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A multicentre, randomised, double-blind, double-dummy, parallel-controlled, phase 3 clinical trial assessing the efficacy and safety of intravenous nemonoxacin malate vs. levofloxacin for community-acquired pneumonia in adult patients

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ABSTRACT

Background: Nemonoxacin malate is a novel non-fluorinated quinolone for oral and intravenous (IV) administration. This phase 3, multicentre, randomised, double-blind, double-dummy, parallel-controlled clinical trial (NCT02205112) evaluated the efficacy and safety of IV nemonoxacin vs. levofloxacin for the treatment of community-acquired pneumonia (CAP) in adult patients.

Methods: Eligible patients were randomised to receive 500 mg nemonoxacin or levofloxacin via IV infusion, once daily for 7–14 days. The primary endpoint was the clinical cure rate at the test-of-cure (TOC) visit in the modified intent-to-treat (mITT) population. Secondary efficacy and safety were also compared between nemonoxacin and levofloxacin.

Results: Overall, 525 patients were randomised and treated with nemonoxacin ($n = 349$) or levofloxacin ($n = 176$). The clinical cure rate was 91.8% (279/304) for nemonoxacin and 85.7% (138/161) for levofloxacin in the mITT population ($P > 0.05$). The clinical efficacy of nemonoxacin was non-inferior to levofloxacin for treatment of CAP. Microbiological success rate with nemonoxacin was 88.8% (95/107) and with levofloxacin was 87.8% (43/49) ($P > 0.05$) at the TOC visit in the bacteriological mITT population. The incidence of drug-related adverse events (AEs) was 37.1% in the nemonoxacin group and 22.2% in the levofloxacin group. These AEs were mostly local reactions at the infusion site, nausea, elevated alanine aminotransferase/aspartate aminotransferase (ALT/AST), and QT interval prolongation. The nemonoxacin-related AEs were mostly mild and resolved after discontinuation of nemonoxacin.

Conclusions: Nemonoxacin 500 mg IV once daily for 7–14 days is effective and safe and non-inferior to levofloxacin for treating CAP in adult patients.

1. Introduction

Community-acquired pneumonia (CAP) is one of the most common infectious diseases in the community. CAP is caused by various pathogens, including *Streptococcus pneumoniae, Haemophilus influenzae*, and atypical pathogens such as *Mycoplasma pneumoniae, Chlamydia pneumoniae*, and *Legionella pneumophila* [1,2]. Recently, community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has become one of the important pathogens of CAP [3,4]. The increasing resistance of CAP pathogens to commonly used antimicrobial agents poses unprecedented challenges to clinical treatment.

The growing resistance to the antimicrobial therapies for CAP, such as penicillins and macrolides, has complicated CAP treatment. In the CHINET Antimicrobial Resistance Surveillance Program, 1495 strains of *S. pneumoniae* were isolated from non-meningitis adults in 2019. All of the penicillin-nonsusceptible *S. pneumoniae* strains, including penicillin-intermediate (PISP) and penicillin-resistant (PRSP) *S. pneumoniae*, were resistant to erythromycin [5]. In recent years, respiratory fluroquinolones have become one of the important therapies for CAP in adults because of the in vivo and in vitro antimicrobial activities of these drugs against the major pathogens of CAP, such as *S. pneumoniae* (including penicillin-nonsusceptible strains), *H. influenzae*, and atypical pathogens. The clinical practice guideline of the American Thoracic Society and Infectious Disease Society of America for the diagnosis and treatment of CAP in adults recommends fluroquinolone monotherapy for the empirical treatment of CAP in adult inpatients and outpatients who have cardiopulmonary disease or other underlying diseases [6].

Nemonoxacin malate is a non-fluorinated quinolone antimicrobial agent developed by TaiGen Biopharmaceuticals Co., Ltd. This agent is a selective inhibitor of bacterial DNA topoisomerase. In vitro pharmacodynamic studies have shown that nemonoxacin has broad-spectrum antimicrobial activities [7–10], with particularly potent activity against multidrug-resistant pathogens, including PRSP, MRSA, and ertapenem-nonsusceptible Enterobacterales [11-14], and good activity against *H. influenzae, Moraxella catarrhalis, M. pneumoniae, C. pneumoniae*, and *L. pneumophila*. Unlike other fluoroquinolones, nemonoxacin is not as active against *Mycobacterium tuberculosis*. Therefore, the use of nemonoxacin in management of CAP will not delay or disturb the diagnosis of tuberculosis [15–17].

Nemonoxacin malate is available as oral and intravenous (IV) formulations. Oral nemonoxacin malate was launched in mainland China in 2016 for the treatment of mild or moderate CAP in adults (aged ≥18 years). The conventional dosage of nemonoxacin is 500 mg once daily for adults. For some critically ill patients, and in cases where oral treatment is inappropriate, antimicrobial treatment via IV infusion is mandatory and effective.

Nemonoxacin malate injection has been studied in a phase 1 clinical study. The results showed that nemonoxacin was safe and well-tolerated within the dose range from 25 to 1250 mg after single dose IV infusion in healthy adults. The maximum tolerated dose was 1250 mg [18]. There were no accumulation or safety concerns for nemonoxacin after IV infusion of 500 to 750 mg once daily for 10 consecutive days in healthy subjects. Monte Carlo simulation indicates that the cumulative fraction of response (CFR) is close to 100% for the dosing regimen of nemonoxacin 500 to 750 mg once daily against *S. pneumoniae*. Furthermore, the probability of target attainment (PTA) of nemonoxacin is > 98% when the minimum inhibitory concentration (MIC) of nemonoxacin against *S. pneumoniae* is ≤ 1 mg/L, indicating that 500 to 750 mg nemonoxacin IV infusion once daily will result in good clinical and microbiological efficacy [19].

A phase 2 clinical trial of nemonoxacin malate IV 500 mg and 650 mg, once daily, for 7–14 days in the treatment of CAP in adult patients also demonstrated good clinical and microbiological efficacy. The majority of the adverse events (AEs) reported were tolerable, mild, and transient.

