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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:
Vancomycin-resistant *Enterococcus faecium* infections, nosocomial pneumonia, complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis, uncomplicated skin and skin structure infections, community-acquired pneumonia.

NCT NO.: NCT00087490

PROTOCOL NO.: A5951002

PROTOCOL TITLE: Linezolid in the Treatment of Subjects with Complicated Skin and Soft Tissue Infections Proven to be Due to Methicillin-Resistant Staphylococcus Aureus

Study Center(s): Argentina (4), Belgium (5), Brazil (5), Chile (2), Colombia (5), Germany (4), Ireland (2), Italy (7), Malaysia (3), Mexico (3), Portugal (5), Russian Federation (6), Singapore (1), South Africa (5), Spain (4), United Kingdom (4), United States (66), Venezuela (5)

Study Initiation and Completion Dates: 30 October 2004 to 24 July 2007

Phase of Development: Phase 4

Study Objectives:

Primary Objective: To compare the clinical efficacy of linezolid to vancomycin in the treatment of complicated soft tissue infections (cSSTIs) due to methicillin-resistant *Staphylococcus aureus* (MRSA) in adult subjects at the end-of-study (EOS) visit.

Secondary Objectives:

To compare the clinical efficacy, and safety and tolerability of linezolid to vancomycin in the treatment of cSSTI due to MRSA in adult subjects at the end-of-treatment (EOT) visit.

To compare the microbiological efficacy, and safety and tolerability of linezolid to vancomycin in the treatment of cSSTI due to MRSA in adult subjects at the EOT and the EOS visits.

To compare the medical resource utilization of linezolid and vancomycin for this subject population.

METHODS

Study Design: This was a multinational, multicenter, Phase 4 randomized, open-label, active-controlled study comparing clinical and microbiological efficacy, safety, and tolerability of linezolid to vancomycin in subjects with confirmed MRSA cSSTI. This study also compared economic and direct medical resource utilization, as measured by length of hospital stay and duration of intravenous (IV) therapy of the 2 treatment groups.

Eligible subjects were randomized in a 1:1 ratio to the following groups: linezolid IV infusion or oral (PO) tablets (600 mg every 12 hours), or vancomycin IV infusion 15 mg/kg per dose every 12 hours in subjects with normal renal function.

Potential subjects were examined for signs and symptoms of infection and the investigator assessed the infection site/wound. A specimen was obtained for Gram stain, culture, and susceptibility testing of recovered pathogens. The subject must have had an infection site/wound with a culturable sample. Subjects in whom MRSA was documented as a pathogen continued the study.

Study treatment was administered for a duration of 7 to 14 days with a minimum of 5 subject visits, which includes the EOS visit 6 to 28 days after EOT. Subjects with documented MRSA bacteremia could continue treatment for up to 21 days at the discretion of the investigator, and with prior approval from the Pfizer Medical Monitor. The estimated time to complete the entire study (from enrollment of the first subject to completion of the last subject) was approximately 24 months.

Subjects who discontinued from the study had an abbreviated EOS visit within 72 hours after discontinuing study medication.

Medical resource utilization information was collected on a daily basis. This included a daily log of the subject's location in the hospital and outside of the hospital as well as a daily log of study drug dosing.

Standard hematology, blood chemistry, and urinalysis tests were performed, as well as tests for C-reactive protein. Women of childbearing potential underwent a serum or urine pregnancy test, which had to be negative.

Number of Subjects (Planned and Analyzed): Approximately1000 subjects were planned, to achieve approximately 425 evaluable subjects with proven MRSA cSSTI. A total of 544 subjects were randomized to receive linezolid, and 537 subjects received at least 1 dose of study drug. In the vancomycin group, 533 subjects were randomized and 515 subjects received at least 1 dose of study drug.

