SYNOPSIS

Name of Company: Pharmacia & Upjohn **Name of Finished Product:** **Name of Active Ingredient:** Linezolid (PNU-100766)	**Individual study table**	(For national authority use only)

Title of study: Linezolid for the Treatment of Methicillin-Resistant *Staphylococcus* Species (MRSS) Infections: A Randomized, Open-label Trial Comparing Linezolid IV/PO and Vancomycin IV

Protocol number: M/1260/0031 **Document number:** a0052076

Investigator(s): 104 investigator sites; a list of all participating investigators is presented in Appendix 4 of the clinical study report.

Study centers: Multicenter *(North America, Europe, Latin America, Asia)*

Publication (reference): None

Studied period (years): 02 July 1998 – 21 July 1999 **Phase of development:** III

Objectives: To assess the efficacy (clinical and microbiological), safety, and tolerance of intravenously and orally administered linezolid when compared with vancomycin in the treatment of MRSS infections and to determine the direct medical costs required to achieve an acceptable clinical outcome in this population of patients with documented MRSS infections.

Methodology: This Phase III, randomized, open-label, comparator-controlled, multinational, multicenter study was conducted in patients at least 13 years of age with known or suspected MRSS infections. Patients were randomized in a 1:1 ratio to receive one of the following regimens:

- linezolid IV 600 mg every 12 hours for the entire treatment period or switched to linezolid oral 600 mg every 12 hours
- vancomycin IV 1 gram every 12 hours for the entire treatment period

The study consisted of a Baseline/Screening visit, hospitalization during at least the first intravenous dose of study medication, outpatient or inpatient treatment evaluations every 6 days while on treatment after Day 3, an End of Treatment (EOT) visit within 72 hours of the last dose of study medication, follow-up visits based on the type of infection. Clinical and microbiological assessments were performed throughout the study; the Test-of-Cure (TOC) assessments were completed at the short-term follow-up (F-U) visit. Safety was evaluated throughout the study by physical examination, vital sign assessments, laboratory assessments, and adverse events.

Number of patients (planned and analyzed): Approximately 710 (355 per treatment group) patients were to be enrolled. A total of 529 patients were enrolled; 243 patients were randomized to linezolid and 225 patients were randomized to vancomycin; 51 patients were randomized to an arm of the study that was discontinued and not included in the analysis; and 10 treated patients were not included in the analysis because their CRFs were not available when the database was closed (these patients will be described in an addendum to the report).

Diagnosis and main criteria for inclusion: Hospitalized (including chronic care facilities) patients were at least 13 years of age and at least 40 kg in weight. Patients were also required to satisfy all of the following criteria: patients must have a known or suspected *Staphylococcus* infection as determined by laboratory findings consistent with *Staphylococcus* infection (eg, Gram's stain or culture results) and have signs and symptoms of an active infection of pneumonia, skin and soft tissue infection, right-sided endocarditis, urinary tract infection, or bacteremia.

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Exclusion criteria: Patients were excluded from participation in the study if they met any of the following criteria: Females of childbearing potential who were unable to take adequate contraceptive precautions, were pregnant or breastfeeding; had left-sided endocarditis, osteomyelitis, or CNS infections; had infected devices that could not be removed; known to have pheochromocytoma, carcinoid syndrome, untreated hyperthyroidism, or uncontrolled hypertension; were previously enrolled in this protocol or another linezolid protocol; were hypersensitive to linezolid or vancomycin or one of the excipients in either drug formulation; had absolute neutrophil count < 500/mm^3, known liver disease with total bilirubin > 5.0 x upper limit of normal (ULN); had more than 24 hours of treatment with a potentially effective antibiotic within 48 hours of study entry (unless the therapy had failed or the pathogen showed drug resistance, with the exception of vancomycin); concurrent use of another investigational medication, or had infection due to organisms known to be resistant to the study medications.