The phase 3, multicentre, randomised, double-blind, double-dummy, parallel-controlled clinical trial reported herein was conducted in Chinese adult patients with CAP from 17 June 2014 to 14 October 2015 to further confirm the efficacy and safety of nemonoxacin malate injection. Levofloxacin was used as comparator drug because it is currently recommended by the CAP practice guidelines and is widely used to treat CAP.

2. Methods

2.1. Study design

This was a multicentre, randomised, double-blind, double-dummy, parallel-controlled clinical trial (ClinicalTrials.gov identifier: NCT02205112). Eligible patients were randomised to receive nemonoxacin 500 mg or levofloxacin 500 mg (control group) in a ratio of 2:1. Nemonoxacin was provided in a 250 mL bag, and the comparator levofloxacin was provided in a 100 mL bag. Both drugs were administered by IV infusion, once daily, for 7–14 days. The specific treatment duration was determined by the investigator according to the disease severity and patient condition. This study was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the Declaration of Helsinki. The study protocol and the supporting documents were approved by the Institutional Review Board of Huashan Hospital, Fudan University (approval number 2014-150) and the respective local research Ethics Committees before initiation of study procedures. The informed consent form was signed by the study patients, or their legal representative, before enrolment into the study.

2.2. Study patients

The enrolled patients were aged 18–80 years, had a body weight of 40–100 kg and body mass index $\geq$18 kg/m^2, and were able to provide appropriate samples for bacterial culture and identification. All the study patients had a diagnosis of CAP with a PORT score/Pneumonia Severity Index (PSI) of Class II, III, or IV [20]. The study patients were eligible to receive IV infusion of the study treatments.

CAP diagnosis was based on the presence of three or more of the following conditions: (1) presence or worsening of cough, associated with purulent sputum; (2) dyspnoea or shortness of breath; (3) chest pain or discomfort; (4) fever (oral temperature $\geq$ 38.0 °C, axillary temperature $\geq$ 37.5 °C or tympanic temperature $\geq$ 38.5 °C) or hypothermia ($\leq$ 35 °C); (5) signs of lung consolidation (abnormal findings on auscultation, such as bronchial breath sounds, and/or local moist rales); (6) white blood cell (WBC) count $>$ 9500/mm^3 or $<$ 3500/mm^3, neutrophils $>$ 75% (abnormal WBC/neutrophils were indispensable); AND new inflammatory exudation or infiltration consistent with acute pneumonia detected by chest X-ray examination or CT scan (from 2 days before signing the informed consent form to the day of first dose administration).

Patients were excluded if they were due to Class I or V penumonia based on PORT/PSI score, required invasive mechanical ventilation or might use vasoconstrictors due to septic shock. Patients were also excluded if they had any of the following conditions: infection acquired in hospital or healthcare facilities, simple viral pneumonia, inhalation pneumonia, bronchial asthma, bronchiectasis, lung abscess, or lung tumour; medical history of heart rate-corrected QT (QTc) interval prolongation, or requiring the use of medication to treat QTc interval prolongation; severe heart failure, active viral hepatitis, compensatory cirrhosis with severe ascites, recurrent liver and brain lesions, renal dysfunction, liver dysfunction, or neutropenia; use of systemic antibiotics for more than 24 h within 72 h before the first administration of the study drug, or use of quinolones or fluoroquinolones within 14 days before the first administration of the study drug. The full list of the inclusion and exclusion criteria is provided in the online Supplementary Material.

2.3. Randomisation and visits

Block randomisation was implemented via the Interactive Web Response System (IWRS). All eligible patients were randomised by study centre and initially stratified by geographical region, then further stratified by PORT/PSI score. The study drugs were coded and provided in sequentially numbered containers. Patients were randomly assigned to receive 500 mg nemonoxacin or levofloxacin in a ratio of 2:1. The study patients, investigators, care providers, study nurses, and those assessing outcomes were blinded to the study interventions. The drugs were administered in identical bags by a blinded study nurse. The IWRS monitored the severity of disease to ensure that at least 75% of the patients enrolled had a PORT/PSI score of Class III or IV. Patients had to receive treatment for at least 3 days to be evaluable for efficacy. Patients were assessed at the following time points: Visit 1 (24 h before administration), Visit 2 (study day 4 $\pm$ 1), Visit 3 (within 24 h after discontinuation), Visit 4 (7–14 days after discontinuation), and Visit 5 (28 $\pm$ 2 days after enrolment).

The following populations were defined for statistical analysis. The randomised population (RP) included all screened and randomised patients. The intent-to-treat (ITT) population was a subset of RP patients who took at least one full dose of study drug. The modified ITT (mITT) population was a subset of ITT patients who met the minimum disease criteria and had at least one clinical efficacy evaluation. The clinically evaluable (CE) population was a subset of mITT patients who met the criteria for per-protocol analysis. The bacteriological mITT (b-mITT) population was a subset of mITT patients who had at least one baseline pathogenic isolate. The bacteriologically evaluable (BE) population was a subset of b-mITT patients who met the criteria for per-protocol analysis. The safety population (SP) included all patients who received study drug.

2.4. Study endpoints

The primary efficacy endpoint was defined as non-inferiority of nemonoxacin to levofloxacin in clinical cure rate at the test-of-cure (TOC) visit (Visit 4) in treatment of CAP in the mITT population. The main secondary efficacy endpoints included whether nemonoxacin was inferior to levofloxacin at the TOC visit in the CE and ITT populations, whether the clinical efficacy of nemonoxacin was inferior to levofloxacin at the end of treatment (EOT) visit (Visit 3) in the mITT, CE, and ITT populations, as well as the microbiological efficacy evaluation at the EOT and TOC visits in the b-mITT and BE populations.

2.5. Clinical efficacy evaluation

The investigators evaluated the clinical efficacy at the EOT and TOC visits based on the changes of relevant symptoms, signs, and laboratory tests, and the findings on chest X-ray film or CT images. Clinical efficacy was considered as cure or failure based on the following evidence.

