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 Community-Acquired Pneumonia: an Investigator-Blind, Randomized, Comparator-Controlled Study in Outpatients.

Protocol number: M/1260/0051 **Document number:** a0051432

Investigator(s): 103 investigator sites; a list of all participating investigators is presented in Appendix 4 of the clinical study report.

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

Publication (reference): none

Studied period (years): 30 September 1998 to 14 April 1999 **Phase of development:** III

Objectives: To assess the comparative efficacy (clinical and microbiologic) of linezolid versus cephalosporin (cefpodoxime) therapy in the outpatient treatment of adult community-acquired pneumonia (CAP), and to assess safety and tolerance.

Methodology: This Phase III, investigator-blind, comparator-controlled study was conducted in adult patients with CAP. Patients were randomized in a 1:1 ratio to receive orally either of the following regimens:

- 600 mg linezolid every 12 hours for 10 to 14 consecutive days
- 200 mg cefpodoxime proxetil every 12 hours for 10 to 14 consecutive days

The study consisted of five visits: a Baseline/Screening visit, Patient Treatment Evaluation visits (Days 3 and 9 ± 1 day) after treatment initiation, an End-of-Treatment (EOT) visit within 72 hours of the last dose of study medication, and a Follow-up (F-U) visit 15 to 21 days after study medication was stopped. Clinical assessments were performed at each visit; the Test-of-Cure (TOC) assessments were completed at the F-U visit. Safety was evaluated throughout the study by physical examination, vital sign assessments, laboratory assessments, and adverse events (AEs).

Number of patients (planned and analyzed): Approximately 406 (203 per treatment group) patients were to be enrolled. A total of 548 patients were enrolled; 278 patients were randomized to linezolid and 270 patients were randomized to cefpodoxime.

Diagnosis and main criteria for inclusion: Adult patients who developed pneumonia while living in the community (ie, CAP) with at least 2 of the following symptoms were eligible for participation in the study: 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 organism consistent with a respiratory pathogen isolated from respiratory, sputum, or blood cultures.

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Main exclusion criteria: Patients were excluded from participation in the study if they had an infection due to organisms known to be resistant to either of the study medication regimens before study entry or had received 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).

Test product, dose and mode of administration, manufacturing lot numbers: 600-mg oral linezolid tablets, one tablet every 12 hours (manufacturing lot Nos. 38,188; 38,197)

Reference therapy, dose and mode of administration, manufacturing lot numbers: 200-mg oral cefpodoxime tablets, one tablet every 12 hours (manufacturing lot Nos. 82BWX; 32BWC)

Duration of treatment: 10 to 14 consecutive days for both treatments

Criteria for evaluation: The primary efficacy evaluation was based on the resolution or improvement in clinical signs and symptoms of infection at the TOC visit. Safety was evaluated by analyzing adverse events (AEs) and changes in vital signs, physical examinations, and laboratory test results.

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

- The patient had a positive chest radiograph at Baseline (within 48 hours of study entry), indicative of pneumonia.
- The patient did not start taking an antibiotic before taking the first dose of study medication that continued during treatment.
- The patient did not discontinue study medication before study Day 7 and 14 doses for any reason other than lack of efficacy.
- The patient received at least 80% of the prescribed study medication without missing 2 or more consecutive doses during the first 7 days of treatment.
- The patient did not receive a potentially effective concomitant antibiotic during the study (unless the antibiotic was given due to lack of efficacy).
- The patient had a post-Baseline assessment in the F-U analysis window 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 at any time during the study.

Microbiologically Evaluable Analyses: To be Microbiologically Evaluable, in addition to the criteria listed above, patients were required to have a confirmed pathogen from a respiratory or blood specimen at Baseline and the confirmed pathogen 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 (investigator's and sponsor's assessments) and secondary efficacy was evaluated by patient microbiologic outcome, patient overall outcome (combined clinical/microbiologic), individual pathogen eradication rates, and clinical signs and symptoms.

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 variable in this study was patient clinical outcome (investigator's and sponsor's assessments) and the secondary efficacy variables were patient microbiologic outcome and patient overall outcome, individual pathogen eradication rates, and clinical signs and symptoms. For patient clinical outcome, patient microbiologic 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 at F-U 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 via Chi-square tests or one-way analysis of variance models. Safety laboratory results and vital signs were analyzed for statistical changes from Baseline to each post-Baseline visit 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, systolic and diastolic blood pressure, calculated mean arterial pressure [MAP], pulse, respiration rate), weight, sex, race, medical history, physical examination data, diagnosis, clinical signs and symptoms, and safety laboratory parameters.

Disposition of patients:

	Linezolid	Cefpodoxime
ITT Patients	272	268
MITT Patients	60	60
Clinically Evaluable Patients	205	212
Microbiologically Evaluable Patients	50	47

Efficacy Results: Linezolid and cefpodoxime were equally effective in treating CAP. 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, and Patient Overall Outcome. In the linezolid group, the cure rate at F-U for the Investigator's Assessment of Clinical Outcome was 96.8% in the Clinically Evaluable population versus 96.4% for cefpodoxime–treated patients. For the Sponsor's Assessment of Clinical Outcome, the cure rate at F-U for the Clinically Evaluable population was 89.6% for patients in the linezolid treatment group and 90.8% for patients in the cefpodoxime treatment group. For both assessments of clinical outcome, 95% CIs for treatment group differences in cure rate were consistent with equivalence for Clinically Evaluable patients, and success rates (cured or improved) at EOT were similar to F-U cure rates The cure rate for Patient Overall Outcome in the MITT population was 81.8% for linezolid-treated patients and 80.8% for cefpodoxime–treated patients. The results for microbiologic outcome were similar between the two treatment groups among the MITT, Clinically Evaluable, and Microbiologically Evaluable patients. In the Microbiologically Evaluable population, the microbiologic success rate was 87.8% for linezolid-treated patients and 89.4% for cefpodoxime-treated patients. Clinical and microbiologic results were not influenced by the Baseline pathogen.

