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 (PNU-100766) in the Treatment of *Streptococcus pneumoniae* Pneumonia: An Open-Label Study of Intravenously Administered Linezolid with Oral Continuation Compared with Intravenously Administered Ceftriaxone Sodium Followed by Orally Administered Cefpodoxime Proxetil

Protocol number: M/1260/0033 **Document number:** a0052354

Investigator(s): All of the 110 investigators recruited for this study (located in 30 countries worldwide) enrolled patients in the study; a list of the investigators is provided in Appendix 4 of the clinical study report.

Study center(s): Multicenter (North America, Latin America, Asia, and Europe [including Australia and South Africa])

Publication (reference): None

Studied period (years): 04 January 1998
25 May 1999 **Phase of development:** III

Objectives: The objectives of this study were to assess the efficacy (clinical and microbiological) of linezolid when compared with cephalosporin therapy in the treatment of *Streptococcus pneumoniae* pneumonia, and to assess the safety and tolerance of linezolid in the treatment of *S pneumoniae* pneumonia.

Methodology: This Phase III, randomized, open-label (initially evaluator-blinded), comparator controlled, multicenter study was conducted in patients with demonstrated or presumptive *S pneumoniae* pneumonia. Patients were randomized in a 1:1 ratio to receive either of the following regimens:

- Linezolid IV 600 mg every 12 hours followed by oral linezolid 600 mg every 12 hours for 7 to 14 consecutive days
- Ceftriaxone IV 1 g every 12 hours followed by oral cefpodoxime 200 mg every 12 hours for 7 to 14 consecutive days

The study consisted of a Baseline/Screening visit; inpatient treatment (if necessary, patients could be hospitalized for the entire study); outpatient treatment, including a study visit at Day 7 (± 2 days), an EOT visit; and a Follow-up (F-U) visit. The Test-of-Cure (TOC) evaluation was conducted at the F-U visit, 15 to 21 days after the final dose of study medication. Safety was evaluated throughout the study by clinical observations, vital sign assessments, laboratory evaluations, and assessment of adverse events.

Number of patients (planned and analyzed): Approximately 650 patients (325 per treatment group) were to be enrolled. A total of 759 patients were enrolled. Of these, 747 received study medication; 381 patients received linezolid and 366 patients received ceftriaxone/cefpodoxime.

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Diagnosis and main criteria for inclusion: Patients at least 13 years of age with demonstrated or presumptive *S pneumoniae* pneumonia were eligible for enrollment if they had at least 2 of the following symptoms: cough; production of purulent sputum or a change (worsening) in character of the sputum, auscultatory findings on pulmonary exam of rales and/or pulmonary consolidation (dullness on percussion, bronchial breath sounds, or egophony); dyspnea, tachypnea, or hypoxemia, particularly if any or all of these were progressive in nature; or an organism consistent with a respiratory pathogen isolated from sputum or blood cultures. In addition, eligible patients had at least 1 of the following conditions: fever, elevated total peripheral white blood cell (WBC) count >10,000/mm^3, >15% immature neutrophils (bands) regardless of total peripheral WBC, or leukopenia with total WBC <4,500/mm^3. A chest radiograph at Baseline or within 48 hours had to be consistent with a diagnosis of pneumonia. Eligible patients had to provide a respiratory, blood, or pleural fluid specimen for microbiological evaluation that proved consistent with *S pneumoniae* infection, and eligible patients had to have a survival expectancy of at least 60 days.