Clinical cure was defined if all the baseline symptoms, signs, and laboratory abnormalities related to pneumonia at the time of enrolment disappeared or returned to the state before infection, without any new clinical symptoms, signs, laboratory abnormalities or complications. Clinical cure was also justified if chest X-ray film or CT scan images showed cure or improvement of lesions, and it was not required to continue other antibacterial treatment targeting pneumonia. In addition, clinical cure was considered in cases where significant improvement was documented (i.e., all the baseline symptoms, signs, and laboratory abnormalities related to pneumonia at the time of enrolment improved), there were still some clinical symptoms, signs, and/or laboratory abnormalities, or some abnormal findings on chest X-ray film or CT images, but it was not required to use other antibiotics targeting pneumonia.

The presence of any of the following would justify clinical failure: the main baseline symptoms, signs, laboratory abnormalities related to pneumonia at the time of enrolment persisted or got worse, or aggravated even after transient improvement; the emergence of new symptoms or signs related to pneumonia made the patient's condition worse, or chest X-ray film or CT scans showed deterioration of the disease; occurrence of complex complications, such as empyema or lung abscess; requiring other antibacterial drugs to target pneumonia due to treatment failure; or the patient died due to CAP.

2.6. Microbiological efficacy evaluation

When a patient was enrolled, appropriate sputum, blood, and urine samples were collected for culture and identification of bacterial pathogens. Sputum samples from the deep respiratory tract were prepared for sputum smear microscopy. A sputum specimen was considered as qualified when the number of squamous epithelial cells in the sample was less than 10 per low-power field (LPF) and the number of white blood cells was greater than 25/LPF. Only qualified sputum specimens were subjected to bacterial culture to exclude potential contaminant microorganisms. Sputum sample was collected for culture of pathogens at each visit if qualified sample was available. Colonising bacteria from sputum were excluded according to the results of sputum culture in combination with clinical conditions. The isolate was considered a coloniser when the patient had no clinically relevant signs of infection after treatment and infection-related markers were normal, indicating that the infection was cured. Blood samples were collected for culture of bacterial pathogens and serological tests of atypical pathogens. If the result of blood culture was positive, the blood culture was repeated at the next visit until negative conversion of blood culture. Serological tests for atypical pathogens were conducted at the Screening visit and Visit 4. Urine samples were also collected for urine-specific antigen assay.

Microbiological success included eradication (the baseline isolate from the original infection site was not detected after treatment) and presumed eradication (the patient was clinically cured and symptoms and signs disappeared, so that no appropriate specimen was available for detecting the pathogen). Microbiological failure included pathogen persistence (the baseline pathogen was still detected from the original infection site after treatment) and presumed persistence (when the pathogen culture was missing or impossible in case of clinical failure for a patient).

The MICs of nemonoxacin and levofloxacin against baseline isolates were determined using the agar dilution method. The results were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) breakpoints (2015).

2.7. Safety evaluation

Patients were monitored and observed closely for the occurrence of any abnormalities in terms of clinical AEs, laboratory test results, and other special examinations during this clinical trial. Electrocardiogram (ECG) measurements (including QT intervals) were required at the Screening visit and repeated at Visit 2 and Visit 3. If the ECG results at Visit 3 were abnormal, ECG examination was repeated at Visit 4. If the results of follow-up ECG at Visit 4 were still abnormal, ECG was followed up at regular intervals until the abnormal ECG measurements recovered to normal, became not clinically significant, or returned to the pre-treatment state. Haematological tests and blood chemistry were followed up at each of the 4 visits. Urinalysis was followed up at Visit 1, Visit 3, and Visit 4. AEs were assessed as definitely related, probably related, possibly related, possibly unrelated, or definitely unrelated to the study drug, based on the criteria for analysing the correlation between AE and the study drug.

2.8. Statistical analysis

All statistical analyses were conducted using SAS 9.4 statistical software. Two-sided test with a significance level of 0.05 was used for all between-group comparisons except for the noninferiority test. $P < 0.05$ indicated statistically significant difference between the two treatment groups. Overall, 44 study centres participated in this study; however, one centre did not enrol any patients. The statistical analysis was not adjusted for centre effect because the patients were enrolled competitively among all centres.

Assuming that the clinical efficacy of the nemonoxacin 500 mg group and the control group (levofloxacin 500 mg) is 85.0%, with a non-inferiority margin of 10%, a significance level of 0.025 (one-sided, $\alpha = 0.025$), and a statistical power of 80%, a total of 302 evaluable patients were needed in the nemonoxacin group and 151 evaluable patients were required in the control group if the patients were randomised in a ratio of 2:1. Considering that about 20% of the randomised patients would not be evaluable, it was planned to enrol 360 patients in the nemonoxacin group and 180 patients in the control group.

3. Results

3.1. Study population

This study was conducted in 44 centres in China. A total of 519 eligible patients were randomised to receive nemonoxacin ($n = 343$) or levofloxacin ($n = 176$). There were 480 patients in the mITT set, including 314 patients in the nemonoxacin group and 166 patients in the levofloxacin group. The disposition of patients is detailed in Figure 1.

3.2. Baseline patient characteristics

In the mITT population, the patients were balanced and comparable between the two treatment groups in terms of age, age distribution, sex, race, ethnicity, height, weight, body mass index, PORT/PSI score, smoking and alcohol consumption. The PORT/PSI score belonged to Class III in most of the patients in both groups. The most common underlying diseases were hypertension and chronic obstructive pulmonary disease (Table 1). The baseline patient characteristics were also comparable between the two groups in the CE and ITT populations. The mean (± SD) duration of treatment was 9.2 ± 3.21 days in the nemonoxacin group and 9.0 ± 3.09 days in the levofloxacin group ($P = 0.544$).