Diagnosis and Main Criteria for Inclusion: Treatment groups were composed of male or female subjects of at least 18 years of age, with cSSTIs such as surgical wound infections, traumatic wound infections, abscesses, infected decubitus ulcers, other acutely infected

ulcers, infected burn wounds (<20% body surface area), infected diabetic ulcers, and other skin or soft tissue infections requiring significant systemic antimicrobial therapy. Subjects must have had an infection site/wound with a culturable sample.

The 2 types of infected diabetic ulcers allowable in this study were a superficial, nonischemic infected wound that did not involve the tendon, capsule, or bone, or a wound that was penetrating to tendon or capsule. Simple cellulitides were excluded. Subjects with a significant likelihood of an MRSA cSSTI were selected. Subjects must have had venous access for dosing.

Subjects must have presented with at least one of the following criteria:

Elevated body temperature: oral ≥38ºC/100.4ºF; rectal, tympanic, via temporal artery, or core ≥38.4ºC/101.1ºF; or axillary ≥37.5ºC/99.5ºF

Hypotension: systolic BP <90mmHg

Elevated total peripheral white blood cell (WBC) count >10,000 mm^3

>15% immature neutrophils (bands) regardless of total peripheral WBC count

OR

Subjects with diabetic foot infections were enrolled if ALL of the following criteria were met:

There was evidence of a deep infection extending below the subcutaneous tissue of the foot/ankle/lower leg

Infection required a surgical procedure in the operating room (eg, incision and drainage [I&D], debridement) or a procedure of similar extent as an outpatient (for patients not needing anesthesia due to neuropathy)

Deep infection was a minimum of 2 cm in diameter, or there was a minimum of 2 cc (mL) of purulent material, or surgeon was able to probe more that 2 cm in any direction from the original deep infection

OR

Subjects with diabetic foot infections were enrolled if they met the following criteria:

An identifiable wound (ie, open lesion, ulcer, puncture wound) with evidence of purulence and ONE of the following signs:

Erythema in more than 50% of the surface area of the foot/ankle/lower leg

Medial arch streaking

Subjects previously treated with antibiotics (not including vancomycin, linezolid, or teicoplanin) active against subject's MRSA isolate and were a treatment failure had signs and symptoms present within the 24 hours prior to enrollment.

Study Treatment: Subjects were treated with 600 mg linezolid (IV or PO) or with IV vancomycin beginning on the day of randomization. Subjects received the first dose of study drug in a hospital environment. When discharged from the hospital, subjects were given a sufficient quantity of their assigned study drug for administration at home. The investigator arranged home IV therapy for those subjects on IV study medication.

Linezolid IV: IV linezolid was provided as a sterile isotonic solution containing 2 mg of active drug for 1 mL diluent (2 mg/mL), and was supplied in single-use IV infusion bags of 300 mL. No further dilution was necessary. IV linezolid was administered approximately every 12 hours (twice daily) at a dose of 600 mg over a period of 60 to 120 minutes.

Linezolid oral tablets: A single 600-mg oral tablet was administered every 12 hours with or without food. Oral linezolid was supplied as 600 mg film-coated compressed tablets packaged in bottles of 20 tablets for up to 10 days of treatment. If a subject was treated for more than 10 days, additional bottle(s) were dispensed. For some sites outside of the US, linezolid was supplied in blister packs containing 10 tablets for up to 5 days of treatment. Additional blister packs were dispensed for the 7 to 14 days of planned treatment duration.

Vancomycin IV: Vancomycin was infused approximately every 12 hours (twice daily) over a period of 60 to 120 minutes at an initial dose of 15 mg/kg in subjects with normal renal function. Doses could be adjusted based on vancomycin levels at the investigator's discretion. More frequent doses (eg, every 8 hours) could occur per local site practices and weight specifications. Final concentrations of no more than 5 mg/mL and infusion rates of no more than 10 mg/min were recommended. For patients with renal insufficiency, subsequent doses and frequency were adjusted according to renal function, based on a standard nomogram, or serum levels obtained at the site's local laboratory.

