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Original Article

Safety and efficacy of oral nemonoxacin versus levofloxacin in treatment of community-acquired pneumonia: A phase 3, multicenter, randomized, double-blind, double-dummy, active-controlled, non-inferiority trial

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KEYWORDS
Clinical outcome;
Community-acquired pneumonia;
Levofloxacin;
Nemonoxacin;
Randomized controlled trial;
Safety

Abstract *Background/Purpose:* Nemonoxacin is a novel nonfluorinated quinolone with excellent *in vitro* activity against most pathogens in community-acquired pneumonia (CAP), especially Gram-positive isolates. The purpose of this study was to assess the efficacy and safety of nemonoxacin compared with levofloxacin in patients with CAP.
Methods: A phase 3, multicenter, randomized (2:1) controlled trial was conducted in adult CAP patients receiving nemonoxacin 500 mg or levofloxacin 500 mg orally once daily for 7–10 days. Clinical, microbiological response and adverse events were assessed. Non-inferiority was determined in terms of clinical cure rate of nemonoxacin compared with that of levofloxacin in a modified intention-to-treat (mITT) population. NCT registration number: NCT01529476.
Results: A total of 527 patients were randomized and treated with nemonoxacin ($n = 356$) or levofloxacin ($n = 171$). The clinical cure rate at test-of-cure visit was 94.3% (300/318) for nemonoxacin and 93.5% (143/153) for levofloxacin in the mITT population [difference (95% CI), 0.9% (−3.8%, 5.5%)]. The microbiological success rate was 92.1% (105/114) for nemonoxacin and 91.7% (55/60) for levofloxacin in the bacteriological mITT population [difference (95% CI), 0.4% (−8.1%, 9.0%)]. The incidence of adverse events (AEs) was comparable between nemonoxacin (33.1%, 118/356) and levofloxacin (33.3%, 57/171) ($P > 0.05$).
Conclusion: Nemonoxacin 500 mg once daily for 7–10 days is as effective and safe as levofloxacin for treating adult CAP patients in terms of clinical cure rates, microbiological success rates, and safety profile.
ClinicalTrials.gov identifier: NCT01529476.

Introduction

Community-acquired pneumonia (CAP) is a common infectious disease of lower respiratory tract.[1,2] *Streptococcus pneumoniae* remains the most frequently isolated pathogen in CAP patients.[3,4] Other typical pathogens such as *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Klebsiella pneumoniae*[1,4,5] and atypical organisms such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila* have also been implicated.[6–10] Recently, methicillin-resistant *Staphylococcus aureus* (including community-acquired MRSA) is becoming a major pathogen of CAP.[1,12] Widespread antibiotic resistance of common respiratory pathogens is a major challenge in treating this life-threatening condition. The increasing prevalence of penicillin-intermediate *S. pneumoniae* and penicillin-resistant *S. pneumoniae* (PRSP) are of great concern.[11] PRSP strains are typically resistant to the common antibiotics used to treat CAP, such as β-lactams and macrolides. However, for such respiratory pathogens, quinolones are more suitable. The current Infectious Diseases Society of America/American Thoracic Society guidelines on the management of CAP in adults strongly recommend monotherapy with a respiratory fluoroquinolone as an appropriate empirical treatment for adult CAP inpatients and complicated CAP outpatients with cardiopulmonary disease and/or other comorbidities.[12]

Nemonoxacin is a new non-fluorinated quinolone under clinical development for the intravenous treatment of CAP and the oral treatment of diabetic foot ulcer infections, and skin and soft tissue infections. Oral nemonoxacin has been approved in Taiwan and China for the treatment of CAP in adults. It acts on target microorganisms by inhibiting bacterial DNA gyrase and topoisomerase IV. Nemonoxacin has shown broad spectrum of activity against clinically relevant bacteria both *in vitro* and *in vivo*,[13–18] particularly Gram-positive pathogens, including multi-drug resistant strains such as PRSP and MRSA. Nemonoxacin also exhibits potent antibacterial activity against *H. influenzae*, *M. catarrhalis*, *M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila in vitro*.[14,19]

In previous phase 1 clinical trials, doses ranging from 75 to 1000 mg once daily for 10 consecutive days are safe and well-tolerated in healthy subjects. The long half-life of 9–16 h and no accumulation after 10-day dosing support its once daily oral dosing regimen.[20–22]

Phase 2 studies demonstrated that an oral dose of 500 or 750 mg nemonoxacin once daily for 7–10 days resulted in good clinical and microbiological efficacy in the treatment of CAP.[23,24]

The present phase 3 study compared the efficacy and safety of oral nemonoxacin to oral levofloxacin in outpatients with CAP (NCT registration number: NCT01529476). Levofloxacin was chosen as the comparator because it is commonly prescribed worldwide and it is recommended in guidelines for the treatment of CAP.

