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ORIGINAL ARTICLE

A randomized, double-blind, multicenter Phase II study comparing the efficacy and safety of oral nemonoxacin with oral levofloxacin in the treatment of community-acquired pneumonia

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Abstract *Background/Purpose:* To compare the clinical efficacy and safety of nemonoxacin with levofloxacin in treating community-acquired pneumonia (CAP) in a Phase II clinical trial.
Methods: One hundred ninety-two patients with CAP were randomized to receive oral nemonoxacin (500 mg or 750 mg) or levofloxacin (500 mg) once daily for 7—10 days. Clinical and bacteriological responses were determined at the test of cure (TOC) visit in the full analysis set (FAS).
Results: The clinical cure rate of nemonoxacin (500 mg), nemonoxacin (750 mg), and levofloxacin (500 mg) was 93.3%, 87.3%, and 88.5%, respectively, in the FAS ($n = 168$), and 93.0%, 93.9%, and 88.9%, respectively in the per protocol set ($n = 152$). At the TOC visit, nemonoxacin at 500 mg and 750 mg was proven to be noninferior to levofloxacin at 500 mg in the FAS in terms of clinical efficacy. The overall bacteriological success rate was 83.3% in both nemonoxacin groups and 80.0% in the levofloxacin 500 mg group in the bacteriological FAS. The comprehensive efficacy rate was comparable among the three groups (87.5% for the nemonoxacin 500 mg group, 93.8% for the nemonoxacin 750 mg group, and 81.3% for the levofloxacin 500 mg group). Most drug-related adverse events were mild and transient, mainly gastrointestinal symptoms such as nausea and vomiting, transient neutropenia, and elevated liver enzymes. No drug-related serious adverse events occurred.
Conclusion: Either 500 mg or 750 mg of oral nemonoxacin taken once daily for 7—10 days demonstrated high clinical and bacteriological success rates in Chinese adult patients with CAP. Nemonoxacin at 500 mg once daily for 7—10 days is recommended for future Phase III clinical trials.
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Introduction

Community-acquired pneumonia (CAP) is a common lower respiratory tract infection with high morbidity and mortality.[1,2] Community-acquired pneumonia can be caused by a variety of pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenza*, and *Mycoplasma pneumoniae*.[3,4] In recent years the emergence and spread of antibiotic-resistant pathogens has become big challenge in the clinical management of CAP. In 2013, the China net (CHINET) of bacterial resistance surveillance data showed that the prevalence of penicillin-intermediate *S. pneumoniae* (PISP) and penicillin-resistant *S. pneumoniae* (PRSP) increased up to 32.9% (PISP 11.6%; PRSP, 21.3%) and 9.4% (PISP, 5.4%; PRSP, 4.0%) in isolates from children and adults, respectively.[5] Surveillance studies also showed a high prevalence of *S. pneumoniae* strains that were resistant to erythromycin or clindamycin, especially in PISP and PRSP strains.[6] Quinolone drugs are active against CAP pathogens such as penicillin nonsusceptible *S. pneumoniae* and are recommended for adult CAP.[2]

Nemonoxacin, a nonfluorinated quinolone targeting DNA gyrase and topoisomerase IV, has broad-spectrum activity against gram-positive pathogens and some atypical

pathogens, which include penicillin-resistant *S. pneumoniae* and methicillin-resistant *Staphylococcus aureus* (MRSA).[7–11] Nemonoxacin is also active against gram-negative bacteria such as *H. influenzae* and *Klebsiella pneumoniae*.[7,11] One study in mice showed that the efficacy of nemonoxacin was better than that of levofloxacin in treating gram-positive bacterial infections such as infection by PRSP and MRSA.[12]

Previous Phase I studies have been conducted in healthy volunteers in the United States and China to examine the safety and clinical pharmacokinetics (PK) of nemonoxacin after single and multiple oral doses.[6,13,14] After oral administration, nemonoxacin is absorbed rapidly and well tolerated. Within 1–2 hours after oral administration, nemonoxacin attains peak plasma concentration (C_{max}), and exhibits a linear PK profile within a dose range of 250–750 mg. The C_{max} [i.e., area under the curve from 0 to infinity ($AUC_{0-\infty}$)] was dose-dependent after multiple doses. Nemonoxacin is excreted primarily in urine. Approximately 60–70% of the drug was eliminated within 72 hours in its unchanged form. The elimination half-life is 9–16 hours. There is no accumulation after administering it for 10 consecutive days.[6,13]

In 2010, Van Rensburg et al[15] reported a clinical trial that investigated the efficacy and safety of nemonoxacin, compared to that of levofloxacin in CAP outpatients.[15] They found that nemonoxacin was noninferior to levofloxacin in either the evaluable intent-to-treat population or clinical per protocol (PPc) population. Both treatments were well tolerated without any serious drug-related adverse reactions.