In the mITT population, fever, cough, sputum, dyspnoea/breathlessness, and signs of lung consolidation were documented for most of the patients. The baseline pneumonia-related clinical symptoms and signs were similar and comparable between the two groups of patients. Baseline pathogens were detected from sputum in 23.2% (73/314) of patients, and from blood culture in

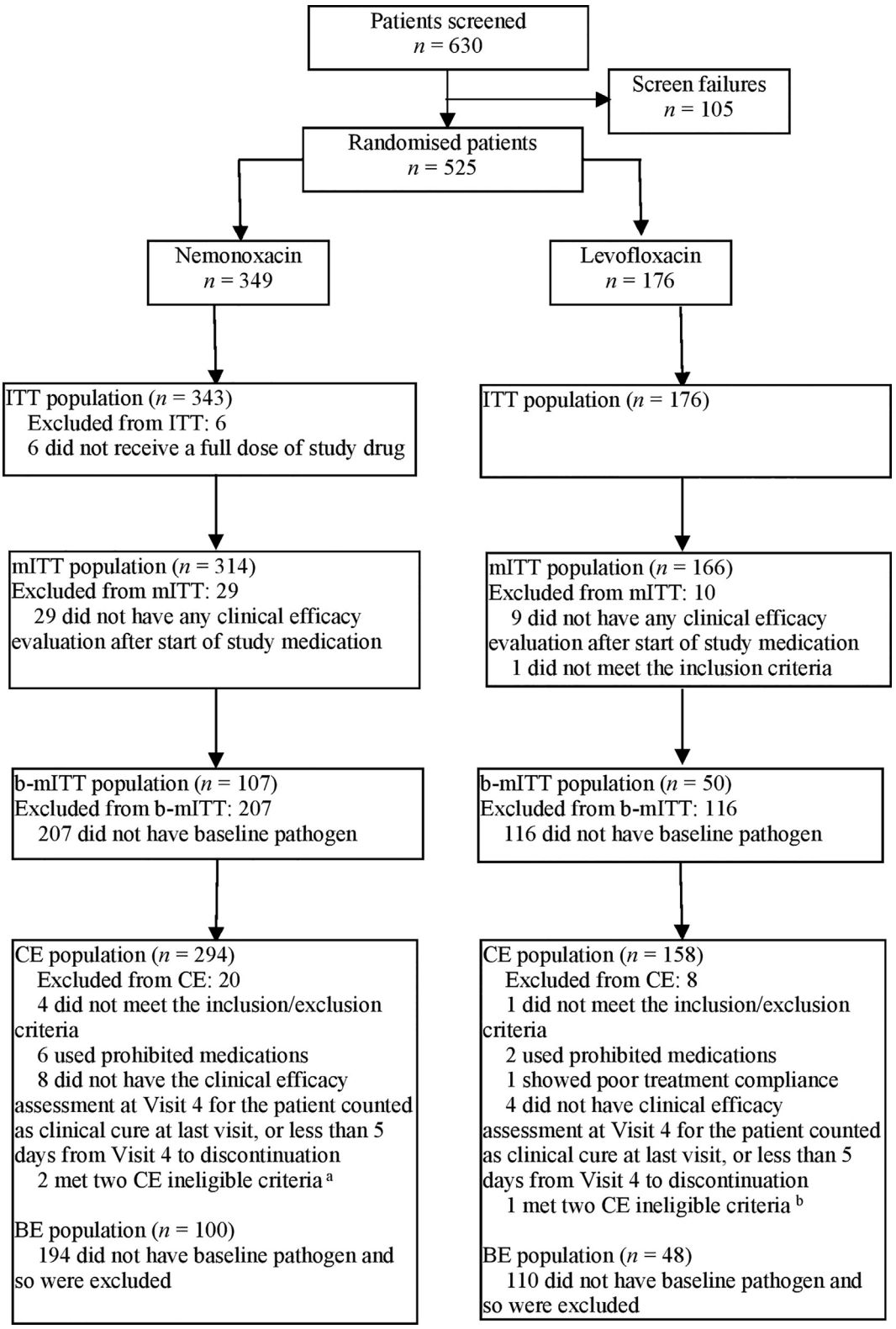

Fig. 1. Flow diagram for patient disposition. ITT, intent-to-treat; mITT, modified intent-to-treat; b-mITT, bacteriological modified intent-to-treat; BE, bacteriologically evaluable; CE, clinically evaluable. [a] One patient did not meet the inclusion/exclusion criteria, and did not have clinical efficacy assessment at Visit 4, or less than 5 days from Visit 4 to discontinuation; the other patient used prohibited medications, and did not have clinical efficacy assessment at Visit 4, or less than 5 days from Visit 4 to discontinuation. [b] One patient met two CE exclusion criteria (poor medication compliance, and did not have clinical efficacy assessment at Visit 4, or less than 5 days from Visit 4 to discontinuation).

Table 1
Demographic and baseline characteristics of patients in the modified intent-to-treat population.

Characteristic	Nemonoxacin (n = 314)	Levofloxacin (n = 166)	Total (n = 480)	P value
Age (years), mean (SD)	57.8 (14.18)	56.5 (14.62)	57.3 (14.33)	0.320
Sex (male)	195 (62.1)	104 (62.7)	299 (62.3)	0.906
Body mass index (kg/m^2), mean (SD)	22.9 (3.18)	22.8 (3.23)	22.8 (3.19)	0.904
Underlying disease				0.715
Hypertension	74 (23.6)	39 (23.5)	113 (23.5)	
Chronic obstructive pulmonary disease	48 (15.3)	22 (13.3)	70 (14.6)	
Diabetes mellitus	20 (6.4)	8 (4.8)	28 (5.8)	
Coronary artery disease	20 (6.4)	6 (3.6)	26 (5.4)	
Cerebral infarction	13 (4.1)	6 (3.6)	19 (4.0)	
Hepatic steatosis	11 (3.5)	7 (4.2)	18 (3.8)	
Chronic bronchitis	16 (5.1)	4 (2.4)	20 (4.2)	
PORT/PSI score				0.780
Class I	0	0	0	
Class II	76 (24.2)	44 (26.5)	120 (25.0)	
Class III	220 (70.1)	111 (66.9)	331 (69.0)	
Class IV	18 (5.7)	11 (6.6)	29 (6.0)	
Class V	0	0	0	

PSI, Pneumonia Severity Index; SD, standard deviation.
Data are number (%) unless otherwise specified.