In subgroup analyses by sex, age, race, and region, the effectiveness of the two treatments was generally similar among subgroups and comparable to that observed in the overall analyses. Sponsor's assessment of clinical outcome, patient microbiologic outcome, and patient overall outcome at F-U were comparable for both treatment groups for the major pathogens *H influenzae*, *S aureus*, and *S pneumoniae*.

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Safety results: The percentages of patients with any AEs, drug-related AEs, SAEs, and AEs resulting in study medication discontinuation were statistically greater in linezolid-treated patients compared with cefpodoxime-treated patients. However, most reported AEs were mild or moderate, and only 1 SAE was considered drug related, suggesting that the differences between treatment groups in overall AE frequency do not represent substantial differences in patient risk. There were only a small number of adverse events experienced by ≥2% of either treatment group. The most common adverse events occurred at similar frequencies between treatment groups, and some of the more commonly reported events such as diarrhea and nausea are often experienced during antibiotic treatment. There were 2 deaths reported in the linezolid treatment group; neither was deemed related to the study medication. The clinical laboratory data, physical examination observations, vital sign results, and noninvestigational medications use were unremarkable and typical of this patient population. There did not appear to be any clinically significant treatment group differences in hematologic, pancreatic, or liver function parameters. Analysis of subgroups receiving concomitant MAOIs or MAOI-interacting medications showed no evidence of drug-drug interaction.

Conclusion: In this clinical trial, linezolid and cefpodoxime were equally effective in the treatment of CAP. Although the percentage of patients who experienced study-emergent or drug-related AEs was greater in the linezolid group compared with cefpodoxime, the reported AE intensity was largely mild to moderate, and there were few SAEs reported. There were two deaths reported in the linezolid group in this study, but neither was related to the study medication.

Date of the report: 26 August 1999

Table 1. Frequencies of Study-Emergent AEs ≥ 2% Within Body Systems: ITT

COSTART Body System/MET	Linezolid N=272		Cefpodoxime N=268	
	No.	%†	No.	%†
Patients With None	108	39.7	153	57.1
Patients With at Least One	164	60.3	115	42.9
DIGESTIVE				
Diarrhea	27	9.9	24	9.0
Dyspepsia	11	4.0	2	0.7
Liver Function Tests Abnormal NOS	6	2.2	0	-
Nausea	22	8.1	13	4.9
Vomiting	11	4.0	6	2.2
BODY				
Abdominal Pain, Generalized	9	3.3	0	-
Chest Pain	9	3.3	7	2.6
Fatigue	6	2.2	4	1.5
Headache	28	10.3	20	7.5
RESPIRATORY				
Abnormal Lung Sounds	3	1.1	9	3.4
Cough	10	3.7	9	3.4
Dyspnea	9	3.3	3	1.1
Pneumonia	12	4.4	6	2.2
Rhinitis	10	3.7	4	1.5
Sputum Increased	3	1.1	8	3.0
NERVOUS				
Dizziness	8	2.9	8	3.0
Insomnia	12	4.4	7	2.6
SKIN				
Rash	6	2.2	0	-

† Percentages were based on the number of patients reporting.
MET (Medically Equivalent Term): standardized terminology based on COSTART conventions and the verbatim description of the adverse event.
NOS = not otherwise specified.
Study Report Reference: Section 14, Table 7.3; Appendix 15 Listing S-4.

Table 2. Frequencies of Study-Emergent Drug-related AEs ≥ 2% Within Body Systems: ITT

COSTART Body System/MET	Linezolid N=272		Cefpodoxime N=268	
	No.	%†	No.	%†
Patients With None	186	68.4	220	82.1
Patients With at Least One	86	31.6	48	17.9
DIGESTIVE				
Diarrhea	22	8.1	16	6.0
Nausea	15	5.5	9	3.4
Vomiting	6	2.2	2	0.7
BODY				
Headache	11	4.0	8	3.0
NERVOUS				
Insomnia	7	2.6	5	1.9

† Percentages were based on the number of patients reporting.
MET (Medically Equivalent Term) = standardized terminology based on COSTART conventions and the verbatim description of the adverse event.
Study Report Reference: Section 14, Table 7.6; Appendix 15, Listing S-4.

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

Laboratory Assay	Criteria*	Linezolid			Cefpodoxime		
		n	N	%	n	N	%
WBC (x 1000/cu mm)	<75% of LLN	11	266	4.14	4	266	1.50
Neutrophils (x 1000/cu mm)	<0.5 LLN	9	266	3.38	2	266	0.75
Platelet Count (x 1000/cu mm)	<75% of LLN	4	265	1.51	1	266	0.38
RBC (x million/cu mm)	<75% of LLN	0	266	0.00	1	266	0.38
Hemoglobin (g/dL)	<75% of LLN	2	266	0.75	1	266	0.38
Hematocrit (%)	<75% of LLN	1	266	0.38	3	266	1.13
ALT (U/L)	>2 x ULN	13	265	4.91	14	266	5.26
AST (U/L)	>2 x ULN	8	265	3.02	8	266	3.01
Amylase (U/L)	>2 x ULN	1	266	0.38	2	266	0.75

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