Test product, dose and mode of administration, batch numbers: Linezolid 600 mg IV or oral every 12 hours, Linezolid IV Batch No. - 97C19M99; 97D17M99; 97E21M91; 97F11M98; 98H26Z14; 97L10M99, Linezolid Oral Batch No. - 38,089; 38,197; 38,078
Reference therapy, dose and mode of administration, batch numbers: Vancomycin IV 1 g every 12 hours (dose may have been adjusted by blood level determinations to maintain therapeutic trough), Batch No. 1NA70M; OL,9521; or purchased locally

Duration of treatment: 7 to 28 consecutive days

Criteria for evaluation: The primary efficacy evaluations were based on the resolution of clinical and microbiologic signs and symptoms of infection at the Test-of-Cure visit. Adverse events and changes in vital signs, physical examinations, laboratory test results, and concomitant medication therapy were used to evaluate safety.

Clinically Evaluable Analyses: All of the following criteria were to be satisfied for a patient to be considered Clinically Evaluable:
- The patient fulfilled the study entry criteria
- The patient received at least 80% of the total prescribed study medication without missing 2 or more consecutive doses during the first 7 days of treatment
- The patient returned for a follow-up visit (unless the patient failed at EOT or took another antibiotic due to lack of efficacy)
- The patient did not receive a concomitant antibiotic during the study (unless the antibiotic was given due to lack of efficacy)

Microbiologically Evaluable Analyses: To be Microbiologically Evaluable, in addition to the criteria listed above, patients were required to have a confirmed pathogen(s) from the infection site or blood culture at Baseline and the confirmed pathogen(s) must not have been resistant to either study medication.

Intent to Treat (ITT) and Modified Intent to Treat (MITT) Analyses: The ITT population included all randomized patients who received at least one dose of study medication, and the MITT population included all patients in the ITT population who also had a pathogen isolated at Baseline.

Efficacy: Primary efficacy was assessed by evaluating patient clinical outcome, patient microbiological outcome, and patient overall outcome; secondary efficacy was assessed by evaluating clinical signs and symptoms, individual pathogen eradication rates, body temperature, and white blood cell counts.

Safety: Safety was assessed by the collection and analysis of data on adverse events, clinical laboratory assays, physical examinations, vital signs, and concomitant medications.

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Statistical methods: The primary efficacy variables in this study were patient clinical outcome (investigator's and sponsor's assessment), patient microbiological outcome, and patient overall (combined clinical/microbiological) outcome. For each of these, the proportions of patients in each outcome category were compared between treatment groups at F-U using a chi-square test for homogeneity of proportions. In addition, for all primary efficacy variables, 95% confidence intervals (CI) for the differences in success rates between the treatment groups were calculated. These analyses were done separately for Clinically Evaluable, Microbiologically Evaluable, ITT, and MITT patients. Other endpoints, including secondary efficacy variables, safety, and Baseline demographics, were analyzed for treatment differences using a chi-square test or a one-way analysis of variance F tests. Laboratory safety results and vital signs were analyzed for changes from Baseline to each post-Baseline visit within treatment groups using a paired t-test and for treatment group comparisons of mean changes from Baseline using a one-way analysis of variance F-test. Details of the statistical methods are presented in Section 9.8 of the clinical study report.

Results:

Demographic and other Baseline characteristics:
In general, patients in both treatment groups were comparable at Baseline with respect to mean weight and the distribution of patients by race, sex, and geographic region. There was a statistically significant difference between treatment groups with regard to mean age: the linezolid group had a mean age of 63.9 years and the vancomycin group had a mean age of 59.8 years (p=0.0157). Patients were also comparable at Baseline with respect to vital signs (temperature, systolic and diastolic blood pressure, mean arterial pressure [MAP] [calculated], pulse, and respiration rate), lesion size (length, width, and area), duration of infection, medical history, physical examination data, diagnosis, primary site of infection, degree of involvement, clinical signs and symptoms, and safety laboratory parameters.