Table 2
Clinical cure rates at the TOC and EOT visits in the mITT and CE populations.

Assessment visit	mITT population (n = 480)			CE population (n = 452)		
	Nemonoxacin n (%)	Levofloxacin n (%)	Difference, % (95% CI)	Nemonoxacin n (%)	Levofloxacin n (%)	Difference, % (95% CI)
TOC visit						
Clinical cure	279 (91.8)	138 (85.7)	6.1 (-0.2, 12.3)	271 (92.2)	136 (86.1)	6.1 (-0.1, 12.3)
Clinical failure	25 (8.2)	23 (14.3)		23 (7.8)	22 (13.9)	
Missing or indeterminate	10 (-)	5 (-)		0 (-)	0 (-)	
EOT visit						
Clinical cure	291 (92.7)	145 (87.9)	4.8 (-1.0, 10.6)	273 (92.9)	137 (87.3)	5.6 (-0.4, 11.6)
Clinical failure	23 (7.3)	20 (12.1)		21 (7.1)	20 (12.7)	
Missing or indeterminate	0 (-)	1 (-)		0 (-)	1 (-)	

Clinical cure rate was calculated as the number of patients with a cure response divided by the number of patients in respective populations at each visit when they were assessed as cure or failure.
CE, clinically evaluable; CI, confidence interval; EOT, end of treatment; mITT, modified intent-to-treat; TOC, test of cure.

20.5% (34/166) of patients. The pathogen detection rate was also similar between the two groups in the CE and ITT populations.

3.3. Clinical efficacy

The clinical efficacy evaluation was missing or indeterminate for 10 patients in the nemonoxacin group and 5 patients in the levofloxacin group at the TOC visit in the mITT population. These patients were assessed as clinical cure at the EOT visit. One patient in the levofloxacin group was clinically not evaluable at the EOT visit in both the mITT and CE populations due to missing corresponding symptoms, signs, and laboratory test results.

Excluding the patients with missing clinical evaluation, the clinical cure rate in the nemonoxacin group and the levofloxacin group was 92.7% and 87.9%, respectively, at the EOT visit, and 91.8% and 85.7%, respectively, at the TOC visit in the mITT population. For the CE population, the clinical cure rate in the nemonoxacin group and the levofloxacin group was 92.9% and 87.3%, respectively, at the EOT visit, and 92.2% and 86.1%, respectively, at the TOC visit. Statistical analysis indicated that the primary efficacy endpoint was met. The difference in clinical cure rate between nemonoxacin and levofloxacin was 6.1% at the TOC visit in the mITT population (95% confidence interval [CI]: -0.2%, 12.3%). The lower limit of the CI was $>$ -10%. This result confirmed that the clinical cure rate for nemonoxacin was non-inferior to levofloxacin at the TOC visit in the mITT population (Table 2).

A total of 70.1% (220/314) of patients in the nemonoxacin group and 66.9% (111/166) of patients in the levofloxacin group belonged to Class III based on PORT/PSI score. The clinical cure rate for nemonoxacin was 94.5%, 91.6%, and 81.3%, whereas that for levofloxacin was 82.9%, 86.2%, and 90.9% for the patients in the PORT/PSI Class II, III, and IV subsets, respectively, at the TOC visit in the mITT population.

3.4. Clinical efficacy by pathogen species

Overall, baseline pathogen was detected in 53.3% (255/480) of the patients in the mITT population. A total of 21.3% (102/480) of the pathogens were bacteria, 23.1% (111/480) of the patients were infected with atypical pathogens, such as *M. pneumoniae*, and 8.8% (42/480) were co-infected with bacteria and atypical pathogens. The detection rate of pathogens in the nemonoxacin group was similar to that in the levofloxacin group. The clinical cure rate of nemonoxacin was 93.8–100% for the patients infected with *S. pneumoniae, Haemophilus, Klebsiella*, and other bacteria; however, the cure rate was slightly lower for the CAP caused by non-fermenting bacteria, such as *Pseudomonas aeruginosa*. Nemonoxacin also showed good efficacy, comparable to levofloxacin, for the patients infected with atypical pathogens, such as *M. pneumoniae* (Table 3).

3.5. Microbiological efficacy

Microbiological efficacy was assessed in terms of microbiological eradication rate at the EOT and TOC visits in the b-mITT and BE populations. Microbiological efficacy was not evaluated for four

Table 3
Clinical efficacy of nemonoxacin vs. levofloxacin for CAP caused by different pathogens at the TOC visit in the mITT population.

Pathogen	Number of isolates	Nemonoxacin n/N[a] (%)	Levofloxacin n/N[a] (%)
Bacteria			
Single			
Streptococcus pneumoniae[b]	15	7/7 (100)	8/8 (100)
Haemophilus spp	23	15/16 (93.8)	6/7 (85.7)
Klebsiella spp	35	23/24 (95.8)	10/11 (90.9)
Staphylococcus aureus	2	2/2 (100)	0
Moraxella catarrhalis	3	2/2 (100)	1/1 (100)
Other Enterobacterales[c]	8	6/7 (85.7)	1/1 (100)
Non-fermenting bacteria[d]	14	7/8 (87.5)	6/6 (100)
Multiple[e]	2	2/2 (100)	0
Atypical pathogen	111	74/75 (98.7)	34/36 (94.4)
Bacteria + atypical pathogen[f]	42	30/31 (96.8)	11/11 (100)