Subjects with documented MRSA bacteremia could continue treatment for up to 21 days at the discretion of the investigator, and with prior approval from the Pfizer Medical Monitor.

Aztreonam (1 to 2 grams every 8 to 12 hours) could be administered at randomization for suspected Gram-negative pathogens.

Metronidazole IV or oral tablets (500 mg every 8 hours) could be used in both treatment groups for suspected anaerobic pathogens as required throughout the study.

Efficacy Evaluations: Clinical and microbiologic evaluations were performed for efficacy outcome on each subject. Variables included clinical observations of infection, changes in vital signs and signs/symptoms, number of days study drug was received, and microbiologic assessment of the infection site/wound.

Three analysis sets were defined in this study: intent-to-treat (ITT), modified intent-to-treat (mITT) and per protocol (PP). The ITT set included all subjects who received at least 1 dose of active study medication. The mITT set included those ITT subjects who in received at

least 1 dose of study medication and had a positive culture for MRSA pathogen at baseline. The PP set included those subjects who met key inclusion/exclusion criteria, and demonstrated adequate compliance with the study regimen.

The primary efficacy endpoint was clinical outcome at the EOS visit in the PP population.

The secondary efficacy endpoints were clinical outcome at EOT based on the PP subjects, clinical outcome at EOT and EOS based on the mITT subjects, and microbiological outcome at the EOT and EOS, based on the mITT and PP sets.

In addition, secondary endpoints included assessment of clinical signs and symptoms, and health economic factors (length of hospital stay and duration of IV study drug).

Clinical response was evaluated at the EOT visit as Cure, Improvement, Failure, or Unknown and at the EOS visit as Cure, Failure, or Unknown. Clinical response was based primarily on the investigator's global assessment of the clinical presentation of the subject at that evaluation timepoint. Subjects who used antibiotics with activity against MRSA, or had unplanned surgical procedures were considered treatment failures from that point on.

For those subjects in whom a pathogen was isolated at baseline, microbiological outcome was assessed at the EOT and EOS visits. Microbiological outcome was classified as microbiologic success if the culture result no longer showed the presence of MRSA or if there was no culture but there was a clinical outcome of success.

Safety Evaluations: Safety data (ie, adverse events [AEs], vital signs, and standard laboratory tests) were subject to clinical review.

For all AEs, the investigator pursued and obtained information adequate to determine the causality and outcome of the AE and to assess whether it met the criteria for a serious AE (SAE) requiring immediate notification to Pfizer or its designated representative. For AEs which, in the investigator's opinion, had a causal relationship to the investigational product, the investigator followed-up the AE until the event or its sequelae resolved or stabilized at a level acceptable to the investigator, provided Pfizer concurred with that assessment. Nonserious AEs were recorded on the CRF from the time the subject took at least one dose of study treatment through the EOS visit.

SAEs were reported immediately (within 24 hours) to Pfizer, or its designated representative, beginning from the time the subject provided informed consent, through and including 28 calendar days after the last administration of the investigational product. Any SAE occurring any time after the reporting period was promptly reported if a causal relationship to investigational product was suspected. Lack of efficacy in an approved indication was reported as an SAE.

Vital signs and safety laboratory evaluations were obtained at baseline/screening, Days 3, 7, at EOT, EOS, and abbreviated EOS (if applicable). Weight was obtained at screening/baseline only.

Females of childbearing potential had a serum or urine human chorionic gonadotropin (HCG) test at baseline/screening at EOT, which must have been negative for the subject to continue the study.

Statistical Methods: This was a noninferiority study with a nested superiority hypothesis. Approximately 1004 subjects (502 per treatment group) were randomized. Assuming an 84% success rate in both treatment groups, sample size calculations revealed that 211 subjects per group was sufficient, at a 0.05 level of significance and a power >80%, to declare linezolid noninferior to vancomycin.