Main exclusion criteria: Patients were excluded from participation in the study if they had loculated empyema or lung abscess; cystic fibrosis or known or suspected tuberculosis; known bronchial obstruction or a history of post-obstructive pneumonia; untreated hyperthyroidism, pheochromocytoma, carcinoid syndrome, or uncontrolled or untreated hypertension; known or suspected pulmonary conditions, eg, granulomatous diseases, lung cancer, or another malignancy metastatic to the lungs; previous antibiotic treatment for the current episode of pneumonia for more than 24 hours, unless documented to be a treatment failure (72 hours treatment and not responding); females of child-bearing potential who were unable to take adequate contraceptive precautions, had a positive pregnancy test result within 24 hours prior to study entry, were otherwise known to be pregnant, or were currently breastfeeding an infant; had received another investigational drug within 30 days prior to Baseline; had previously been enrolled in any study using linezolid; had hypersensitivity to oxazolidinones or any of the excipients in either the oral or IV formulation of linezolid, or hypersensitivity to aztreonam, ceftriaxone, or cefpodoxime; had liver disease or neutropenia as defined by laboratory criteria (total bilirubin > 5 X Upper Limit of Normal, or neutrophil count < 500 cells/mm^3; or infection due to organisms known to be resistant to either of the study medication regimens before study entry.

Test product, dose and mode of administration, batch numbers:

Linezolid (Pharmacia & Upjohn)	Manufacturing Lot
2 mg/mL (100-mL IV bag):	97B27M98, 97C19M99, 97L10M99
2 mg/mL (200–mL IV bag):	97D30M98, 97K19M99
2 mg/mL (300-mL IV bag):	98H26Z14
600 mg oral tablet:	38,089, 38,188

Reference therapy, dose and mode of administration, batch numbers:

Cefpodoxime (Pharmacia & Upjohn):	200 mg oral tablet; 56BRB, 98BKM
Ceftriaxone (Roche Laboratories): 1 g/vial;	5899-01, 5927, PM9420B

Duration of treatment: 7 to 14 consecutive days for both treatment groups

Criteria for evaluation: The primary efficacy evaluation was based on Patient Microbiological Outcome. Secondary evaluations were based on the resolution or improvement of clinical signs and symptoms at the TOC visit. Safety was evaluated throughout the study by clinical observations, vital sign assessments, laboratory evaluations, and assessment of adverse events.

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Clinically Evaluable Analyses: Patients were considered Clinically Evaluable if the following criteria were met:

- The patient had a positive chest radiograph at Baseline (within 48 hours of study entry) consistent with the diagnosis of pneumonia.
- The patient did not start taking a potentially effective antibiotic before taking the first dose of study medication that continued during treatment.
- The patient did not discontinue study medication, for any reason other than lack of efficacy, before 7 days and 14 doses.
- The patient received at least 80% of the prescribed study medications without missing 2 or more consecutive doses through the first 7 days of treatment.
- The patient did not receive a potentially effective concomitant noninvestigational antibiotic for an adverse event or intercurrent illness (unless the antibiotic was given due to lack of efficacy).
- The patient had a post-Baseline assessment in the F-U analysis window (12-28 days after end of treatment) unless the Investigator's Clinical Outcome was a failure at the end of treatment, or the patient was given an antibiotic for lack of efficacy any time during study.

Microbiologically Evaluable Analyses: To be Microbiologically Evaluable, in addition to meeting the criteria for Clinical Evaluability, patients were required to have a causative pathogen isolated from a respiratory specimen or blood culture at Baseline that was not resistant to linezolid or cephalosporin therapy.

Intent to Treat (ITT) and Modified Intent to Treat (MITT) Analyses: The ITT population included all randomized patients who received at least 1 dose of study medication and the MITT population included all patients in the ITT population who also had a pathogen isolated at Baseline.

Efficacy: The primary efficacy evaluation was based on Patient Microbiological Outcome. Secondary efficacy evaluations were based on the resolution or improvement of clinical signs and symptoms at the TOC visit.

Safety: Safety was evaluated throughout the study by clinical observations, vital sign assessments, laboratory evaluations, and assessment of adverse events

Statistical methods: The primary efficacy variable was Patient Microbiological Outcome and the secondary efficacy variables were Patient Clinical Outcome (Investigator's and Sponsor's assessments) and Patient Overall Outcome, clinical signs and symptoms, chest radiograph results, body temperature, respiration rate, WBC counts, and individual pathogen eradication rates. For Patient Microbiological Outcome, Patient Clinical Outcome, and Patient Overall Outcome, the proportions of patients in each category were compared between treatment groups at F-U using a chi-square test for homogeneity of proportions. In addition, 95% confidence intervals (CI) for the differences in success rates between the treatment groups were calculated. These analyses were done separately for the Clinically Evaluable, Microbiologically Evaluable, ITT, and MITT patients. Other endpoints, including safety and Baseline demographics, were analyzed for treatment differences using a chi-square test or a one-way analysis of variance model. 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 model. Details of the statistical methods are presented in Section 9.8 of the clinical study report.