We conducted a randomized, double-blind, multicenter clinical trial to evaluate the safety and efficacy of 500 mg and 750 mg oral doses of nemonoxacin, compared to 500 mg levofloxacin, administered once daily for 7–10 days in treating patients with CAP in the Chinese population.

Methods

Study design

A Phase II, randomized, double-blind, double dummy, multicenter study was designed to compare the efficacy and safety of oral nemonoxacin with that of levofloxacin in Chinese adult patients with CAP. The primary objective of this study was to demonstrate the noninferiority of nemonoxacin versus levofloxacin with regard to safety and clinical efficacy. The study was conducted in compliance with good clinical practice guidelines and the Declaration of Helsinki. The study protocol was approved by the Ethics Committees of all participating institutions. All patients provided written informed consent before enrollment in the study.

Study treatments

Eligible patients were randomized from August 2009 to August 2010 to one of three treatment groups in a 1:1:1 ratio to receive an oral dose of 500 mg or 750 mg nemonoxacin (TaiGen Biotechnology Co., Ltd., Taipei, Taiwan) or 500 mg levofloxacin and a matched placebo. The drugs were administered once daily for 7–10 days. Immediately after enrollment, the first dose was administered on site in the clinic. For all subsequent doses, the patients took their study drug in the every morning.

Inclusion criteria

Male and female patients were eligible if they were 18–70 years old, had a body weight within the range of 40–100 kg, had a body mass index (BMI) of $\geq 18\ kg/m^2$, and had a diagnosis of mild to moderate CAP. The diagnosis was based on two or more of the following clinical manifestations and a chest radiograph showing new lobar or multilobar infiltrates consistent with CAP within 48 hours. Clinical manifestations included (1) productive cough with purulent sputum or deterioration of existing respiratory symptoms; (2) fever (i.e., oral temperature $\geq 37.3^{\circ}C$); (3) evidence of pulmonary consolidation and/or rales; (4) peripheral white blood cell count of $> 10 \times 10^9$ cells/L or $< 4 \times 10^9$ cells/L or a neutrophil level $> 70\%$. Criterion (2) or (4) had to be present when patients were enrolled.

Exclusion criteria

Pregnant or lactating women were excluded from the study. Individuals were also excluded if they had any of the following conditions: lung diseases such as active tuberculosis, bronchiectasis, lung abscess, aspiration pneumonia, lung malignancies, noninfectious interstitial lung disease, pulmonary edema, atelectasis, pulmonary embolism, pulmonary eosinophilia or pulmonary vasculitis, nosocomial pneumonia; history of hypersensitivity or allergic reaction to any quinolone drug; history of epilepsy, mental disorders, or other diseases of the central nervous system; renal failure; liver dysfunction; malabsorption syndrome or other gastrointestinal disease; immunodeficiency status such as HIV infection, CD4+ count of $<200/mm^3$ or neutropenia, or blood or solid organ malignancies; long-term use of steroids; severe pneumonia; 12-lead electrocardiogram that shows abnormal cardiac conduction or QT interval prolongation (male, QTc $>$ 430 milliseconds; female, QTc $>$ 450 milliseconds); treatment with chemotherapeutic drugs or oncolytics within 6 months before randomization or requiring such agents during the trial; alcohol or drug abuse; administration of any quinolone within 2 weeks before randomization; received any investigational drug within 3 months before enrollment; donation of 500 mL of blood within 3 months; or requiring combined antimicrobial therapy because of dual infection.

Primary and secondary endpoints

Clinical response at the test of cure (TOC) visit (i.e., 7–10 days posttreatment) was the primary efficacy endpoint of this study. Cinical efficacy was defined as "clinical cure" (i.e., complete resolution of all signs and symptoms of pneumonia, or recovery to the pretreatment state); as "clinical failure" (i.e., persistence or worsening of signs and symptoms after therapy, or the emergence of

new pneumonia-related symptoms or signs and/or use of other antimicrobial therapy targeting pneumonia; or discontinuation within 3 days after the initiation of study treatment because of an adverse drug reaction); or as "unevaluable" (e.g., missing posttreatment information, use of systemic antimicrobial agents for other indications not permitted by protocol, or early discontinuation of treatment because of other causes unrelated to the study drug).

