respiratory arrest, Therapy cessation	36
F/84	Coronary artery disease	30
M/73	Cardiac arrest	10
F/70	Peritoneal infection	39
F/55	Condition aggravated, Brain herniation, Brain edema, Coma scale abnormal	43
M/53	Respiratory arrest	26
M/75	Multiple myeloma	12
F/70	Multi-organ failure, Sepsis	27
M/83	Respiratory failure	6
F/79	Respiratory failure, Chronic obstructive pulmonary disease, Cor pulmonale chronic	30
F/78	Pneumonia	23
F/68	Multi-organ failure, Renal failure, Cardiac failure, Atrial fibrillation	9
M/64	Respiratory failure	54
M/56	Nervous system disorder, Anoxic encephalopathy	45
M/75	Pneumonia	8
F/71	Acute respiratory failure	7
Treatment at Death: Vancomycin		
F/84	Acute respiratory failure	13
F/53	Respiratory arrest	8
M/85	Respiratory failure	7
M/57	Cerebrovascular accident	9
M/56	Respiratory failure	15
M/86	Pneumonia	14
F/55	Hemorrhage	17
M/84	Respiratory failure	24
F/88	Cerebral hemorrhage	26
F/74	Renal failure	196
F/66	Shock hemorrhagic	5
M/61	Renal failure acute, Shock, Respiratory failure	11
F/88	Sepsis	4
F/66	Pneumonia bacterial	27
F/77	Hemoptysis, Hypoxic Encephalopathy	30
M/79	Respiratory failure	35
M/62	Respiratory failure	15
M/85	Respiratory failure	21
F/60	Subarachnoid hemorrhage	7
M/70	Acute respiratory failure	3
M/79	Respiratory failure	39
M/56	Multi-organ failure	31
F/64	Respiratory failure	17
M/67	Pneumonia[b]	15
M/75	Pneumonia	39
M/87	Pulmonary embolism, Respiratory failure, Cardiac arrest, Sepsis	3
M/75	Shock hemorrhagic, Gastrointestinal hemorrhage, Sepsis	23

MedDRA (v13.0) coding dictionary applied.
Abbreviations: M = male, F = female, MedDRA = Medical Dictionary for Regulatory Activities
[a] Day of death relative to start of study.
[b] MedDRA (v13.1) coding dictionary applied.

Table 8. Deaths

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Sex/Age (years)	Causality of Death (MedDRA Preferred Term)	Day of Death[a]
M/84	Respiratory failure	4
F/44	Hemorrhage intracranial	6
M/72	Shock, Pneumonia	7
M/68	Not available	10
M/82	Multi-organ failure	7
F/88	Cardio-respiratory arrest	25
M/51	Death	3
M/51	Multi-organ failure	18
F/77	Multi-organ failure, Septic shock	2
M/84	Septic shock	14
M/58	Sepsis	22
M/58	Hemorrhage intracranial	1
M/84	Sepsis	18
F/83	Respiratory failure	26
M/69	Pneumonia	11
F/78	Sepsis	9
M/81	Sepsis	2
F/51	Sepsis	11
F/46	Hepatic cirrhosis, Pneumonia staphylococcal, Sepsis	20
M/75	Pneumonia	4
M/74	Systemic candida, Pneumonia	20
F/62	Pneumonia	21
M/61	Multi-organ failure	16
M/78	Cardiac arrest	2
F/88	Death[b]	33
M/76	Acute respiratory distress syndrome	30
M/44	Pneumonia	15
M/69	Lipoma, Brain edema	33
M/74	Respiratory distress	28
F/70	Toxic shock syndrome staphylococcal	5
M/47	Respiratory failure	15
F/75	Gastrointestinal necrosis	8
F/52	Not available	5
M/33	Septic shock	3
F/78	Acute myocardial infarction	70
F/73	Respiratory failure	14
M/84	Respiratory failure	7
M/67	Cardio-respiratory arrest	8
M/68	Cardio-respiratory arrest	6
F/70	Sepsis	10
M/67	Hemorrhage intracranial	2
M/68	Death[b]	32
M/85	Cardiopulmonary failure	11
M/74	Ischemic stroke	17
F/67	Respiratory failure	5
M/51	Pneumonia	11

MedDRA (v13.0) coding dictionary applied.
Abbreviations: M = male, F = female, MedDRA = Medical Dictionary for Regulatory Activities
[a] Day of death relative to start of study.
[b] MedDRA (v13.1) coding dictionary applied.