The primary efficacy endpoint was the clinical outcome at the EOS visit based on the PP subjects. The clinical efficacy of linezolid was compared to that of vancomycin using the PP subjects' clinical outcomes at the EOS visit. A nested hypothesis testing procedure was used. A noninferiority test based on a 95% confidence interval (CI) was performed. Linezolid was declared noninferior to vancomycin if the lower limit of this CI was above -0.10. If linezolid was found to be noninferior to vancomycin, the lower limit of the 95% CI was compared against zero (0). If the lower limit was above zero, linezolid would be declared superior to vancomycin. A Chi-square test was also performed to compute the actual corresponding p-value.

Secondary endpoints were analyzed using the same statistical methodology as the primary endpoints.

Sensitivity analyses were performed to assess the impact of missing values and indeterminate values,by setting them to failure.

Outcomes research endpoints included duration of hospitalization and duration of IV treatment (pre- and post-discharge). Statistical comparison of length of stay (LOS) used survival analysis methods taking into account subjects with censored data. Kaplan-Meier curves of LOS were constructed, and the differences between treatments were tested using the Wilcoxon statistic. Duration of IV therapy was compared using the Student's t-test.

Safety data were subject to clinical review and were summarized by appropriate descriptive statistics in accordance with Pfizer safety standards in place at the time of data collection and analysis. Safety and tolerability were assessed in the ITT population.

RESULTS

Subject Disposition and Demography: A total of 544 subjects were randomized to receive linezolid, and 537 subjects received at least 1 dose of study drug. In the vancomycin group, 533 subjects were randomized and 515 subjects received at least 1 dose of study drug. The percentage of subjects who completed the study was similar for the linezolid (286 subjects [53.3%]) and vancomycin (264 subjects [51.3%]) treatment groups. See Table S1, below.

Table S1. Subject Disposition

	Linezolid n (%)	Vancomycin n (%)
Randomized to Treatment	N = 544	N = 533
Received Treatment	537 (100.0)	515 (100.0)
Discontinued Treatment[a]	245 (45.6)	247 (48.0)
Discontinued Study	251 (46.7)	251 (48.7)
Completed Study	286 (53.3)	264 (51.3)
Subjects at EOT visit	306 (57.0)	304 (59.0)
Subjects at EOS visit	498 (92.7)	464 (90.1)
Efficacy Analysis		
Modified Intent to Treat (mITT)	322 (60.0)	318 (61.7)
Per Protocol (PP)		
Clinical EOT	240 (44.7)	222 (43.1)
Clinical EOS	229 (42.6)	210 (40.8)
Microbiological EOT	240 (44.7)	222 (43.1)
Microbiological EOS	229 (42.6)	210 (40.8)
Safety Analysis	537 (100.0)	515 (100.0)

CRF = case report form, EOT=end of treatment, EOS= end of study, MRSA = methicillin-resistant *Staphylococcus aureus*, N = number of subjects per treatment group, n = number of subjects in each category within the treatment group

[a]The majority discontinued due to absence of MRSA upon culture.

As per protocol, non-MRSA subjects had an abbreviated EOS visit, but not an EOT visit.

Subjects who were randomized, but did not receive treatment, are not addressed further in subsequent tables.

Subject 10281008 had an incorrect randomization number recorded in the CRF, but was not treated; therefore, correct randomization counts are linezolid = 545, vancomycin = 532.

Demographic characteristics were similar among females and males between treatment groups. Overall, there were more male participants (305/537 [56.8%] of linezolid subjects, 315/515 [61.2%] of vancomycin subjects) than female. Mean ages and weights were comparable between treatment groups, and most subjects were less than 64 years of age. With regard to race, most subjects were white, followed by subjects who were black and subjects of other racial origins. Very few subjects were Asian. The mean weight of the linezolid subjects was 85.4 kg (range 36.0-295.5 kg) and of vancomycin subjects it was 85.9 kg (range 42.0-244.1 kg)

Efficacy Results: For the primary analysis, clinical outcome based on the PP population at EOS, the success rates for linezolid and vancomycin were 84.1% (191/227) and 79.9% (167/209), respectively. Linezolid was found to be noninferior to vancomycin (CI: -3.0%, 11.5%) but the difference (p=0.249) fell short of that required for statistical superiority. (Table S2).