Secondary endpoints included clinical and bacteriological response at the end of treatment in the full analysis set (FAS) and per protocol set and at the TOC in the per protocol set.

Microbiological assessment

Before the first dose of study drug, sputum samples were collected by every reasonable effort for Gram stain and culture. Atypical pathogens were identified by serological assay. Microbiological response was categorized as "eradication" (i.e., the original pathogens were absent at the TOC visit), "presumed eradication" (i.e., the patient was considered clinically cured but a repeat sputum/blood culture was absent), and "persistence" (i.e., the original pathogens persisted at the TOC visit), and "presumed persistence" (i.e., the patient still had clinical signs and symptoms but a repeat sputum culture was absent). Antimicrobial susceptibility test of nemonoxacin and levofloxacin was performed by microdilution assay, based on Clinical and Laboratory Standard Institute document M100-S21 (2011). Only patients with positive admission cultures were included in the bacteriological response analysis.

Comprehensive efficacy assessment

Clinically evaluable patients with positive bacterial culture at baseline were included for comprehensive assessment. The clinical signs and symptoms, radiologic and laboratory tests, and microbiological examination were combined to evaluate the comprehensive efficacy. Comprehensive response was categorized as "cure" (i.e., at the TOC visit, the clinical response was cure and the microbiological response was eradication or presumed eradication) and "failure" (i.e., at the TOC visit, the clinical response was failure or the microbiological response was persistence or presumed persistence). Comprehensive efficacy was evaluated as "failure" if one clinical or microbiological response was a failure and another response was missing, and evaluated as "unknown" if one clinical or microbiological response was cure/presumed eradication and the other response was missing.

Safety assessment

All clinical and laboratory adverse events that occurred during clinical trial were carefully observed and recorded for all patients who received at least one dose of the study drug. The adverse events were categorized as "definitely related," "probably related," "possibly related," "possibly unrelated" or "definitely unrelated," based on their relation to the study drug.

Patient populations

The following five patient populations were defined in this study for the analysis of clinical and microbiological efficacy.

(1) Full analysis set (FAS): all patients were included in the full analysis set, except for patients who did not receive any study drug, did not have the target disease, were noncompliant with good clinical practice, or were missing follow-up information after the first visit.
(2) Per protocol set (PPS): all patients in the FAS were included in the per protocol set, except for patients inadequately enrolled with an exclusion criterion; patients who required treatment by other effective antibiotics, but not patients who were evaluated as a failure at the end of treatment and then received other antibiotic therapy; or noncompliant patients, as evidenced by taking $< 80\%$ or $> 120\%$ of the individual's prescribed dose.

The FAS and PPS were applicable for efficacy analysis. Clinical response at the TOC visit in FAS was the primary efficacy endpoint of this study.

(3) Safety set (SS): all patients who received at least one dose of the study drug were included in the SS. The SS was applicable for safety analysis.
(4) Bacteriological full analysis set (BFAS): all patients in the FAS whose first sputum culture or blood culture was positive were included.
(5) Bacteriological per protocol set (BPPS): all patients in the PPS whose first sputum culture or blood culture was positive were included.

Statistical analysis

SAS 9.1.3 software (North Carolina, USA) was used for all statistical analysis. Noninferiority was defined as the lower limit of the 95% confidence interval (CI) for the difference between groups being greater than -15%. In addition to noninferiority analysis, two-sided exact 95% CI was used to compare the difference of clinical success rates between treatment groups.

Results

Patient disposition

One hundred and ninety-two patients were randomized in this study from 21 centers in China: 168 patients who received at least one dose of the study drug in the FAS (60 patients in the nemonoxacin 500 mg group, 56 patients in the nemonoxacin 750 mg group, and 52 patients in the levofloxacin group); 152 patients in the PPS (57 patients in the nemonoxacin 500 mg group, 50 patients in the nemonoxacin 750 mg group, and 45 patients in the levofloxacin group); 177 patients in the SS (62 patients in the nemonoxacin 500 mg group, 59 patients in the nemonoxacin