Table 8. Deaths

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Sex/Age (years)	**Causality of Death (MedDRA Preferred Term)**	**Day of Death[a]**
M/77	Sepsis	7
F/68	Neutropenia, Septic shock	20
M/33	Cardio-respiratory arrest	13
M/61	Cardiac arrest	10
M/74	Not available	35
F/73	Cardiac arrest	18
F/69	Cardiac arrest	13
M/Unknown	Cardiac arrest	Not available
M/75	Cardiac arrest	26
M/75	Cardiac arrest	32
M/75	Respiratory distress	4
F/82	Cardiac arrest, Sepsis	7
M/65	Cardiopulmonary failure	7
M/54	Drug ineffective, Multi-organ failure, Sepsis	13
F/81	Cardiopulmonary failure, Bacterial sepsis	14
M/69	Septic shock	25
F/19	Brain injury	12
F/72	Myocardial infarction, Cardiac arrest	13
M/81	Cerebral hemorrhage	5
M/67	Thrombotic thrombocytopenic purpura, Septic shock	34
F/79	Myocardial infarction	16
M/76	Sepsis, pneumonia	24
M/66	Thrombocytopenia, Arrhythmia	3
M/56	Pneumonia	14
M/62	Squamous cell carcinoma	6
M/60	Septic shock	3
M/82	Septic shock	52
M/76	Sepsis	12
F/64	Coronary artery disease	13
M/60	Sepsis, Empyema, Anastomotic complication	44
F/57	Lower respiratory tract infection	9
M/86	Multi-organ failure	27
M/72	Anoxic encephalopathy	28
M/53	Cerebral hemorrhage	8
M/51	Withdrawal of life support	9
M/69	Cardiac failure congestive	23
F/64	Acute respiratory distress syndrome	11
F/61	Respiratory distress	4
F/79	Renal failure acute, Pneumonia	10
M/70	Cardiac arrest, Pneumonia	2
M/74	Cardiac failure congestive	16
F/86	Cerebrovascular accident	11
M/39	Sepsis	10
M/83	Respiratory distress	78

MedDRA (v13.0) coding dictionary applied.
Abbreviations: M = male, F = female, MedDRA = Medical Dictionary for Regulatory Affairs
[a] Day of death relative to start of study.

Overall, 427 subjects had 657 SAEs based on the corporate safety database, and 20 of these subjects (4.7%) had SAEs that were considered by the investigators to be treatment related (ITT population). One linezolid subject had a fatal event (shock) and 3 vancomycin subjects had fatal events (renal failure acute, sepsis, septic shock and neutropenia) that the investigators considered treatment related (Table 9).

Table 9. Treatment-Related Serious Adverse Events (Investigator Assessment)

Sex/Age (years)	MedDRA Preferred Term	Outcome	Action Taken
Treatment at SAE onset: Linezolid			
M/85	*Clostridium difficile* colitis	Recovering	Post-Therapy. Treatment Completed
F/68	Shock	Fatal	Post-Therapy. Treatment Completed
M/67	Thrombocytopenia	Recovered	Permanently Withdrawn
F/57	Renal failure	Not Recovered	Dose Reduced
M/38	Rash	Recovered	Permanently Withdrawn
F/82	*Clostridium* test positive	Not Recovered	Dose Not Changed
F/73	Renal failure chronic	Recovered	Dose Not Changed
Treatment at SAE onset: Vancomycin			
F/73	Anemia	Recovered	Dose Not Changed
M/61	Renal failure acute	Fatal	Permanently Withdrawn
F/50	Renal failure acute	Not Recovered	Dose Reduced
F/51	Renal failure acute	Not Recovered	Dose Not Changed
	Sepsis	Fatal	Dose Not Changed
F/25	Renal failure acute	Not Recovered	Dose Not Changed
	Lung infiltration	Recovered	Permanently Withdrawn
	Respiratory tract infection	Recovered	Permanently Withdrawn
	General physical health deterioration	Recovered	Permanently Withdrawn
M/74	Atrial fibrillation	Recovered	Dose Not Changed
F/84	Renal failure acute	Recovered	Dose Not Changed
F/68	Septic shock	Fatal	Permanently Withdrawn
	Neutropenia	Fatal	Permanently Withdrawn
F/69	Renal failure	Not Recovered	Post-Therapy. Treatment Completed
M/27	Renal failure acute	Recovered	Permanently Withdrawn
M/54	Azotemia	Recovered	Dose Not Changed
	Hyperkalemia	Recovered	Dose Not Changed
F/38	Renal failure acute	Recovered	Dose Not Changed
M/60	Hypersensitivity	Recovered	Permanently Withdrawn

MedDRA = Medical Dictionary for Regulatory Activities (v13.0), SAE = serious adverse event

A total of 14 (2.3%) linezolid subjects and 23 (3.9%) vancomycin subjects discontinued the study due to AEs in the ITT population. Four subjects had the study drug temporarily stopped due to AEs and 1 subject had his dose reduced due to an AE in the ITT population. Table 10 summarizes the permanent discontinuations due to AEs.