Methods

Ethical approval

The study was conducted in accordance with the guidelines of the International Conference on Harmonization and the Declaration of Helsinki. The protocol was approved by the independent ethics committees of each participating study site. All patients or their legally authorized representatives provided written informed consent prior to study enrolment.

Study design and participants

This study was a Phase 3, multicenter, randomized, double-blind, double-dummy, active comparator-controlled trial designed to assess the non-inferiority of nemonoxacin versus levofloxacin for the treatment of CAP in adult Chinese patients. This study was registered at ClinicalTrial.gov (NCT01529476). A total of 53 study centres in China and Taiwan region participated in the trial. The study period was from March 2011 to August 2012.

Eligible patients were 18—70 years of age with CAP (defined as fever or white blood cell (WBC) count >10,000/mm^3, or neutrophil count >70%) and at least three of the following: cough, purulent sputum, dyspnoea or tachypnoea, chest pain, and evidence of pulmonary consolidation, and suitable for outpatient therapy with an oral antimicrobial agent. Patients were required to have evidence of new pulmonary exudation or infiltrate (within 48 h before enrolment) and were required to provide a sputum sample that revealed <10 squamous epithelial cells and >25 leukocytes under low-power field.

Patients were excluded if they had severe pneumonia requiring invasive endotracheal ventilation or requiring vasoconstrictor due to septic shock, or at least three of the following: partial pressure arterial oxygen/fraction of inspired oxygen ≤250; respiratory rate ≥30 per min; chest radiograph indicating the presence of multilobar infiltrates; disorder of consciousness; blood urea nitrogen ≥20 mg/dL; hypotension requiring fluid resuscitation; non-diabetic hypoglycemia; acute alcoholism; hyponatremia (Na^+ <130 mM); metabolic acidosis of unknown origin or elevated lactic acid; liver cirrhosis; asplenia syndrome. Additional exclusion criteria included patients with infection acquired during hospitalization or at nursing homes; hospitalization within 14 days before enrolment; viral pneumonia, aspiration pneumonia; history of lung diseases, corrected QT interval (QTc) prolongation, severe cardiac insufficiency, epileptic seizure, hypersensitivity or allergic reaction to any quinolone, fluoroquinolone tendinopathy, myasthenia gravis; 12-lead electrocardiogram (ECG) at screening revealing clinically significant abnormality or QTc interval prolongation; immunodeficiency disease; active hepatitis or decompensated hepatic cirrhosis; chronic renal insufficiency or serum creatinine more than 1.1-fold the upper limit of normal (ULN) at screening; alanine aminotransferase (ALT) or aspartate aminotransferase (AST) more than 3-fold the ULN; total bilirubin or direct bilirubin more than 1.1-fold the ULN within 48 h before enrolment; <1500 neutrophils/mm^3 within 48 h before randomization; or treatment with systemic antimicrobial agent for more than 24 h and within 72 h before enrolment; current or anticipated long-term use (>2 weeks) of prednisone 20 mg per day or equivalent. (Complete list of inclusion/exclusion criteria is available as Supplementary Data).

Randomization and interventions

Block randomization stratified by geographical region using an interactive web response system was adapted to assign patients in a 2:1 ratio to receive nemonoxacin or levofloxacin, both oral 500 mg once daily for 7—10 days. Patients were required to receive a minimum of 3 days of treatment in order to evaluate efficacy assessments. Patients were assessed at the following visits: pretreatment (within 24 h prior to dosing), on treatment (days 4 ± 1), end-of-therapy (1—2 days post-therapy), and test-of-cure (7—14 days post-therapy or early-termination).