Table S2. Clinical Outcomes in PP and mITT Sets at EOT and EOS

		Linezolid N (%)	Vancomycin N (%)	P-value	95% CI
PRIMARY ANALYSIS					
Timepoint					
EOS	PP				
	Subjects in analysis	227 (100)	209 (100)		
	Success	**191 (84.1)**	**167 (79.9)**	**0.249**	**(-3.0%, 11.5%)**
	Cure	191	167		
	Failure	36 (15.9)	42 (20.1)		
	Unknown[a]	2	1		
SECONDARY ANALYSES					
EOS	mITT				
	Subjects in analysis	276 (100)	266 (100)		
	Success	**223 (80.8)**	**196 (73.7)**	**0.048**	**(0.1%, 14.2%)**
	Cure	223	196		
	Failure	53 (19.2)	70 (26.3)		
	Unknown/Missing/indeterminate[a]	46	52		
EOT	PP				
	Subjects in analysis	239 (100)	220 (100)		
	Success	**219 (91.6)**	**193 (87.7)**	**0.168**	**(-1.7%, 9.5%)**
	Cure	161	142		
	Improvement	58	51		
	Failure	20 (8.4)	27 (12.3)		
	Unknown[a]	1	2		
EOT	mITT				
	Subjects in analysis	284 (100)	287 (100)		
	Success	**254 (89.4)**	**243 (84.7)**	**0.090**	**(-0.7%, 10.3%)**
	Cure	191	175		
	Improvement	63	68		
	Failure	30 (10.6)	44 (15.3)		
	Unknown/Missing/indeterminate[a]	38	31		

CI = confidence interval; EOS = end of study; EOT = end of treatment; mITT = modified intent-to-treat set; PP = per protocol set, N= number of subjects per treatment group

[a]Excluded from analysis. Sensitivity analyses were conducted with unknown, missing and indeterminate values set to failure.

Note: Success at EOT was defined as cure and improvement; success at EOS was defined as cure

P-value based on Chi-square test, 95% confidence interval based on normal approximation to the binomial.

For the secondary analysis of clinical outcome based on the mITT population at EOS, linezolid was found to be statistically superior to vancomycin (p=0.048; CI: 0.1%, 14.2%) with success rates of 80.8% (223/276) and 73.7% (196/266), respectively.

In the analysis at EOT linezolid was noninferior to vancomycin in both the PP and mITT populations. Although the linezolid success rate was higher than that for vancomycin in both populations, the difference fell short of statistical significance (PP: p=0.168, mITT: p=0.090).

Sensitivity analyses were performed to assess the impact of missing and indeterminate values by setting them to failure. The results of the sensitivity tests were similar to results above, where linezolid was again superior to vancomycin at EOS in the mITT population (p=0.043; CI: 0.3%, 15.0%).

Microbiological outcome was assessed at EOT and EOS for the PP and mITT populations based on culture results. Microbiological outcome was classified as microbiologic success if the culture result no longer showed the presence of MRSA or if there was no culture but there was a clinical outcome of success.

The microbiological success rates in the PP population for linezolid and vancomycin at EOT were 85.4% and 68.8%, respectively. At EOS, microbiological success rates were slightly lower for both compounds, at 75.0% (linezolid) and 68.4% (vancomycin). The numerical success rates were higher for linezolid both at EOT and EOS. At EOT, the p-value (p<0.001) and CIs (9.1%, 24.2%) showed that linezolid was statistically superior to vancomycin. At EOS the CIs showed that linezolid was noninferior to vancomycin (-1.9%, 15.0%) but did not result in statistical superiority (p=0.127).