Table 10. Discontinuations from Treatment due to Treatment-Emergent Adverse Events

Sex/Age (years)	Preferred term[a]	Start day[b]	Stop day[b]	Severity	Outcome	Causality	SAE
Linezolid							
M/62	Endocarditis	2	14	Severe	Resolved	Other	Yes
F/25	Tachycardia	1	1	Moderate	Resolved	Study drug	No
M/54	Pleural infection	14		Moderate	Not recovered	Other	No
F/82	Ischemic hepatitis	1	[>7]	Severe	Died due to other causes	Concomitant treatment	Yes
F/56	Rash	2	25	Moderate	Resolved	Study drug	No
M/38	Rash	2	7	Moderate	Resolved	Study drug	Yes
M/62	Rash	3	7	Mild	Resolved	Study drug	No
M/73	*Stenotrophomonas* infection	6	[>8]	Mild	Died due to other causes	Other	No
M/64	Abdominal pain	6	9	Moderate	Resolved	Other	Yes
	Diverticular perforation	6	14	Severe	Resolved	Other	Yes
M/54	Rash	1	15	Moderate	Resolved	Study Drug	No
Vancomycin							
F/64	Enterococcal bacteremia	1	15	Mild	Resolved	Other	No
M/85	Rash	2	[>3]	Mild	Died due to other causes	Study Drug	No
F/73	Abdominal infection	12	[>29]	Moderate	Died due to	Study Drug	No
	Enterococcal infection	12	[>29]	Moderate	other causes	Study Drug	No
M/61	Renal failure acute	8	[>11]	Severe	Died due to this AE	Study Drug	Yes
F/80	Dermatitis allergic	2	3	Mild	Resolved	Study drug	No
M/35	Hepatitis toxic	4	22	Severe	Resolved	Study drug	No
F/25	Staphylococcal infection	5	17	Severe	Resolved	Study drug	Yes
	Acute respiratory failure	5	17	Severe	Resolved	Study drug	Yes
	Lung infiltration	5	17	Severe	Resolved	Study drug	Yes
M/67	Hemorrhage intracranial	1	[>2]	Severe	Died due to this AE	Other	Yes
M/27	Renal failure acute	4	[>5]	Severe	Not yet recovered	Study drug	Yes
M/23	Dermatitis contact	2	19	Mild	Resolved	Other	No
M/54	Thrombocytopenia	7	[>13]	Moderate	Died due to	Study drug	No
	Pneumonia *Klebsiella*	7	[>13]	Severe	other causes	Study drug	No
	Sepsis	7	[>13]	Severe	Died due to this AE	Disease under study	Yes
M/64	Renal failure	9	33	Severe	Not yet recovered	Other	Yes
M/60	Hypersensitivity	4	4	Moderate	Resolved	Study drug	Yes
F/83	Renal failure acute	4	[>5]	Moderate	Not yet recovered	Study drug	No

MedDRA = Medical Dictionary for Regulatory Activities, M = male, F = female, SAE = serious adverse event, AE = adverse event. [a]MedDRA v13.0, [b]Day relative to start of study treatment, [ ] Values in brackets were imputed from incomplete dates and times

The distributions of AEs by system organ class were similar between treatment groups for all-causality and treatment-related AEs. A total of 3051 AEs were reported in this study,

1471 AEs by 378 (63.3%) linezolid subjects and 1580 AEs by 410 (69.8%) vancomycin subjects (Table 11). The most frequently reported AE was diarrhea (116 subjects; 59 and 57 subjects in linezolid and vancomycin groups, respectively) followed by hypokalemia (87 subjects; 44 and 43 subjects in linezolid and vancomycin groups, respectively) (Table 12).

Table 11. Summary of Treatment-Emergent (All Causality) Adverse Events

	Linezolid	Vancomycin
Number (%) of subjects:		
Subjects evaluable for adverse events	597	587
Number of adverse events	1471	1580
Subjects with adverse events	378 (63.3)	410 (69.8)
Subjects with serious adverse events	145 (24.3)	141 (24.0)
Subjects with severe adverse events	136 (22.8)	142 (24.2)
Subjects who discontinued due to adverse events[a]	14 (2.3)	23 (3.9)
Subjects with dose reductions or who temporarily discontinued due to an adverse event	1 (0.2)	4 (0.7)

[a] This information was derived from the adverse event log and was present if the action taken for that adverse event was discontinued treatment. The information in Table 1 was derived from the subject summary page and was the primary reason of subject discontinuation from treatment or study. If that reason was an adverse event then that was reflected in Table 1.