Study populations

The intention-to-treat (ITT) population included all the randomized patients who received at least one whole dose of study drug (Figure. 1). The modified ITT (mITT) population included ITT patients who met the minimal disease criteria of CAP and had at least one clinical assessment of cure or failure. The clinically evaluable (CE) population included all the mITT patients who adhered to the protocol without any major protocol violation. The bacteriological mITT (b-mITT) population included the mITT patients who had at least one typical pathogen isolated at baseline. The bacteriologically evaluable (BE) population included the CE patients who had at least one typical pathogen isolated at baseline.

Study endpoints

The primary endpoint was to determine non-inferiority [lower limit of 95% confidence interval (CI) ≥ −10%] of nemonoxacin in terms of the clinical cure rates compared with levofloxacin in the mITT population, with clinical cure or failure determined at the test-of-cure (TOC) visit. Prespecified sensitivity analysis for the primary endpoint was conducted in the mITT population using worst case imputation, namely, a missing or indeterminate clinical assessment was deemed a failure. The following secondary endpoints were evaluated in different populations, for which they were assessed as favourable or unfavourable responses (but not missing or indeterminate): clinical cure rate at the TOC visit in the CE population; clinical cure rate at the end-of-therapy (EOT) visit in the mITT and CE populations; microbiological success rates at the TOC and EOT visits in the b-mITT and BE populations; per-pathogen clinical and microbiological response, and safety.

Efficacy assessment

Clinical response was defined as cure (complete resolution of signs and symptoms of pneumonia with chest radiographs resolved or improvement, no further antibiotic therapy required), failure (persistence or worsening of sign, symptoms and chest radiographs) or indeterminate (unable to determine clinical outcome) at the TOC visit in the mITT populations.

Microbiological success was defined as eradication (the baseline pathogen was absent) and presumed eradication (if an adequate source specimen was not available to culture, but the patient was assessed as clinically cured) at the TOC visit in the b-mITT population. Microbiological failure was defined as persistence and presumed persistence of the baseline pathogen.