CAP, community-acquired pneumonia; mITT, modified intent-to-treat; TOC, test of cure.
[a] n, number of patients clinically cured; N, number of patients with baseline pathogens (excluding those without clinical evaluation or clinical efficacy indeterminate).
[b] Including positive sputum culture in 9 cases, positive sputum culture and urinary antigen testing in 6 cases.
[c] Including *Escherichia coli* in 5 cases, *Enterobacter aerogenes* in 2 cases, and *Citrobacter koseri* in 1 case.
[d] Including *Pseudomonas aeruginosa* in 8 cases and *Acinetobacter baumannii* in 6 cases.
[e] Including *S. pneumoniae* (sputum culture) + *K. pneumoniae* in 1 case, *S. pneumoniae* + *Haemophilus parahaemolyticus* in 1 case.
[f] Including *S. pneumoniae* + *Legionella pneumophila* (2 cases), *S. pneumoniae* + *Mycoplasma pneumoniae* (2), *S. pneumoniae* + *M. pneumoniae* + *L. pneumophila* (1), *S. pneumoniae* + *M. pneumoniae* + *Chlamydia pneumoniae* + *L. pneumophila* (1), *S. pneumoniae* + *K. pneumoniae* + *M. pneumoniae* + *L. pneumophila* (1), *Haemophilus* + *M. pneumoniae* (9), *Haemophilus* + *M. pneumoniae* + *L. pneumophila* (1), *Haemophilus* + *K. pneumoniae* + *M. pneumoniae* + *L. pneumophila* (1), *Haemophilus* + *L. pneumophila* (1), *S. aureus* + *M. pneumoniae* (1), *S. aureus* + *Enterobacter cloacae* + *M. pneumoniae* (1), *K. pneumoniae* + *M. pneumoniae* (9), *K. pneumoniae* + *C. pneumoniae* (1), *K. pneumoniae* + *L. pneumophila* (1), *K. pneumoniae* + *M. pneumoniae* + *L. pneumophila* (3), *K. pneumoniae* + *M. pneumoniae* + *C. pneumoniae* (1), other *Enterobacterales* + *M. pneumoniae* (2), nonfermenting bacteria + *C. pneumoniae* (1), single non-fermenting organism + *L. pneumophila* (2).

Table 4
Microbiological efficacy of nemonoxacin vs. levofloxacin at the TOC and EOT visits in the b-mITT and BE populations[a].

	b-mITT (n = 157)			BE (n=148)		
	Nemonoxacin (n = 107) n (%)	Levofloxacin (n = 50) n (%)	Difference, % (95% CI)	Nemonoxacin (n = 100) n (%)	Levofloxacin (n = 48) n (%)	Difference, % (95% CI)
TOC						
Eradication[b]	92 (89.3)	43 (87.8)	1.6 (-9.4, 12.5)	90 (90.9)	42 (87.5)	3.4 (-7.5, 14.3)
Persistence[c]	11 (10.7)	6 (12.2)		9 (9.1)	6 (12.5)	
Indeterminate	4 (-)	1 (-)		1 (-)	0 (-)	
EOT						
Eradication	99 (92.5)	47 (94.0)	4.8 (-1.0, 10.6)	94 (94.0)	45 (93.8)	0.2 (-8.0, 8.5)
Persistence	8 (7.5)	3 (6.0)		6 (6.0)	3 (6.3)	
Indeterminate	0 (-)	0 (-)		0 (-)	0 (-)	

[a] Microbiological eradication rate, including confirmed and presumed eradication of baseline pathogens.
[b] Including confirmed and presumed eradication.
[c] Including confirmed and presumed persistence of baseline pathogens.
BE, bacteriologically evaluable; b-mITT, bacteriologically modified intent-to-treat population; CI, confidence interval; EOT, end of treatment; TOC, test of cure.

patients in the nemonoxacin group at the TOC visit in the b-mITT population. The baseline pathogens of these patients included two strains of *K. pneumoniae* and two strains of *H. influenzae*. Microbiological success was documented for these patients at the EOT visit. One of the patients treated with levofloxacin did not participate in the evaluation of microbiological efficacy at the TOC visit. The baseline pathogen was *S. aureus*. The microbiological efficacy of this patient was documented as success at the EOT visit.

After treatment, the by-patient bacterial eradication rate was 89.3% (92/103) in the nemonoxacin group and 87.8% (43/49) in the levofloxacin group at the TOC visit in the b-mITT population. Similar results were demonstrated in the BE population. There was no statistically significant difference in microbiological efficacy between the two groups ($P > 0.05$) (Table 4).

The by-strain bacterial eradication rate (including confirmed and presumed eradication) in the nemonoxacin group was 88.8% (95/107) at the TOC visit in the b-mITT population (103 patients). The corresponding eradication rate in the levofloxacin group was 87.8% (43/49) at the TOC visit in the b-mITT population (49 patients) (Table 5). The persistent strains in both groups were mainly *K. pneumoniae* and *A. baumannii*. Multiple pathogens were isolated from two patients. These strains were presumed persistent after the end of treatment.

3.6. MIC of study drugs against baseline pathogens

The MICs of nemonoxacin and levofloxacin against baseline pathogens were determined using the agar dilution method (Table 6). Nemonoxacin showed high antibacterial activity against *S. pneumoniae, H. influenzae*, and *K. pneumoniae*, as shown by MIC_{90} values of 0.125 mg/L, 0.25 mg/L, and 1 mg/L, respectively.

3.7. Safety evaluation

A total of 524 patients were evaluable for safety, including 348 patients in the nemonoxacin group and 176 patients in the levofloxacin group. The overall incidence of AEs in the nemonoxacin group was 58.3% (203/348). Specifically, the incidence of clinical AEs was 42.5% (148/348) and the incidence of laboratory abnormalities was 31.9% (111/348). The overall incidence of AEs in the levofloxacin group was 46.6% (82/176), specifically 35.2% (62/176) for clinical AEs and 23.3% (41/176) for laboratory abnormalities. All drug-related AEs were mild or moderate; there

Table 5
Eradication rate of nemonoxacin vs. levofloxacin for different pathogens at the TOC visit in the b-mITT population.