Comparable analyses were done for the mITT population. The microbiological success rates in the mITT population for linezolid and vancomycin at EOT were 84.3% and 69.2%, respectively. At EOS, microbiological success rates were slightly lower for both compounds, at 73.6% (linezolid) and 66.0% (vancomycin). The numerical success rates were higher for linezolid both at EOT and EOS. Linezolid was shown to be statistically superior to vancomycin at EOT (p=0.000; CI: 8.3%, 21.9%), and approached statistical superiority at EOS (p=0.055; CI: -0.1%, 15.2%).

Sensitivity analyses for other acquired organisms in the mITT set showed linezolid to be statistically superior to vancomycin both at EOT (p=0.001; CI: 4.8%, 19.1%) and at EOS (p=0.032; CI: 0.7%, 15.9%).

Other Results: Outcomes research result endpoints of duration of hospitalization and IV treatment for the mITT and PP sets were also examined.

There was a statistically significant difference between treatments with respect to length of hospital stay, where the mean length of hospital stay was 7.6 days in the linezolid group (range 1-29 days) compared to 8.9 days in the vancomycin group (range 1-25 days) for the PP set (p=0.022). In the mITT set, the mean length of hospital stay was 7.7 days for linezolid (range 1-34 days) and 8.9 days for vancomycin (range 1-31 days) (p=0.016).

There was a statistically significant difference in length of IV therapy between linezolid and vancomycin, where the mean duration of IV therapy was 5.6 days in the linezolid group (range 1-22 days) and 10.4 days in the vancomycin group (range 4-21 days) for the PP set (p<0.001). In the mITT set, the mean duration of IV therapy was 5.3 days in the linezolid group (range 1-22 days) compared to 9.8 days in the vancomycin group (range 1-25 days) (p<0.001).

Safety Results: Eighteen subjects died during this study: 11 in the linezolid group, and 7 in the vancomycin group. No deaths were judged to be related to the study treatments. Deaths are summarized in Table S3.

Table S3. Deaths

Treatment at Death	Causality of Death (MedDRA PT)	Day of Death[a]
Linezolid	Brain death	4
	Cardiac arrest, respiratory arrest[b]	36
	Multi-organ failure	23
	Arrhythmia	16
	Urinary tract infection[c]	16
	Cardiac failure	8
	Cardiac failure, renal failure	13
	Myocardial infarction[d]	7
	Sepsis	>1[f]
	Cardio-respiratory arrest	9
	Septic shock	19
Vancomycin		
	Cardio-respiratory arrest[e]	35
	Lung disorder	31
	Pneumonia	15
	Intestinal ischemia, intestinal gangrene	49
	Renal impairment	9
	Cardiac arrest	18
	Renal failure, acute	11

MedDRA = Medical Dictionary for Regulatory Activities, PT = treferred term
[a]Day of death relative to start of study treatment
[b]This subject also received 4 grams aztreonam
[c]Subject CIOMS form listed 'new septic episode'
[d]This subject also experienced myocardial ischemia; however, the event associated with the clinical outcome of death was myocardial infarction.
[e]The serious adverse event of renal failure for this subject was considered related to vancomycin (Table S4); however, the cause of death was recorded as cardio-respiratory arrest.
[f]Imputed from incomplete date and time.

Permanent discontinuations occurred due to SAEs and nonserious AEs; in addition, dose reductions or temporary discontinuations due to AEs occurred.

Overall, 84 subjects had 123 SAEs, and 10 of these subjects (11.9%) had treatment-related SAEs. Two subjects had SAEs that were considered by investigators to be related to linezolid and 8 subjects had SAEs judged related to vancomycin. Table S4 summarizes treatment-related SAEs.