RESULTS:

Demographic and other baseline characteristics: Patients in both treatment groups were comparable at Baseline with respect to age, vital signs (temperature, blood pressure, calculated mean arterial pressure [MAP], pulse and respiration rate), weight, sex, race, medical history, physical examination data, diagnosis, clinical signs and symptoms, and safety laboratory parameters.

Disposition of patients:

	Linezolid	Ceftriaxone/Cefpodoxime
ITT Patients	381	366
MITT Patients	128	126
Clinically Evaluable Patients	276	258
Microbiologically Evaluable Patients	90	95

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Efficacy results: Linezolid and ceftriaxone/cefpodoxime were equally effective in treating community-acquired pneumonia (CAP), including *S pneumoniae* pneumonia. This effect was consistent across all primary and secondary efficacy assessments, including Microbiological Outcome, Investigator's Assessment of Clinical Outcome, Sponsor's Assessment of Clinical Outcome, and Patient Overall Outcome. In the Microbiologically Evaluable population, microbiological success rates (Microbiological Outcome) were 89.9% for linezolid-treated patients and 87.1% for ceftriaxone/cefpodoxime-treated patients; the same percentages were observed for clinical cure rates (Sponsor's Assessment of Clinical Outcome) in this population. Linezolid was clinically and microbiologically more effective than cephalosporin treatment in patients with *S pneumoniae* bacteremia. For patients with bacteremia in the Microbiologically Evaluable population, microbiological success rates (Microbiological Outcome) were 93.3% for linezolid-treated patients and 69.6% for ceftriaxone/cefpodoxime-treated patients (p=0.0224); the same percentages were observed for clinical cure rates (Sponsor's Assessment of Clinical Outcome) for Microbiologically Evaluable patients with bacteremia. In the ITT and MITT study populations, linezolid was significantly more effective than ceftriaxone/cefpodoxime in patients less than 65 years of age. However, in general, the effectiveness of the 2 treatments was similar among subgroups and comparable to that observed in the overall analyses. The microbiological eradication rates for linezolid and ceftriaxone/cefpodoxime were comparable for the primary pathogens (*H influenzae*, *S aureus*, and *S pneumoniae*). Serologic outcome will be analyzed and reported in a separate study report.

Safety results:
The percentage of patients who experienced study-emergent adverse events was similar between treatment groups, but the percentage of patients with drug-related adverse events was significantly greater in the linezolid group than in the ceftriaxone/cefpodoxime group. This was not caused by a difference in the frequencies of adverse events in any particular body system. There were only a small number of adverse events experienced by ≥2% of either treatment group, and most adverse events were of mild or moderate intensity and of limited duration; the majority of adverse events did not lead to study medication discontinuation. The most common adverse events occurred at similar frequencies between treatment groups and included events such as diarrhea, nausea, and headache which are often experienced during antibiotic treatment. Vomiting occurred more frequently in the linezolid than the ceftriaxone/cefpodoxime group. The percentage of patients who discontinued due to an adverse event was slightly higher in the linezolid group than in the ceftriaxone/cefpodoxime group; however, serious adverse events and deaths occurred in similar percentages of patients in each group. The clinical laboratory data, physical examination observations, vital sign results, and noninvestigational medications use were unremarkable and typical of this patient population. In addition, there was no evidence of an interaction involving monoamine oxidase inhibition between linezolid and any concomitant noninvestigational medications. There did not appear to be any substantial difference in clinical risk between treatment groups indicated by these parameters.