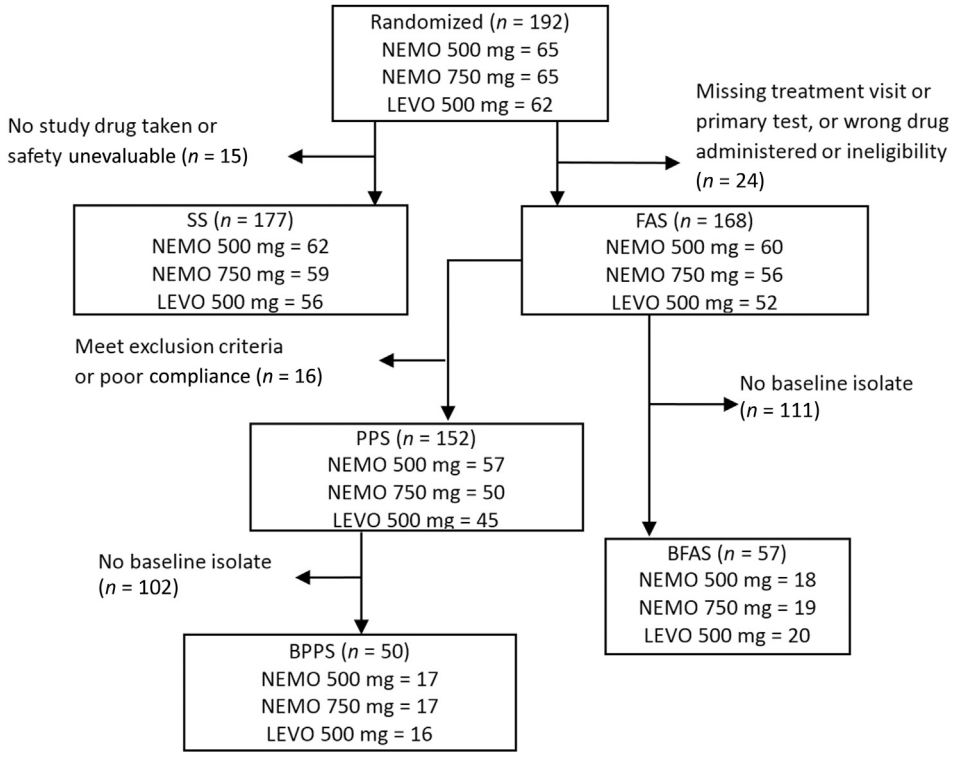

Figure 1. Patient disposition flow chart. BFAS = bacteriological full analysis set; BPPS = bacteriological per protocol set; FAS = full analysis set; LEVO = levofloxacin; NEMO = nemonoxacin; PPS = per protocol set; SS = safety set.

750 mg group, and 56 patients in the levofloxacin group). There were 57 patients in the BFAS and 50 patients in the BPPS (Figure 1).

Demographic characteristics such as age, sex, race, height, weight, BMI, history of smoking and drinking were comparable between the three treatment groups. The mean age of the patients was 38.5 ± 14.4 years in the nemonoxacin 500 mg group, 38.3 ± 15.4 years in the nemonoxacin 750 mg group, and 39.7 ± 15.1 years in the levofloxacin 500 mg group. The mean BMI was 22.5 ± 3.6 kg/m^2 in the nemonoxacin 500 mg group, 22.6 ± 3.0 kg/m^2 in the nemonoxacin 750 mg group, and 22.2 ± 3.4 kg/m^2 in the levofloxacin 500 mg group. Most patients had no history of smoking (85.7—93.3%) or drinking (76.9—83.9%).

Underlying diseases

The most common underlying disease was hypertension (5.0—7.1%), followed by diabetes mellitus (0—5.4%), tuberculosis (1.8—3.3%), and chronic bronchitis (1.7—3.6%). There was no significant difference between the three groups with regard to underlying diseases in the FAS.

Dose and duration

In the FAS, the mean duration of therapy was 9.4 ± 1.3 days in the nemonoxacin 500 mg group, 9.2 ± 1.9 days in the nemonoxacin 750 mg group, and 9.4 ± 1.7 days in the levofloxacin 500 mg group. The mean total dose administered during the study was 4708.3 ± 619.5 mg in the nemonoxacin 500 mg group, 6910.7 ± 1428.2 mg in the nemonoxacin 750 mg group, and 4682.7 ± 851.9 mg in the levofloxacin 500 mg group.