Pathogen	b-mITT	
	Nemonoxacin (n = 107) n /N[b] (%)	Levofloxacin (n = 49)[a] n/N[b] (%)
Streptococcus pneumoniae	11/11 (100.0)	10/10 (100.0)
Haemophilus spp	28/31 (90.3)	8/9 (88.9)
Moraxella catarrhalis	2/2 (100.0)	1/1 (100.0)
Staphylococcus aureus	3/4 (75.0)	2/2 (100.0)
Klebsiella spp[c]	34/38 (89.5)	14/17 (82.4)
Other Enterobacterales[d]	8/9 (88.9)	2/2 (100.0)
Nonfermenting bacteria[e]	9/12 (75.0)	6/8 (75.0)

[a] One of the levofloxacin-treated patients (Subject 115-03) did not participate in the evaluation of microbiological efficacy at the TOC visit. The baseline pathogen was *Staphylococcus aureus*. The microbiological efficacy of this patient was documented as success at the EOT visit.
[b] n, number of eradicated strains (confirmed or presumed); N, number of baseline strains isolated from sputum or blood cultures.
[c] Including 53 strains of *Klebsiella pneumoniae*, 1 strain of *Klebsiella ozaenae*, and 1 strain of *Klebsiella oxytoca*.
[d] Including 6 strains of *Escherichia coli*, 1 strain of *Enterobacter sakazakii*, 2 strains of *Enterobacter aerogenes*, 1 strain of *Enterobacter cloacae*, and 1 strain of *Citrobacter koseri*.
[e] Including 10 strains of *Pseudomonas aeruginosa*, 9 strains of *Acinetobacter baumannii*, and 1 strain of *Stenotrophomonas maltophilia*.
b-mITT, bacteriological modified intent-to-treat; TOC, test of cure.

Table 6
Minimum inhibitory concentrations of nemonoxacin and levofloxacin against baseline pathogens (mg/L)[a].

Species (n)	Antibiotic	MIC range	MIC_{50}	MIC_{90}
Streptococcus pneumoniae (21)	Nemonoxacin	0.03-0.25	0.125	0.125
	Levofloxacin	0.05-2	1	1
Staphylococcus aureus (7)[b]	Nemonoxacin	0.03-1	-	-
	Levofloxacin	0.125-16	-	-
Haemophilus influenzae (21)[c]	Nemonoxacin	≤0.008-0.25	0.015	0.25
	Levofloxacin	≤0.008-0.5	0.015	0.125
Haemophilus parainfluenzae (10)[d]	Nemonoxacin	0.125-8	1	4
	Levofloxacin	0.125-16	2	8
Moraxella catarrhalis (3)	Nemonoxacin	0.03-0.06	-	-
	Levofloxacin	0.03-0.06	-	-
Klebsiella spp (57)[e]	Nemonoxacin	≤0.06->32	0.25	1
	Levofloxacin	≤0.06->32	≤0.06	0.25
Other Enterobacterales (10)[f]	Nemonoxacin	≤0.06->32	0.25	>32
	Levofloxacin	≤0.06->32	≤0.06	>32
Pseudomonas aeruginosa (10)	Nemonoxacin	0.5-4	2	4
	Levofloxacin	0.25-2	1	2
Acinetobacter baumannii (7)	Nemonoxacin	≤0.06-16	-	-
	Levofloxacin	≤0.06->32	-	-

[a] Only MIC range is provided without MIC_{50} and MIC_{90} if number of strains <10.
[b] Including 1 strain of methicillin-resistant *Staphylococcus aureus*.
[c] Including 2 strains of β-lactamases-producers.
[d] Including 2 strains of β-lactamases-producers.
[e] Including 55 strains of *Klebsiella pneumoniae*, 1 strain of *Klebsiella oxytoca*, and 1 strain of *Klebsiella ozaenae*.
[f] Including 5 strains of *Escherichia coli*, 2 strains of *Enterobacter aerogenes*, 1 strain of *Enterobacter cloacae*, 1 strain of *Enterobacter sakazakii*, and 1 strain of *Citrobacter koseri*.

were no severe drug-related AEs. The incidence of study drug-related AEs was 37.1% (129/348) in the nemonoxacin group and 22.2% (39/176) in the levofloxacin group. The most common study drug-related clinical AEs were local reactions at the infusion site (17.2% in the nemonoxacin group and 6.8% in the levofloxacin group). The symptoms resolved spontaneously or disappeared in most cases by slowing IV infusion or after 2–3 consecutive doses. The most common drug-related laboratory test abnormalities were elevated alanine aminotransferase (ALT) (6.6% in the nemonoxacin group and 3.4% in the levofloxacin group) and elevated aspartate aminotransferase (AST) (5.7% in the nemonoxacin group and 3.4% in the levofloxacin group), QT interval prolongation (3.2% in the nemonoxacin group and 0.6% in the levofloxacin group, $P = 0.069$), and decreased white blood cell count (2.3% in the nemonoxacin group and 2.8% in the levofloxacin group) (Table 7). The main drug-related laboratory test abnormalities in the nemonoxacin group were elevated liver enzymes, all of which were mild except for one case where ALT increased to 7.6 times upper limit of normal (ULN). All the increased liver enzymes had recovered to normal at the follow-up visit, except for two patients whose ALT was still increased up to 2.1 times ULN at the last follow-up (outcome unknown due to loss to follow-up).

No patients died in this study. A total of 21 patients experienced serious adverse events (SAEs), including 3 SAEs possibly related to the study drug (one each of drug rash, elevated transaminase, and sinus bradycardia, all in the nemonoxacin group). All of the drug-related SAEs were moderate in severity and improved after treatment. A total of 12 patients discontinued treatment due to AEs, including 11 patients in the nemonoxacin group and 1 patient in the levofloxacin group. Five patients experienced drug-related AEs that led to study withdrawal, all in the nemonoxacin group. The drug-related AEs in the five patients in the nemonoxacin group were itching and redness of the head and face; slowed heart rate, prolonged QT and QTc intervals; skin itching and red rash on the neck and back; palpitations and linear redness along the infusion site; and acute extensive anterior lateral myocardial ischemia (one patient each). All the drug-related AEs leading to study withdrawal resolved after discontinuation of the study drug.

Table 7
The most common treatment-emergent adverse events (TEAEs) (occurred in ≥ 2% of the patients in either group) and drug-related TEAEs.