Disposition of patients:	Linezolid	Vancomycin
ITT Patients	240	220
MITT Patients	157	144
Clinically Evaluable Patients	124	130
Microbiologically Evaluable Patients	64	70

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Efficacy results:

Linezolid and vancomycin were equally effective in treating MRSA and MRSE infections, including pneumonia, SST, UTI, Other, and bacteremia of unknown source. This effect was consistent across all primary and secondary efficacy assessments, including the Investigator's Assessment of Clinical Outcome, Sponsor's Assessment of Clinical Outcome, Patient Microbiological Outcome, and Patient Overall Outcome. The cure rate for the Investigator's Assessment of Clinical Outcome was 94.2% (97/103) in the linezolid treatment group and 87.3% (96/110) in the vancomycin treatment group in the Clinically Evaluable population. For the Sponsor's Assessment of Clinical Outcome, the cure rate for Clinically Evaluable patients at F-U was 77.0% (94/122) for the linezolid group and 74.4% (87/117) for the vancomycin group.

In the Microbiologically Evaluable population, the microbiological success rate was 59.4% (38/64) for linezolid-treated patients and 64.2% (43/67) for vancomycin-treated patients. The cure rate for Patient Overall Outcome was 57.8% (37/64) for linezolid-treated patients and 60.9% (39/64) for vancomycin-treated patients. Clinical and microbiological results were not influenced by the primary source of infection or pathogen. In general, the effectiveness of the two treatments was similar among subgroups and comparable to that observed in the overall analyses. Linezolid was as effective as vancomycin in eradicating *S aureus* and coagulase negative *Staphylococcus*, regardless of primary source of MRSS infection.

Safety results:

There were no treatment-group differences in the percentage of patients with one or more treatment-emergent adverse event (68.3% [164/240] of the linezolid group and 61.8% [136/220] of the vancomycin group). The percentage of patients with drug-related adverse events was significantly greater in the linezolid group compared with the vancomycin group (18.3% [44/240] of the linezolid group and 8.2% [18/220] of the vancomycin group). However, the percentages of patients experiencing drug-related adverse events resulting in the discontinuation of study medication were comparable between treatment groups. A total of 4.2% (10/240) of patients in the linezolid group and 4.5% (10/220) of patients in the vancomycin group experienced adverse events resulting in the discontinuation of study medication. Most adverse events were of mild or moderate intensity. Most adverse events occurred at similar frequencies between treatment groups, with the exception of events in the digestive system, such as diarrhea and nausea. These events are often experienced during oral antibiotic treatment. A total of 26.7% (64/240) of patients in the linezolid treatment group and 25.5% (56/220) of patients in the vancomycin treatment group experienced at least one serious adverse event. A total of 16.7% (40/240) of patients in the linezolid treatment group and 13.6% (30/220) of patients in the vancomycin treatment group died; however, no deaths were judged to be related to the study medication. The clinical laboratory data, physical examination observations, vital sign results, and noninvestigational medication use were generally similar among treatment groups and typical for a patient population undergoing treatment for methicillin-resistant *Staphylococcus* species infections. There did not appear to be any clinically significant treatment-group differences in these parameters.

Health Economics results are reported separately.

Conclusion:
Linezolid is as safe and effective as vancomycin in the treatment of methicillin-resistant *Staphylococcus* species infections (MRSA and MRSE).