Clinical efficacy

The clinical primary efficacy variable was evaluated at the TOC visit in the FAS of this study. The clinical cure rate at the TOC in the FAS population was 93.3% in the nemonoxacin 500 mg group, 87.3% in the nemonoxacin 750 mg group, and 88.5% in the levofloxacin 500 mg group (Table 1). No significant difference existed between these three treatment groups. The 95% CI for the treatment difference (4.9%) between the nemonoxacin 500 mg and levofloxacin

Table 1 Clinical response at the test of cure visit

	Nemonoxacin 500 mg *N* (%)	Nemonoxacin 750 mg *N* (%)	Levofloxacin 500 mg *N* (%)
Full analysis set			
Clinical cure	56 (93.3)	48 (87.3)	46 (88.5)
Clinical failure	4 (6.7)	7 (12.7)	6 (11.5)
Unevaluable	0	1	0
Per protocol set			
Clinical cure	53 (93.0%)	46 (93.9%)	40 (88.9%)
Clinical failure	4 (7.0%)	3 (6.1%)	5 (11.1%)
Unevaluable[a]	0	1	0

[a] Unevaluable cases are not included in the denominator.

500 mg groups ranged from −5.86% to 15.61%, whereas the 95% CI for the treatment difference (−1.2%) between the nemonoxacin 750 mg and levofloxacin 500 mg groups ranged from −13.56% to 11.18%. The treatment efficacy of either 500 mg or 750 mg of nemonoxacin was noninferior to that of levofloxacin 500 mg in the FAS population because the lower limit of 95% CI of the treatment difference was greater than −15%. The noninferiority of nemonoxacin at 500 mg or 750 mg to levofloxacin at 500 mg was demonstrated in the treatment of adult CAP patients.

The PPS population at the TOC visit also showed no significant difference between these three treatment groups (Tables 1 and 2).

Logistic regression analysis showed no significant difference in clinical efficacy between nemonoxacin 500 mg, nemonoxacin 750 mg, and levofloxacin 500 mg groups in the FAS and PPS populations ($p > 0.05$; Table 3).

Clinical response was also assessed at the TOC visit in terms of primary baseline pathogens, which were identified in 90 (53.6%) of the 168 patients in the FAS (Table 4). Sixty-one strains of bacteria were isolated from 57 patients, and 33 atypical pathogens were identified serologically. All patients with *S. pneumoniae* isolates ($n = 11$) or *S. aureus* isolates ($n = 4$) were cured in the three groups, except for treatment failure in one patient with the *S. pneumoniae* isolate in the levofloxacin 500 mg group. Of the 18 patients infected with *H. influenzae*, 15 patients were cured, but there were treatment failures in each of the three groups. One patient in the nemonoxacin 750 mg group and two patients in the levofloxacin 500 mg group who were infected with *K. pneumoniae* were evaluated as treatment failure. The remaining 13 patients with the *K. pneumoniae* isolate at baseline were cured. Thirty-three patients in the FAS were infected with only atypical pathogens, which included *M. pneumoniae* ($n = 29$), *Chlamydia pneumoniae* ($n = 1$), and *Legionella pneumophila* ($n = 3$). Treatment failure was determined for one patient with single *M. pneumoniae* infection in the nemonoxacin 750 mg group. The other 32 patients with atypical pathogen infection were cured.

Bacteriological efficacy

The bacteriological primary efficacy was evaluated at the TOC visit in the BFAS in this study. Sixty-one pathogens were isolated at baseline from 57 patients in the BFAS population, and included 20 strains in the nemonoxacin 500 mg group, 19 strains in the nemonoxacin 750 mg group and 22 strains in the levofloxacin 500 mg group. The bacteriological response at the TOC visit in the BFAS and BPPS populations is presented by the treatment group in Table 5.

The bacteriological success rate for the bacteriological evaluable set was 83.3% (15/18) (in the nemonoxacin 500 mg group and nemonoxacin 750 mg group) and 80.0% (16/20) in the levofloxacin 500 mg group. There was no significant difference between the three treatment groups, based on logistic regression analysis.

The most common pathogens among the 61 pathogens isolated at baseline were *S. pneumoniae*, *H. influenza*, and *K. pneumoniae*, followed by some strains of *S. aureus* (including MRSA) and *Pseudomonas aeruginosa*. At the TOC visit, all baseline strains were eradicated in the nemonoxacin 500 mg and 750 mg groups: *S. pneumoniae* (6 strains), *S. aureus* (including MRSA, 4 strains), and *H. influenzae* (5 strains). The *K. pneumoniae* and *P. aeruginosa* strains were eradicated, except one strain each in the nemonoxacin 750 mg group. All baseline isolates in the levofloxacin 500 mg group were eradicated, except one *S. pneumoniae* strain, one *H. influenzae* strain, and two *K. pneumoniae* strains.