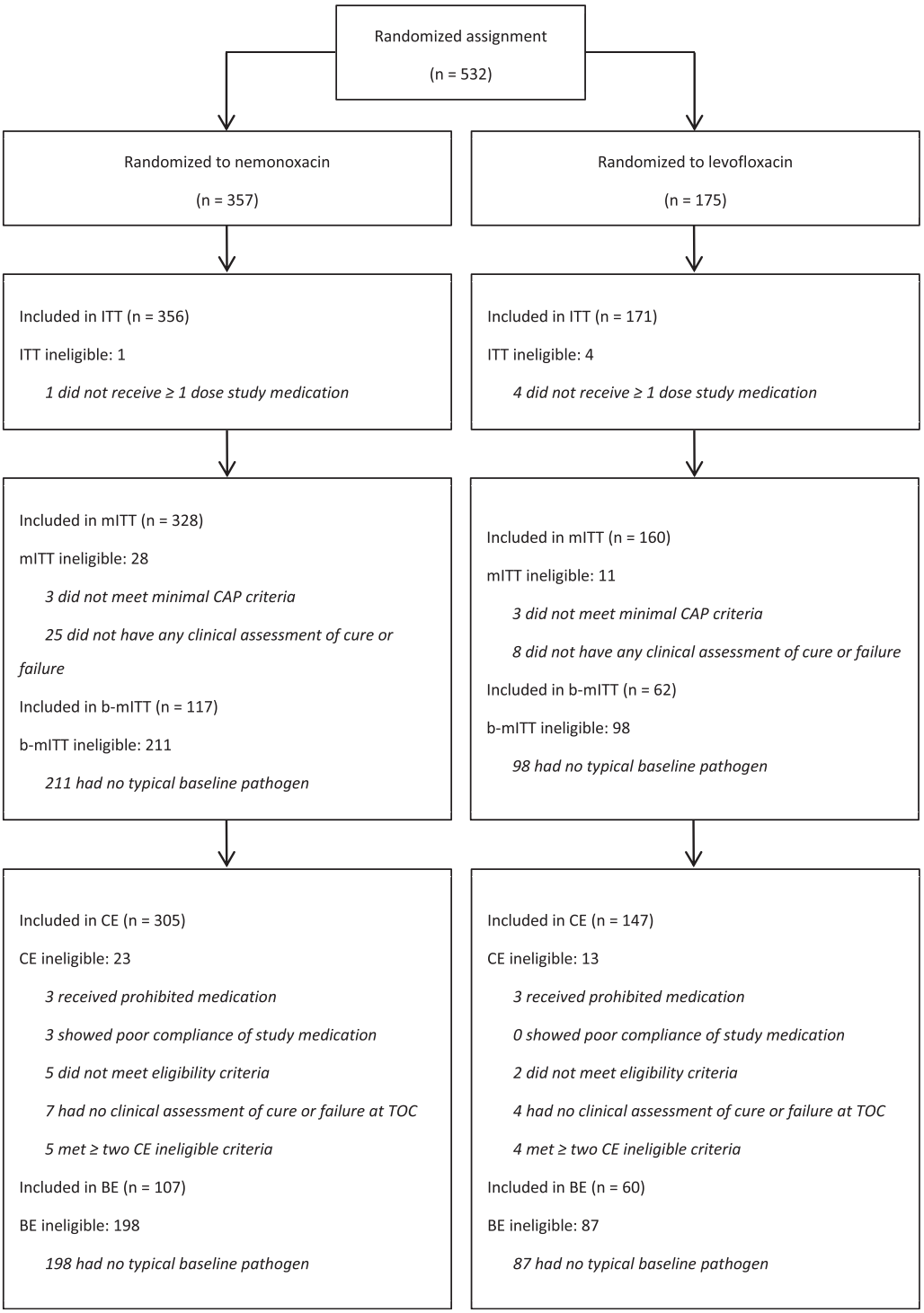

Figure 1. Study flow for enrolment and patient disposition. Proportions of individual analysis populations in all randomized patients (n = 532): ITT, 99.1%; mITT, 91.7%; CE, 85.0%; b-mITT, 33.6%; BE, 31.6%.

Safety assessment

The patients who received at least one dose of the study drug were evaluated for safety (ITT population). Safety evaluation included physical examinations, vital signs, 12-lead electrocardiograms, haematology parameters, serum chemistry tests, urinalysis, and adverse events (AEs). All clinical and investigational AEs or serious adverse events (SAEs) that occurred during study were carefully observed and recorded. AEs and SAEs were defined as per ICH guidelines. Investigators evaluated the severity and relationship to the study drug for each AE. AEs and SAEs were captured from the time after the first dose to 30 days after the last dose of study drug.

Microbiological assessments

Sputum samples were cultured if Gram stain revealed <10 squamous epithelial cells and >25 leukocytes per low-power field. Cultures were performed at local laboratory and all isolates were sent to the central laboratory for re-identification and susceptibility testing using CLSI methodology (CLSI M45-A for the MIC test methods and CLSI M100-S22 for susceptibility interpretive criteria). MICs of nemonoxacin and levofloxacin were determined for all isolates. Serology tests for *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila* were performed at pretreatment and TOC visits. Urine samples were also collected to identify *L. pneumophila* and *S. pneumoniae* by antigen testing.

Statistical analysis

SAS 9.1.3 software was used for all statistical analysis (SAS, Inc., Cary, NC, USA). Two-sided test was used to compare the difference between treatment arms at a significance level of 0.05 except for the test of non-inferiority. The non-inferiority of nemonoxacin to levofloxacin was evaluated using a 2-sided 95% confidence interval (CI) for the difference in clinical cure rate (nemonoxacin minus levofloxacin). Nemonoxacin is considered non-inferior to levofloxacin for the treatment of CAP if the lower limit of the 2-sided 95% CI is greater or equal to −10%. Microbiological response and comprehensive efficacy were assessed based on the results of individual patients and each baseline pathogen. A logistic regression model was used to analyse differences in treatment effect. Microbiological response was also evaluated by visit, specimen source, treatment group, and clinical background using Pearson Chi-square test or Fisher's exact test. Other continuous variables were compared by *t*-test. Categorical variables were compared by Pearson Chi-square test, Fisher's exact test, or Cochran—Mantel—Haenszel chi-square test.

Assuming a point estimate for the clinical cure rate of 85% in both treatment groups, non-inferiority margin of 10%, power of 80%, two-sided 95% CI, and 20% of unevaluable patients, the estimated sample size was 360 for nemonoxacin and 180 for levofloxacin.