Conclusion: Linezolid was well-tolerated, safe, and effective in the treatment of CAP, including *S pneumoniae* pneumonia. Linezolid and ceftriaxone/cefpodoxime were equally effective in treating CAP. Linezolid was clinically and microbiologically more effective than cephalosporin treatment in patients with *S pneumoniae* bacteremia. In general, the effectiveness of the 2 treatments was similar among subgroups and comparable to that observed in the overall analyses. The microbiological eradication rates for linezolid and ceftriaxone/cefpodoxime were comparable. Although drug-related adverse events overall and drug-related events causing treatment discontinuation were more frequent in linezolid-treated patients than in ceftriaxone/cefpodoxime-treated patients, the overall frequencies of these events were low and did not appear to represent a substantial difference in clinical risk for patients.

Date of the report: 03 September 1999

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

COSTART Body System /MET‡	Linezolid N = 381		Ceftriaxone/Cefpodoxime N = 366	
	n	%†	n	%†
Patients With None	163	42.8	166	45.4
Patients With at Least One	218	57.2	200	54.6
DIGESTIVE				
Diarrhea	42	11.0	33	9.0
Nausea	24	6.3	17	4.6
Vomiting	19	5.0	7	1.9
Monilia Oral	14	3.7	3	0.8
Liver Function Tests Abnormal NOS	10	2.6	5	1.4
Constipation	8	2.1	8	2.2
BODY				
Headache	28	7.3	21	5.7
Chest Pain	7	1.8	9	2.5
Fever	7	1.8	12	3.3
Back Pain	2	0.5	9	2.5
SKIN				
Rash	10	2.6	12	3.3
Herpes Simplex Dermatitis	8	2.1	4	1.1
NERVOUS				
Insomnia	9	2.4	12	3.3
Anxiety	8	2.1	2	0.5
UROGENITAL				
Moniliasis Vaginal	9	2.4	2	0.5
RESPIRATORY				
Pneumonia	5	1.3	14	3.8
Dyspnea	3	0.8	11	3.0
Respiratory Failure	3	0.8	8	2.2

† Percentages are based on the number of patients reporting.
‡ MET (Medically Equivalent Term) is a standardized version of the adverse event verbatim based on COSTART conventions.
NOS = Not otherwise specified.
Study Report Reference: Section 14, Table 7.3; Appendix 15, Table S-4.

Table 2. Study-Emergent Drug-Related Adverse Events ≥2% Within Body System: ITT

COSTART Body System/MET‡	Linezolid N = 381		Ceftriaxone/Cefpodoxime N = 366	
	n	%†	n	%†
Patients With None	300	78.7	325	88.8
Patients With at Least One	81	21.3	41	11.2
DIGESTIVE				
Diarrhea	17	4.5	11	3.0
Nausea	13	3.4	5	1.4
Monilia Oral	10	2.6	2	0.5
Liver Function Tests Abnormal NOS	9	2.4	1	0.3
UROGENITAL				
Moniliasis Vaginal	8	2.1	2	0.5

† Percentages are based on the number of patients reporting.

‡ MET (Medically Equivalent Term) is a standardized version of the adverse event verbatim based on COSTART conventions.

Note: Drug-related is defined as events specified as related to or with relatedness not reported.

Study Report Reference: Section 14, Table 7.6; Appendix 15, Table S-4.

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

Laboratory Assay	Criteria*	Linezolid			Ceftriaxone/Cefpodoxime		
		n	N	%	n	N	%
WBC (x 1000/cu mm)	<75% of LLN	7	376	1.86	7	358	1.96
Neutrophils (x 1000/cu mm)	<0.5 LLN	1	353	0.28	5	336	1.49
Platelet Count (x 1000/cu mm)	<75% of LLN	6	374	1.60	4	356	1.12
RBC (x million/cu mm)	<75% of LLN	6	375	1.60	9	358	2.51
Hemoglobin (g/dL)	<75% of LLN	13	376	3.46	8	358	2.23
Hematocrit (%)	<75% of LLN	7	376	1.86	5	358	1.40
ALT (U/L)	>2 x ULN	36	357	10.08	29	339	8.55
AST (U/L)	>2 x ULN	19	358	5.31	20	341	5.87
Amylase (U/L)	>2 x ULN	10	380	2.63	9	361	2.49

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