All the common respiratory pathogens isolated from this study including *S. pneumoniae and H. influenzae* were susceptible to nemonoxacin and levofloxacin (Table 6). *Staphylococcus aureus* including three MRSA strains were also sensitive to nemonoxacin.

Comprehensive efficacy

The comprehensive efficacy was evaluated in terms of clinical and bacteriological efficacy at the TOC visit in the BPPS population of this study. Fifty patients were included for the assessment of comprehensive efficacy, which included 17 patients each in the nemonoxacin 500 mg and 750 mg groups and 16 patients in the levofloxacin 500 mg group. The comprehensive success rate at the TOC in the BPPS population was 87.5% in the nemonoxacin 500 mg group, 93.8% in the nemonoxacin 750 mg group, and 81.3% in the levofloxacin 500 mg group. Logistic regression

Table 2 Clinical efficacy and treatment difference between the three groups at the test of cure visit

	Levofloxacin 500 mg	Nemonoxacin 500 mg			Nemonoxacin 750 mg		
	N (%)	*N* (%)	Treatment Difference (%)	*p* (95% CI)	*N* (%)	Treatment Difference (%)	*p* (95% CI)
Full analysis set	46 (88.5)	56 (93.3)	4.9	0.569 (−5.86, 15.61)	48 (87.3)	−1.2	0.71 (−13.56, 11.18)
Per protocol set	40 (88.9)	53 (93.0)	4.1	0.851 (−7.23, 15.42)	46 (93.9)	5.0	0.62 (−6.39, 16.36)

CI = confidence interval.
Treatment difference = nemonoxacin group − levofloxacin.group.

Table 3 Logistic regression analysis of the efficacy of nemonoxacin treatments compared with levofloxacin at the test of cure visit

	Nemonoxacin 500 mg			Nemonoxacin 750 mg		
	OR 95% CI	Wald χ^2	*p*	OR 95% CI	Wald χ^2	*p*
Full analysis set	1.83 (0.49, 6.86)	0.7947	0.3727	0.89 (0.28, 2.86)	0.0354	0.8508
Per protocol set	1.66 (0.42, 6.57)	0.5155	0.4728	1.92 (0.43, 8.53)	0.7297	0.3930

CI = confidence interval; OR, the ratio between nemonoxacin treatment and levofloxacin in the clinical efficacy rate.

Table 4 Clinical efficacy at the test of cure visit by primary baseline pathogens in the full analysis set

Pathogen	Number of isolates	Nemonoxacin 500 mg	Nemonoxacin 750 mg	Levofloxacin 500 mg
		*n*1/*n*2 (%)[a]	*n*1/*n*2 (%)[a]	*n*1/*n*2 (%)[a]
Typical pathogen				
Streptococcus. pneumoniae	11	2/2 (100)	4/4 (100)[b]	3/4 (75.0)
Staphylococcus aureus[c]	4	2/2 (100)	2/2 (100)	0/0
Haemophilus influenzae	9	3/3 (100)	2/2 (100)	3/4 (75.0)
Haemophilus parainfluenzae	9	2/3 (66.7)	3/4 (75.0)	2/2 (100)
Klebsiella pneumoniae	16	4/4 (100)	2/3 (66.7)	7/9 (77.8)
Atypical pathogen only				
Mycoplasma pneumoniae	29	7/7 (100)	13/14 (92.9)	8/8 (100)
Legionella pneumophila	3	2/2 (100)	0/0	1/1 (100)
Chlamydia pneumoniae	1	0/0	1/1 (100)	0/0

[a] *n*1 = the number of clinical cure; *n*2 = total number of the patients treated.
[b] There were five *Streptococcus pneumoniae* isolates at the end of treatment. One strain was unevaluable because the patient received acetylspiramycin before the test of cure visit.
[c] Among the four *Staphylococcus aureus* isolates, three isolates are methicillin-resistant: two isolates are in the nemonoxacin 500 mg group and one isolate is in the nemonoxacin 750 mg group.

Table 5 Bacteriological efficacy at the test of cure visit by treatment group

	Nemonoxacin 500 mg *N* (%)	Nemonoxacin 750 mg *N* (%)	Levofloxacin 500 mg *N* (%)
Bacteriological full analysis set [a]			
Bacteriological success[b]	15 (83.3)	15 (83.3)	16 (80.0)
Bacteriological failure[c]	3 (16.7)	3 (16.7)	4 (20.0)
Unevaluable	0	1	0
Bacteriological per protocol set			
Bacteriological success	14 (82.4)	15 (93.8)	13 (81.3)
Bacteriological failure	3 (17.7)	1 (6.2)	3 (18.7)
Unevaluable	0	1	0

[a] *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila* are not included.
[b] Bacteriological success includes eradication and presumed eradication.
[c] Bacteriological failure includes persistence, presumed persistence, and partial eradication.

analysis did not reveal a significant difference between the three treatment groups.