Results

Patient disposition and analysis populations

A total of 527 patients were randomized and treated with nemonoxacin ($n = 356$) or levofloxacin ($n = 171$), among which 488 (328 in nemonoxacin group and 160 in levofloxacin group) were in the mITT population and 452 (305 in nemonoxacin group and 147 in levofloxacin group) were in the CE population (Figure. 1). The most frequent reasons for exclusion from the mITT and CE populations are shown in Figure. 1. A total of 179 (117 in nemonoxacin and 62 in levofloxacin group) patients were included in the b-mITT population, and 168 (108 in nemonoxacin group and 60 in levofloxacin group) patients were included in BE population.

Patient demographics and baseline characteristics

The baseline and demographic characteristics of the mITT population are presented in Table 1. All parameters were comparable between the two treatment groups except height and weight, which were slightly lower in nemonoxacin group ($P < 0.05$). However, BMI was not significantly different between the two groups ($P = 0.238$). The baseline signs and symptoms of infection including fever (92.4% in nemonoxacin group, 95% in levofloxacin group), cough, production of purulent sputum, chest pain, dyspnoea and rales, were similar between the two groups ($P > 0.05$).

Clinical efficacy outcomes

This study met its primary endpoint by confirming the non-inferiority of nemonoxacin compared with levofloxacin (Table 2). In the mITT population with evaluable assessment at TOC visit, the clinical cure rate was 94.3% (300/318) for nemonoxacin and 93.5% (143/153) for levofloxacin [difference (95% CI), 0.9% (−3.8%, 5.5%)]. A pre-specified sensitivity analysis using worst case imputation (missing or indeterminate was deemed as failure) supported the primary result, with clinical cure rates of 91.5% (300/328) for nemonoxacin and 89.4% (143/160) for levofloxacin [difference (95% CI), 2.1% (−3.6%, 7.7%)] (available as Supplementary Data). This study also met its key secondary endpoint showing that the clinical cure rate of nemonoxacin was statistically non-inferior to that of levofloxacin in the CE population at the TOC visit (Table 2). The results at the EOT visit in the mITT and CE populations were consistent with the findings of non-inferiority of nemonoxacin at the TOC visit (Table 2).

Microbiological efficacy outcomes

The overall recovery rates of pathogens (typical and atypical combined) in the mITT population were 53.7% (176/328) for nemonoxacin and 52.5% (84/160) for levofloxacin.

Microbiological response rate was evaluated in the b-mITT and BE populations at the TOC visit. In the b-mITT population with evaluable assessment at the TOC visit, the microbiological success rate was 92.1% (105/114) for nemonoxacin compared to 91.7% (55/60) for levofloxacin [difference (95% CI), 0.4% (−8.1%, 9.0%)] (Table 3). Similar results were also observed in BE population. Thus, nemonoxacin was non-inferior to levofloxacin in terms of microbiological efficacy.

Microbiological responses to individual pathogens

The eradication rate of common baseline CAP pathogens (nemonoxacin *vs.* levofloxacin) was 100% (17/17) *vs.* 90.9% (10/11) for *S. pneumoniae*, 94.1% (16/17) *vs.* 87.5% (7/8) for *S. aureus*, 90.6% (29/32) *vs.* 91.7% (11/12) for *Haemophilus species*, and 92.3% (36/39) *vs.* 92.0% (23/25) for *Klebsiella species* (Table 4).

The MICs of nemonoxacin and levofloxacin against major baseline isolates in all randomized patients were determined (available as Supplementary Data). Nemonoxacin

Table 1 Baseline characteristics of patients in modified intention-to-treat population.