Date of the report: 22 September 1999

Table 1. Study-Emergent Adverse Events ≥2% Within Body Systems: ITT Patients

COSTART Body System /MET	Linezolid N = 240		Vancomycin N = 220	
	n	%†	n	%†
Patients With None	76	31.7	84	38.2
Patients With at Least One	164	68.3	136	61.8
BODY				
Abdominal Pain Generalized	2	0.8	5	2.3
Fever	7	2.9	5	2.3
Headache	7	2.9	5	2.3
Infection Bacterial NOS	8	3.3	3	1.4
Localized Edema	6	2.5	4	1.8
Localized Pain	10	4.2	7	3.2
Microbiological Test Abnormal NOS	3	1.3	5	2.3
Sepsis	11	4.6	11	5.0
Trauma	10	4.2	7	3.2
CARDIOVASCULAR				
Congestive Heart Failure	5	2.1	2	0.9
Hypotension	7	2.9	5	2.3
Thrombosis	5	2.1	0	-
DIGESTIVE				
Constipation	11	4.6	6	2.7
Diarrhea	26	10.8	9	4.1
Multiple Organ Failure	4	1.7	5	2.3
Nausea	23	9.6	10	4.5
Vomiting	15	6.3	8	3.6
HEMIC AND LYMPHATIC				
Anemia	13	5.4	8	3.6
Thrombocytopenia	5	2.1	1	0.5
METABOLIC AND NUTRITIONAL				
Healing Abnormal	1	0.4	5	2.3
NERVOUS				
Agitation	5	2.1	4	1.8
Insomnia	6	2.5	3	1.4
RESPIRATORY				
Dyspnea	7	2.9	6	2.7
Pharyngitis	2	0.8	5	2.3
Pneumonia	7	2.9	7	3.2
Respiratory Failure	8	3.3	6	2.7
SKIN				
Pruritus Non-application Site	5	2.1	6	2.7
Rash	9	3.8	8	3.6
UROGENITAL				
Infection Urinary Tract	13	5.4	16	7.3
Kidney Failure	6	2.5	4	1.8

† Percentages are based on the number of patients reporting. Patients are only counted once for each MET.
MET (Medically Equivalent Term) is a standardized version of the adverse event verbatim based on COSTART conventions.
ITT = Intent-to-Treat; NOS = Not otherwise specified; COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms
Study Report Reference: Section 14, Table 7.3; Appendix 15, Table S-4

Table 2. Study-Emergent Drug-Related Adverse Events Within Body System Which Occurred in ≥2% of All Patients: ITT Patients

COSTART Body System/MET	Linezolid N = 240		Vancomycin N = 220	
	n	%†	n	%†
Patients With None	196	81.7	202	91.8
Patients With at Least One	44	18.3	18	8.2
DIGESTIVE				
Diarrhea	9	3.8	0	-
Nausea	6	2.5	1	0.5

† Percentages are based on the number of patients reporting.
Note: Drug-related is defined as events specified as related or with relatedness not reported.
MET (Medically Equivalent Term) is a grammatically synthesized version of the adverse event verbatim.
ITT = Intent-to-Treat; COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms
Study Report Reference: Section 14, Table 7.6; Appendix 15, Table S-6

Table 3. Frequency Table for Selected Substantially Abnormal Laboratory Values (Corrected for Baseline Abnormalities): ITT

Laboratory Assay	Criteria*	Linezolid			Vancomycin		
		n	N	%	n	N	%
WBC (x 1000/cu mm)	<75% of LLN	3	232	1.29	2	212	0.94
Neutrophils (x 1000/cu mm)	<0.5 LLN	2	231	0.87	4	211	1.90
Platelet Count (x 1000/cu mm)	<75% of LLN	23	230	10.00	6	210	2.86
RBC (x million/cu mm)	<75% of LLN	35	232	15.09	19	211	9.00
Hemoglobin (g/dL)	<75% of LLN	37	232	15.95	25	212	11.79
Hematocrit (%)	<75% of LLN	27	231	11.69	15	212	7.08
ALT (U/L)	>2 x ULN	13	231	5.63	19	216	8.80
AST (U/L)	>2 x ULN	9	231	3.90	17	215	7.91
Amylase (U/L)	>2 x ULN	8	233	3.43	6	218	2.75

N = Total number of patients with at least one observation of the given laboratory parameter while on study.
n = Total number of patients with a substantially abnormal value.
* Criteria 1 is displayed. For patients with an abnormality at baseline, Criteria 1 plus Criteria 2 must be met.
LLN = lower limit of normal
ULN = upper limit of normal
Study Report Source: Section 14, Table 8.4