Table S4. Treatment-Related Serious Adverse Events

Treatment at SAE onset	MedDRA PT	Outcome	Action Taken
Linezolid	Anemia	Recovered with sequelae	Post-therapy. Treatment completed
Vancomycin	Anemia	Recovered	Post-therapy. Treatment completed
	Urticaria	Recovered	Permanently discontinued
	Drug hypersensitivity	Recovered	Permanently discontinued
	Superinfection	Recovered	None
	Renal failure	Death[b]	None
	Rash, dyspnea[a]	Recovered	Permanently discontinued
	Erythema, rash, rash generalized, pruritus, pain in extremity[a]	Recovered	Post-therapy. Treatment completed
	Red man syndrome	Recovered	Permanently discontinued
	Thrombocytopenia	Recovered	Post-therapy. Treatment completed

MedDRA = Medical Dictionary for Regulatory Activities, PT = preferred term, SAE = serious adverse event
[a]Each of these events was a separate SAE
[b]This subject's death was not attributed to renal failure. Death was attributed to cardio-respiratory arrest.

Anemia is recognized to be associated with linezolid; however, usually in the setting of longer dosing durations than seen in either of these subjects (11 days and 8 days). Of the 2 linezolid-dosed subjects who experienced anemia, one had a prior history of chronic anemia, and the other subject's anemia was detected 17 days after the discontinuation of her 8 days of study drug. Both subjects recovered.

Allergic drug reactions/histamine release reactions were more common after dosing with vancomycin, and of the 8 subjects with SAEs related to vancomycin, 5 presented either with red man syndrome, rash, drug hypersensitivity or urticaria.

SAEs leading to discontinuation from the study were more frequent in the vancomycin group than in the linezolid group. Neither of the 2 SAEs leading to discontinuation from the study in the linezolid group was related to the study drug (acute myocardial infarction and extradural abscess). In the vancomycin group, 5 of the 9 SAEs leading to discontinuation were related to the study drug, and 4 of these were hypersensitivity reactions to vancomycin or histamine release phenomena (urticaria, red man syndrome [2] and generalized rash).

Of the 3 nonserious AEs leading to discontinuation from the study in the linezolid group, 2 were hypersensitivity reactions to the study drug. Of the 8 nonserious AEs leading to discontinuation from the study in the vancomycin group, 5 were hypersensitivity/histamine release reactions to the study drug, and 1 was a reaction to vancomycin administration.

Of the most frequently reported AEs, nausea, diarrhea, and vomiting were more frequent in the 537 linezolid-dosed subjects (10.6%, 7.4% and 4.5%, respectively), compared with those same events in the 515 vancomycin subjects (5.6%, 2.7% and 2.1% respectively); however, most were mild in severity. Moderate, frequently reported AEs (ie, >2% of subjects) occurred in both groups, and severe AEs were infrequent.

Three treatment-related AEs occurred in >2% of subjects during the study. Nausea and diarrhea were most frequently reported, and were more frequent in subjects who received linezolid. There were 34 linezolid subjects with nausea (6.3%) and 24 with diarrhea (4.5%), compared with 15 (2.9%) and 7 (1.4%), respectively, of vancomycin subjects. Most instances of nausea and diarrhea were mild, and a small number were moderate. Severe diarrhea occurred in 1 subject who received linezolid. Severe diarrhea in this subject resolved on Study Day 21, approximately 15 days after onset. There were 12 vancomycin subjects (2.3%) with pruritus, compared with 3 linezolid subjects (0.6%) with this event.

CONCLUSIONS:

With respect to clinical success, linezolid was proven to be at least as effective as vancomycin, with higher numerical success rates for linezolid at end of study, but not statistically superior, for the treatment of complicated skin and soft tissue infections due to MRSA in a broad range of subjects.

Microbiological outcome showed that linezolid was statistically superior to vancomycin at EOT, and was statistically noninferior at EOS.

Subjects receiving linezolid had statistically significantly shorter hospitalizations and statistically significantly shorter durations of intravenous therapy than those who received vancomycin.

Overall, linezolid has an acceptable safety and tolerability profile for the treatment of complicated skin and soft tissue infections and no unexpected adverse events were seen.