	Nemonoxacin (n = 328)	Levofloxacin (n = 160)	Total (n = 488)	P value
Age, years, mean (SD)	43.6 (14.9)	43.6 (14.5)	43.6 (14.8)	0.978
Sex, *n* (%)				0.121
Male	169 (51.5)	95 (59.4)	264 (54.1)	
Female	159 (48.5)	65 (40.6)	224 (45.9)	
Race, *n* (%)				
Asian	328 (100.0)	160 (100.0)	488 (100.0)	
Ethnic group, *n* (%)				0.927
Han	319 (97.3)	155 (96.9)	474 (97.1)	
Others	9 (2.7)	5 (3.1)	14 (2.9)	
Height, cm, mean (SD)	164.4 (7.9)	166.0 (8.6)	164.9 (8.2)	0.048
Weight, kg, mean (SD)	61.5 (10.7)	63.6 (10.8)	62.2 (10.8)	0.035
BMI, kg/m^2, mean (SD)	22.7 (3.2)	23.0 (3.0)	22.8 (3.2)	0.238
History of smoking, *n* (%)				0.358
Non-smoker	254 (77.4)	117 (73.1)	371 (76.0)	
Ex-smoker	9 (2.7)	8 (5.0)	17 (3.5)	
Current smoker	65 (19.8)	35 (21.9)	100 (20.5)	
History of drinking, *n* (%)				0.279
Non-drinker	266 (81.1)	127 (79.4)	393 (80.5)	
Ex-drinker	9 (2.7)	9 (5.6)	18 (3.7)	
Current drinker	53 (16.2)	24 (15.0)	77 (15.8)	
Underlying diseases, *n* (%)				>0.05
Hypertension	32 (9.8)	14 (8.8)	46 (9.4)	
Diabetes mellitus	11 (3.4)	9 (5.6)	20 (4.1)	
Chronic obstructive pulmonary disease	10 (3.0)	7 (4.4)	17 (3.5)	
Chronic bronchitis	11 (3.4)	4 (2.5)	15 (3.1)	
Hepatitis B	11 (3.4)	1 (0.6)	12 (2.5)	
Hyperlipidaemia	5 (1.5)	4 (2.5)	9 (1.8)	
Allergic rhinitis	7 (2.1)	2 (1.3)	9 (1.8)	

SD, standard deviation.

showed slightly higher activity than levofloxacin against *S. pneumoniae* (including one PRSP strain) and *S. aureus* (including two MRSA strains), with MIC_{50}/MIC_{90} of 0.125/0.125 mg/L (nemonoxacin) and 1.0/1.0 mg/L (levofloxacin) for *S. pneumoniae* and 0.03/0.125 mg/L (nemonoxacin) and 0.125/1.0 mg/L (levofloxacin) for *S. aureus*. Nemonoxacin was also as active as levofloxacin against *Haemophilus* species and *Klebsiella* species.

Safety

A total of 527 patients were included in the safety population (356 in nemonoxacin group and 171 in levofloxacin group). The incidence rate of treatment-emergent AEs (TEAEs) was similar between nemonoxacin (33.1%) and levofloxacin (33.3%). Most TEAEs were mild to moderate in severity. The AEs occurred more frequently in the system

Table 2 Clinical cure rates by study population.[a]

Assessment visit	mITT population			CE population		
	Nemonoxacin *n* (%)	Levofloxacin *n* (%)	Difference, % (95% CI)	Nemonoxacin *n* (%)	Levofloxacin *n* (%)	Difference, % (95% CI)
TOC						
Cure	300 (94.3)	143 (93.5)	0.9 (−3.8, 5.5)	290 (95.1)	138 (93.9)	1.2 (−3.4, 5.8)
Failure	18 (5.7)	10 (6.5)		15 (4.9)	9 (6.1)	
Missing or indeterminate	10 (−)	7 (−)		0 (−)	0 (−)	
EOT						
Cure	302 (93.5)	145 (92.4)	1.1 (−3.8, 6.1)	284 (94.0)	136 (92.5)	1.5 (−3.5, 6.5)
Failure	21 (6.5)	12 (7.6)		18 (6.0)	11 (7.5)	
Missing or indeterminate	5 (−)	3 (−)		3 (−)	1 (−)	

[a] Clinical cure rate was calculated as the number of patients with a cure response divided by the number of patients in different populations at time-points for which they were assessed as cure or failure.

Table 3 Microbiological success rate at the TOC visit by study population.[a]

Assessment visit	b-mITT population			BE population		
	Nemonoxacin *n* (%)	Levofloxacin *n* (%)	Difference, % (95% CI)	Nemonoxacin *n* (%)	Levofloxacin *n* (%)	Difference, % (95% CI)
Favourable[b]	105 (92.1)	55 (91.7)	0.4 (−8.1, 9.0)	100 (93.5)	55 (91.7)	1.8 (−6.6, 10.2)
Unfavourable[c]	9 (7.9)	5 (8.3)		7 (6.5)	5 (8.3)	
Missing or indeterminate	3 (−)	2 (−)		1 (−)	0 (−)	

[a] Microbiological success rate was calculated as the number of patients with a favourable response divided by the number of patients in different populations at TOC that were assessed as favourable or unfavourable.
[b] Defined as eradication or presumed eradication of the baseline pathogen.
[c] Defined as persistence and presumed persistence of the baseline pathogen.