Safety and tolerability

One hundred and seventy-seven patients who received at least one dose of the study drug were included in the SS population. Sixty-two patients received 500 mg of nemonoxacin, 59 patients received 750 mg of nemonoxacin, and 56 patients received 500 mg of levofloxacin. The incidence of treatment emergent adverse events (TEAEs) was 41.9% in the nemonoxacin 500 mg group, 55.9% in the nemonoxacin 750 mg group, and 42.9% in the levofloxacin 500 mg group (Table 7). The incidence of drug-related TEAEs was similar between the nemonoxacin 500 mg, nemonoxacin 750 mg, and levofloxacin 500 mg groups at 30.6%, 35.6%, and 25.0%, respectively ($p > 0.05$).

Twenty-eight drug-related TEAEs occurred in 19 patients in the nemonoxacin 500 mg group: three clinical adverse events (AEs; primarily anorexia, nausea, and epigastric

Table 6 *In vitro* susceptibilities of primary baseline isolates to the study drugs

Bacteria (*n*)	Nemonoxacin			Levofloxacin		
	MIC range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)
Streptococcus pneumoniae[a] (13)	≤0.015−1	0.125	0.25	0.03−1	0.25	0.5
Staphylococcus aureus[b] (4)	0.06−1			0.125−32		
Klebsiella pneumoniae (19)	≤0.06−>32	0.5	32	≤0.06−>32	0.125	>32
Haemophilus influenzae and *Haemophilus parainfluenzae* (16)	≤0.008−1	0.06	1	≤0.008−1	0.06	1

[a] Thirteen *Streptococcus pneumoniae* strains were isolated from all randomized groups. Two strains are excluded from the bacteriological full analysis set because the patient took the wrong drugs.
[b] The MIC_{50} and MIC_{90} were not calculated because of the few number of strains.
MIC = minimal inhibitory concentration; MIC_{50}/MIC_{90} = the lowest concentration of an antibiotic at which 50% and 90% of the isolates are inhibited.

Table 7 Summary of the most common treatment-related adverse events (≥2% in any one group) by system organ and preferred term

System organ class and preferred term	Nemonoxacin 500 mg (*N* = 62) *n* (%)	Nemonoxacin 750 mg (*N* = 59) *n* (%)	Levofloxacin 500 mg (*N* = 56) *n* (%)
Patients with any treatment-related adverse event	19 (30.6)	21 (35.6)	14 (25.0)
Digestive system			
Nausea	1 (1.6)	6 (10.2)	1 (1.8)
Vomiting	0	4 (6.8)	2 (3.6)
Stomach upset	0	2 (3.4)	1 (1.8)
Blood and lymphatic system			
Leukopenia	4 (6.5)	6 (10.2)	4 (7.1)
Neutropenia	2 (3.2)	2 (3.4)	2 (3.6)
Percentage of eosinophils increased	2 (3.2)	1 (1.7)	0
Percentage of neutrophils increased	1 (1.6)	2 (3.4)	1 (1.8)
Abnormal Laboratory Value			
Abnormal liver function	0	3 (5.1)	0
Elevated alanine aminotransferase	3 (4.8)	0	1 (1.8)
Elevated urinary protein	0	1 (1.7)	2 (3.6)
Cardiovascular system			
QT interval prolongation	2 (3.2)	3 (5.1)	1 (1.8)
Bundle branch block	2 (3.2)	0	0

discomfort) in three (4.8%) patients and 25 episodes of laboratory abnormalities (primarily leukopenia and elevated alanine aminotransferase level) in 16 (25.8%) patients. No patient had both drug-related adverse and laboratory abnormalities.

Forty-three drug-related TEAEs occurred in 21 subjects in the nemonoxacin 750 mg group: 22 clinical AEs in 12 (20.3%) patients and 21 episodes of laboratory abnormalities in 13 (22.0%) patients. The most common drug-related TEAEs (≥2%) were nausea, vomiting, leucopenia, and abnormal liver function. Four patients experienced both clinical AEs and laboratory abnormalities during the study.