AE	Nemonoxacin (n = 348)		Levofloxacin (n = 176)	
	n (%)		n (%)	
	TEAE	Drug-related[a]	TEAE	Drug-related[a]
Clinical AE	148 (42.5)	76 (21.8)	62 (35.2)	21 (11.9)
Local reaction at infusion site	60 (17.2)	60 (17.2)	12 (6.8)	12 (6.8)
Nausea	2 (0.6)	2 (0.6)	6 (3.4)	3 (1.7)
Liver cyst	2 (0.6)	0	4 (2.3)	0
Urinary tract infection	7 (2.0)	0	2 (1.1)	0
Laboratory abnormality	111 (31.9)	64 (18.4)	41 (23.3)	21(11.9)
Elevated ALT	30 (8.6)	23 (6.6)	9 (5.1)	6 (3.4)
Elevated AST	25 (7.2)	20 (5.7)	7 (4.0)	6 (3.4)
Hypokalemia	9 (2.6)	1 (0.3)	7 (4.0)	1 (0.6)
QT interval prolongation	13 (3.7)	11 (3.2)	2 (1.1)	1 (0.6)
White blood cell decreased	11 (3.2)	8 (2.3)	6 (3.4)	5 (2.8)
γ-glutamyltransferase increased	9 (2.6)	4 (1.1)	2 (1.1)	1 (0.6)
Presence of white blood cell in urine	1 (0.3)	0	4 (2.3)	0
Neutrophils increased	2 (0.6)	1 (0.3)	4 (2.3)	0
Sinus bradycardia	8 (2.3)	8 (2.3)	1 (0.6)	0
White blood cell count increased	7 (2.0)	2 (0.6)	3 (1.7)	0

[a] Including the TEAEs definitely or probably related to the study drug.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

4. Discussion

This is the first phase 3 clinical trial of intravenous administration of nemonoxacin in the treatment of CAP. Intravenous infusion can provide stable drug exposure, which is not affected by food, at the site of infection. The current study results indicate that parenteral nemonoxacin is safe and non-inferior to levofloxacin for treating CAP. The parenteral preparation is particularly suitable for patients who are unable to take the medication orally. Furthermore, the availability of both parenteral and oral forms of nemonoxacin makes the subsequent IV-to-oral sequential treatment possible for CAP. This study was completed in 2015. However, the handling of the patent transfer for the IV formulation of nemonoxacin malate delayed the approval by relevant stakeholders for publication of the results.

In this study, once daily IV infusion of 500 mg nemonoxacin malate for 7–14 days showed good clinical efficacy in the treatment of CAP in adult patients. The clinical cure rate of nemonoxacin and levofloxacin was 91.8% and 85.7%, respectively, at the TOC visit in the mITT population. The primary efficacy endpoint was met. The clinical efficacy of nemonoxacin malate injection in the treatment of CAP is non-inferior to levofloxacin injection. The results of this study are consistent with the results of three clinical trials of nemonoxacin oral formulations [21–23].

Nemonoxacin showed good clinical efficacy against the main pathogens of CAP, including *S. pneumoniae, H. influenzae*, and *K. pneumoniae*. The clinical cure rate for these pathogens was 100%, 90.5%, and 94.7%, respectively. The cure rate for atypical pathogen infections was also high, up to 95.3–100%. In vitro pharmacodynamic studies demonstrated that nemonoxacin had better antimicrobial activities than other commonly used fluoroquinolones against *S. aureus* (including MRSA), *S. pneumoniae* (including PRSP) and atypical pathogens [11-13,24]. More patients are required in future clinical trials to confirm the efficacy of nemonoxacin against *S. aureus* and PRSP infections. Patients with severe underlying disease were excluded from this study. The results of this study cannot be extrapolated readily to patients with severe underlying disease. Data from further clinical trials in critically ill patients will address this concern.

Nemonoxacin showed higher incidence of drug-related AEs (including clinical AEs and laboratory abnormalities) than levofloxacin. The main clinical AEs were local reactions at the infusion site (17.2% in the nemonoxacin group and 6.8% in the levofloxacin group), most of which were mild and transient. In this study, the drug-related laboratory abnormalities in the nemonoxacin group were mainly elevated liver enzymes. However, none of the patients with elevated liver enzymes also had elevated blood bilirubin levels (≥ 2 times ULN), so drug-induced liver toxicity was not confirmed in this trial and should be monitored closely in future clinical use. These results are similar to the results of oral administration of nemonoxacin [25]. Neither oral nor IV administration of nemonoxacin was associated with liver toxicity. This study supports the good safety profile of nemonoxacin based on the evidence that all drug-related AEs were mostly mild or moderate. The AE profile was similar to the results of three previous clinical studies of nemonoxacin oral formulations.

Some limitations should be considered when interpreting the results of this trial. This study excluded some special populations that are prone to CAP, such as the elderly and those with renal dysfunction or liver dysfunction. Further clinical studies targeting special populations are planned after the marketing of IV nemonoxacin preparations, to support the use of nemonoxacin in these special populations. The safety profile is based on a relatively small number of the selected patients without significant underlying diseases. Therefore, post-marketing safety surveillance is also necessary to observe the long-term safety of IV nemonoxacin preparations.

In summary, IV infusion of nemonoxacin malate 500 mg once daily has good clinical and microbiological efficacy in the treatment of CAP caused by bacteria and atypical pathogens. The AEs are mostly mild, transient, and well-tolerated. It is advisable to use nemonoxacin malate 500 mg, via IV infusion for 7–14 days, for the treatment of CAP.

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Ethical Approval: This study was approved by the Institutional Review Board of Huashan Hospital, Fudan University (approval number: 2014-150).

Sequence Information: Not applicable

Randomised Controlled Trial: NCT02205112

Data availability

The data generated and analysed in this study are available on reasonable request after permission of the corresponding author and sponsor.

Author contributions

Y.Z. designed the study and was the coordinating investigator. Y.L. wrote the first manuscript, which was read, commented on and amended by all the other authors. All authors were involved substantially in the study, including enrolment of patients, conduct of the study, and collection and analysis of study data, and approved the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2024.107235.

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