Table 4 Microbiological response for common typical pathogens and clinical cure rate for atypical pathogens at the TOC visit.

Baseline pathogen	Clinical cure rate in mITT[a]		Microbiological success rate in b-mITT[b]	
	Nemonoxacin n1/n2 (%)	Levofloxacin n1/n2 (%)	Nemonoxacin n1/n2 (%)	Levofloxacin n1/n2 (%)
Typical pathogens				
Streptococcus pneumoniae	27/28 (96.4)	14/14 (100)	17/17 (100)	10/11 (90.9)
Staphylococcus aureus	16/17 (94.1)	7/8 (87.5)	16/17 (94.1)	7/8 (87.5)
Haemophilus species[c]	29/32 (90.6)	11/12 (91.7)	29/32 (90.6)	11/12 (91.7)
Klebsiella species[d]	37/39 (94.9)	23/25 (92.0)	36/39 (92.3)	23/25 (92.0)
Atypical pathogens				
Mycoplasma pneumoniae	43/45 (97.8)	12/13 (92.3)		
Chlamydia pneumoniae	7/7 (100)	8/8 (100)		
Legionella pneumophila	9/9 (100)	2/2 (100)		

[a] Clinical cure rate was calculated as the number of patients with a cure response divided by the number of patients in mITT population at TOC who were assessed as cure or failure. Patients with infection caused by mixed typical and atypical pathogens were excluded from atypical pathogen analysis, but included in typical pathogen analysis.
[b] Microbiological success rate was calculated as the number of patients with a favourable response divided by the number of patients in b-mITT population at TOC who were assessed as favourable or unfavourable. Patients with infection caused by more than one pathogen were counted once per pathogen.
[c] Including 17 strains of *H. influenzae*, 26 strains of *H. parainfluenzae*, and 1 strain of *H. parahaemolyticus*.
[d] Including 62 strains of *K. pneumoniae* and 2 strains of *K. oxytoca*.

organ class of investigations and gastrointestinal disorders in both groups (Table 5). No significant difference was found in study drug-related AEs between nemonoxacin (19.4%) and levofloxacin (17.5%) groups. Common drug-related AEs were ALT elevation (nemonoxacin 5.1%; levofloxacin 4.1%), WBC decreased (nemonoxacin 2.0%; levofloxacin 1.2%), nausea (nemonoxacin 3.1%; levofloxacin 1.8%), and vomiting (nemonoxacin 1.7%; levofloxacin 2.3%). The AEs of 2 patients in levofloxacin group (nausea and vomiting in one patient, and conjugated bilirubin and total bilirubin increased in another patient) and 1 patient in levofloxacin group (rash) were considered to be study drug-related.

No patients died. Six patients (5 in nemonoxacin group and 1 in levofloxacin group) reported SAEs. Only one SAE (type II second-degree atrioventricular block) in levofloxacin group was possibly related to the study drug. The patient did not have any history of cardiovascular disease and 12-lead ECG data were normal at baseline. Eight days after treatment, type I second-degree atrioventricular block was reported. Two days later, 24 h Holter showed type II second-degree atrioventricular block, and the patient was hospitalized for close monitoring. At 19 days after study drug treatment, 24 h Holter showed bradycardia, type I second-degree atrioventricular block, and cardiac arrest; however, the patient did not experience any clinical symptoms throughout the AE and recovered one and half months later.

Discussion

As a leading cause of death, CAP continues to be associated with high morbidity.[25] This phase 3, multicenter, randomized, double-blind clinical trial demonstrates that nemonoxacin is as effective as levofloxacin (both oral 500 mg once daily for 7−10 days) for the treatment of adult CAP patients, achieving high clinical cure rates of 94.3% for nemonoxacin and 93.5% for levofloxacin in the mITT population with evaluable assessment at the TOC visit. Nemonoxacin showed non-inferiority to levofloxacin, a widely used agent in the clinical setting, in terms of the primary endpoint. This finding was supported in the key secondary CE population. The results of this trial are consistent with those of two previous phase 2 studies comparing nemonoxacin with levofloxacin.[23,24]

Table 5 AEs in the safety population.