Twenty-four drug-related TEAEs occurred in 14 patients in the levofloxacin 500 mg group: eight clinical AEs in five (8.9%) patients and 16 episodes of laboratory abnormalities in 11 (19.6%) patients. The most common drug-related TEAEs (≥2%) were nausea, vomiting, leukopenia, neutropenia, and elevated urinary protein. Two patients experienced both clinical AEs and laboratory abnormalities during the study.

Drug-related QT interval prolongation occurred in all three treatment groups: 3.2% ($n = 2$) in the nemonoxacin 500 mg group, 5.1% ($n = 3$) in the nemonoxacin 750 mg group, and 1.8% ($n = 1$) in the levofloxacin 500 mg group. Prolongation of the QT interval was shorter than 30 milliseconds in all patients, except in one female patient in the nemonoxacin 750 mg group (557 milliseconds). There were two (3.2%) cases of drug-related cardiac bundle branch block in the nemonoxacin 500 mg group, and one case of drug-related ventricular premature beats in the levofloxacin 500 mg group.

Drug-related TEAEs were mild to moderate, and >90% of TEAEs were mild. The proportion of AEs classified as mild was 96.4% in the nemonoxacin 500 mg group, 93.0% in

the nemonoxacin 750 mg, and 92.0% in the levofloxacin 500 mg. Only one patient in the nemonoxacin 750 mg group experienced facial twitch, which resulted in the discontinuation of the study drug. This symptom disappeared quickly after discontinuation of the study drug. No drug-related serious adverse event was observed in this study.

Discussion

This study demonstrated that oral nemonoxacin at 500 mg or 750 mg, administered once daily for 7—10 days, achieved excellent clinical and microbiological efficacy in the treatment of CAP in Chinese adults. Both doses (i.e., 500 mg and 750 mg) of nemonoxacin were noninferior to levofloxacin (500 mg) for the treatment of adult CAP in primary efficacy at the TOC visit in the FAS population. The microbiological efficacy or bacteriological eradication rate was comparable between the nemonoxacin and levofloxacin regimens.

Our results prove that nemonoxacin is highly active with broad-spectrum activity against major CAP pathogens. Patients with CAP who were infected with *S. pneumoniae*, *H. influenzae*, *M. pneumoniae*, *C. pneumoniae*, or *L. pneumophila* were all cured clinically at the TOC visit. Three of the four *S. aureus* isolates at baseline were MRSA, and all isolates were obtained from the nemonoxacin treatment group patients. All patients with *S. aureus* infection were successfully cured. The excellent clinical and bacteriological efficacy suggests good activity of nemonoxacin against these resistant strains, although the number of patients with MRSA was fewer. *In vitro* studies have shown that nemonoxacin had good activity against gram-positive bacteria such as MRSA.[16,17]

In this trial, nemonoxacin was well tolerated in both treatment groups. More than 93% of the drug-related TEAEs were mild. Only one patient discontinued the study drug because of a TEAE. Drug-related TEAEs were primarily mild gastrointestinal disorders, transient leucopenia, and elevated liver enzymes. The incidence of drug-related TEAEs in the present study was similar to that reported in a South African Phase II clinical trial in which the incidence of AEs was 30.3% in the nemonoxacin 500 mg group, 31.4% in the nemonoxacin 750 mg group, and 30.0% in the levofloxacin 500 mg group. The most common AEs in the South African study were mild gastrointestinal disorders and transient neutropenia.[15]

The overall incidence of drug-related TEAEs in the nemonoxacin 750 mg group (35.6%) was slightly higher than the incidence in the nemonoxacin 500 mg group (30.6%). These findings suggest that the nemonoxacin 500 mg treatment regimen may be safer than the 750 mg regimen in treating adult CAP. In future Phase III clinical trials, the nemonoxacin 500 mg regimen is recommended, based on its similar efficacy and better safety profile in comparison to the 750 mg regimen.

In summary, 500 mg or 750 mg of oral nemonoxacin administered once daily for 7—10 days showed good clinical and microbiological efficacy in treating adult CAP. Either 500 mg or 750 mg nemonoxacin once daily was proven as noninferior to 500 mg levofloxacin at the TOC visit, and both regimens were well tolerated. The incidence of drug-related TEAEs was slightly higher in the nemonoxacin 750 mg group than in the nemonoxacin 500 mg group, but the difference was not significant. Based on the aforementioned results, 500 mg of nemonoxacin administered once daily for 7—10 days is recommended for future Phase III clinical trials.

Conflicts of interest

TaiGen Biotechnology Co., Ltd. provided the study drug nemonoxacin used in this study. L.C. is an employee of TaiGen Biotechnology Co., Ltd.

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