Table 12. Incidence of Treatment-Emergent (All Causality) Adverse Events in ≥2% Subjects in Any Treatment Group

Body System Class and MedDRA Preferred Term (v13.0) n (%)	Linezolid (N=597)	Vancomycin (N=587)
Blood and Lymphatic System Disorders	**52 (8.7)**	**73 (12.4)**
Anemia	30 (5.0)	42 (7.2)
Thrombocytopenia	8 (1.3)	13 (2.2)
Cardiac Disorders	**83 (13.9)**	**81 (13.8)**
Atrial Fibrillation	12 (2.0)	16 (2.7)
Cardiac Arrest	11 (1.8)	13 (2.2)
Tachycardia	12 (2.0)	12 (2.0)
Gastrointestinal Disorders	**147 (24.6)**	**144 (24.5)**
Constipation	33 (5.5)	37 (6.3)
Diarrhea	59 (9.9)	57 (9.7)
Nausea	22 (3.7)	30 (5.1)
Vomiting	14 (2.3)	15 (2.6)
General Disorders And Administration Site Conditions	**72 (12.1)**	**78 (13.3)**
Edema peripheral	12 (2.0)	13 (2.2)
Pyrexia	22 (3.7)	24 (4.1)
Infections and Infestations	**139 (23.3)**	**152 (25.9)**
Pneumonia	17 (2.8)	20 (3.4)
Sepsis	11 (1.8)	21 (3.6)
Septic Shock	10 (1.7)	19 (3.2)
Urinary tract infection	30 (5.0)	20 (3.4)
Metabolism and Nutrition Disorders	**119 (19.9)**	**132 (22.5)**
Hyperglycemia	10 (1.7)	18 (3.1)
Hyperkalemia	8 (1.3)	13 (2.2)
Hypoglycemia	21 (3.5)	14 (2.4)
Hypokalemia	44 (7.4)	43 (7.3)
Hypomagnesemia	16 (2.7)	15 (2.6)
Hyponatremia	12 (2.0)	13 (2.2)
Psychiatric Disorders	**59 (9.9)**	**66 (11.2)**
Agitation	13 (2.2)	22 (3.7)
Anxiety	11 (1.8)	15 (2.6)
Depression	12 (2.0)	7 (1.2)
Insomnia	14 (2.3)	18 (3.1)
Renal and Urinary Disorders	**38 (6.4)**	**52 (8.9)**
Renal Failure	4 (0.7)	13 (2.2)
Renal failure acute	10 (1.7)	19 (3.2)
Respiratory, Thoracic and Mediastinal Disorders	**98 (16.4)**	**104 (17.7)**
Respiratory failure	22 (3.7)	25 (4.3)
Skin and Subcutaneous Tissue Disorders	**68 (11.4)**	**74 (12.6)**
Decubitus ulcer	16 (2.7)	23 (3.9)
Rash	23 (3.9)	20 (3.4)
Vascular Disorders	**57 (9.5)**	**83 (14.1)**
Hypertension	28 (4.7)	33 (5.6)
Hypotension	26 (4.4)	41 (7.0)

MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with MedDRA coded adverse event; N = number subjects analyzed for adverse events

The median changes from baseline to last observation in laboratory and vital signs parameters were small and not considered to be clinically significant. Extra hematology data

revealed no difference in changes in hemoglobin, platelets, white blood cells or neutrophils between the 2 treatment groups.

CONCLUSIONS: The primary endpoint for this study was sponsor-assessed clinical outcome at EOS based on the PP population. The linezolid and vancomycin clinical success rates were 57.6% and 46.6%, respectively. Using the method of non-inferiority with a nested superiority hypothesis, linezolid was shown to be both statistically non-inferior and statistically superior to vancomycin based on sponsor-assessed clinical outcomes. It may be noted that the linezolid success rates for the key supportive secondary clinical and microbiological endpoints for the PP and mITT populations were also higher than the vancomycin success rates, demonstrating both non-inferiority and statistical superiority as defined.

Additional hematology data revealed no difference in changes in hemoglobin, platelets, white blood cells or neutrophils between the 2 treatment groups.

Based on the aggregate safety data, the results were consistent with the known safety profile of linezolid for the treatment of nosocomial pneumonia infections due to proven MRSA.

In the fecal flora sub-study, linezolid had a greater impact on Gram negative fecal flora compared to vancomycin, with isolation of more resistant *Enterobacteriaceae* and non-fermenters from the linezolid subjects, however, the role of pre-study Gram negative agents on gut microflora must be considered and the overall numbers of subjects were small.

In conclusion, linezolid was non-inferior and statistically superior at EOS to vancomycin in the PP population, the primary analysis population and endpoint. In addition, linezolid had numerically higher success rates at EOT in the PP population and in microbiological outcome. The safety results were consistent with the known safety profile of linezolid.