	Nemonoxacin (N = 356) % (*n*/N)	Levofloxacin (N = 171) % (*n*/N)
TEAEs, regardless of relationship to study drug	33.1 (118/356)	33.3 (57/171)
SAEs	1.4 (5/356)	0.6 (1/171)
Discontinuations due to AE	1.1 (4/356)	2.3 (4/171)
TEAEs related to study drug[a]	19.4 (69/356)	17.5 (30/171)
AE severity		
Mild	84.8 (178/210)	88.1 (96/109)
Moderate	13.3 (28/210)	8.3 (9/109)
Severe	1.9 (4/210)	3.7 (4/109)
Common (≥2%) TEAEs, regardless of relationship to study drug[b]		
Gastrointestinal disorders		
Nausea	3.4 (12/356)	2.9 (5/171)
Abdominal discomfort	2.2 (8/356)	0.6 (1/171)
Vomiting	1.7 (6/356)	2.9 (5/171)
Investigations		
ALT elevation	5.9 (21/356)	4.7 (8/171)
AST elevation	2.5 (9/356)	2.3 (4/171)
WBC decreased	2.0 (7/356)	1.8 (3/171)
Blood bilirubin increased	0.3 (1/356)	2.3 (4/171)
Blood urine present	0.3 (1/356)	2.3 (4/171)
Nervous system disorders		
Dizziness	2.8 (10/356)	1.8 (3/171)
Skin and subcutaneous tissue disorders		
Rash	0.6 (2/356)	2.3 (4/171)

[a] Related = probably and possibly related.
[b] AEs are sorted by system organ class and preferred term in decreasing order of frequency in patients treated with nemonoxacin.
TEAE, treatment-emergent AE.

Nemonoxacin demonstrated excellent microbiological efficacy against all the key CAP pathogens identified in this trial. The microbiological success rate of nemonoxacin was higher than levofloxacin for *S. pneumoniae* (100% *vs.* 90.9%) and *S. aureus* (94.1% *vs.* 84.5%). Preclinical *in vitro* antimicrobial activity of nemonoxacin[16,17,19] and the MICs of nemonoxacin against baseline isolates in this study showed that the antimicrobial activity of nemonoxacin was better than other commonly used quinolones against penicillin-nonsusceptible *S. pneumoniae*, fluoroquinolone-resistant *S. pneumoniae* and MRSA. Nemonoxacin also has good activity against *H. influenzae*, *M. catarrhalis*, and *K. pneumoniae*.

We identified 44 *Haemophilus* species in this study, including 17 strains of *H. influenzae*, 26 strains of *H. parainfluenzae*, and 1 strain of *H. parahaemolyticus*. *H. parainfluenzae* and *H. parahaemolyticus* have been implicated in pneumonia but their roles remain uncertain in view of its assumed low pathogenicity. Since several clinical trials identified these *Haemophilus* species as the causative organism of CAP and case report also claimed having solid evidences to indicate that these pathogens can cause pneumonia with systemic features in the community, we also classified them as typical pathogens in this report.

Nemonoxacin showed good efficacy against atypical CAP pathogens (*M. pneumoniae*, *C. pneumoniae*, *L. pneumophila*). Of the patients with positive pathogens in this study, 26.5% (69/260) were infected with atypical pathogen. The clinical cure rate of nemonoxacin was 97.8%—100% for such pathogens. These findings support the *in vitro* and *in vivo* results, confirming the potent activity of nemonoxacin against atypical pathogens.[14,19]

Safety analysis showed that nemonoxacin was as safe as levofloxacin. In levofloxacin group, the drug-related clinical AEs were mainly ALT elevation, WBC decreased, and nausea. Of the 6 SAEs reported, only one SAE of type II second-degree atrioventricular block in levofloxacin group was considered to be drug-related. The patient was asymptomatic and the event resolved completely. All drug-related AEs were mild to moderate in severity. There was no significant difference between treatment groups in the incidence of adverse events, serious adverse events, and discontinuations. These results were similar to those of previous phase 2 CAP studies.[23,24]

In conclusion, oral nemonoxacin can achieve good clinical and microbiological efficacy in treatment of adult CAP caused by bacteria and atypical pathogens, which is not inferior to levofloxacin. The AEs of nemonoxacin are generally mild and transient. The recommended regimen for adult CAP is oral nemonoxacin 500 mg once daily for 7—10 days.

Conflicts of interest

L.C., is an employee of TaiGen Biotechnology Co., Ltd. All other authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jmii.2017.07.011.