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Original Article

Integrated safety summary of phase II and III studies comparing oral nemonoxacin and levofloxacin in community-acquired pneumonia

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Abstract *Background:* Nemonoxacin, a novel nonfluorinated quinolone, has broad-spectrum antibacterial activity, including activity against antibiotic-resistant strains, and was developed for treating community-acquired pneumonia (CAP). This report provides an integrated safety summary of oral nemonoxacin from two phase II and one phase III clinical studies.
Methods: Patients with mild CAP were randomized for treatment with nemonoxacin 500 mg (NEMO-500MG), nemonoxacin 750 mg (NEMO-750MG), or levofloxacin 500 mg (LEVO), orally, once daily, for 7–10 days. Hematological, gastrointestinal, and hepatic disorders; electrocardiography abnormalities; and reported quinolone-associated clinical concerns were included in this analysis.
Results: A total of 520, 155, and 320 subjects were assigned to receive NEMO-500MG, NEMO-750MG, and LEVO, respectively. The incidence of adverse events (AEs) was the highest (54.8%) in the NEMO-750MG group (NEMO-500MG, 36.9%; NEMO-750MG, 54.8%; LEVO, 39.7%) and that of drug-related AEs was comparable between the three groups (NEMO-500MG,

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22.9%; NEMO-750MG, 31.0%; LEVO, 22.5%). The majority (>80%) of the patients showed mild drug-related AEs and the distribution based on severity was similar between the groups. The most commonly reported drug-related AEs included neutropenia (NEMO-500MG, 2.5%; NEMO-750MG, 8.4%; LEVO, 4.4%), nausea (NEMO-500MG, 2.5%; NEMO-750MG, 7.1%; LEVO, 2.5%), leukopenia (NEMO-500MG, 2.3%; NEMO-750MG, 4.5%; LEVO, 3.1%), and increased alanine aminotransferase level (NEMO-500MG, 4.4%; NEMO-750MG, 0%; LEVO, 2.5%).
Conclusion: Nemonoxacin was well tolerated and no clinically significant safety concerns were identified, suggesting that it possesses a desirable safety and tolerability profile similar to that of levofloxacin, and may be a suitable alternative to fluoroquinolones for treating patients with CAP.

Introduction

Community-acquired pneumonia (CAP) is pneumonia acquired outside of hospitals or extended-care facilities and the leading cause of pneumonia-related morbidity and mortality among all age groups worldwide.[1–3] The Infectious Disease Society of America/American Thoracic Society (IDSA) recommends macrolides and fluoroquinolones as empirical antimicrobial therapy for outpatients.[2] However, development of antimicrobial resistance following treatment poses a great challenge in clinical practice.[4,5] Methicillin-resistant *Staphylococcus aureus* (MRSA), multidrug-resistant (MDR) *Pseudomonas aeruginosa*, and extended spectrum β-lactamase-producing Enterobacteriaceae, which were previously only encountered in hospital settings, have emerged in communities,[6] and new antimicrobials are being developed to tackle these challenges.

Nemonoxacin, a novel C-8-methoxy nonfluorinated quinolone, shows broad-spectrum antibacterial activity against most gram-positive cocci (including penicillin-resistant *Streptococcus pneumoniae* [PRSP] and MRSA), atypical pathogens, and most gram-negative bacteria. The C-8 methoxy substituent in nemonoxacin enables targeting of topoisomerase IV in addition to topoisomerase II, leading to an improved activity spectrum and reduced mutant selection.[7] Clinical trials involving nemonoxacin have been conducted in outpatients with CAP in Taiwan, South Africa, and China.[8–10] Nemonoxacin treatment (500 mg taken orally once daily for 7–10 days) was effective in CAP patients, with a clinical cure rate of >90%. In addition, high clinical cure rates were achieved for nemonoxacin in patients with CAP caused by atypical pathogens, including *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila*.

Absence of the fluorine moiety from nemonoxacin's quinolone structure is possibly associated with a reduced incidence of toxic side effects.[11] The common safety concerns associated with quinolones include peripheral neuropathy, central nervous system (CNS) toxicity, retinal detachment, dermatologic events or phototoxicity, gastrointestinal events, QT interval prolongation, glucose homeostasis imbalance, musculoskeletal events, and tendon disease.[12–16] Gastrointestinal symptoms including dyspepsia, nausea, vomiting, and diarrhea are the most frequent adverse reactions associated with quinolone use with a prevalence of up to 20%. The most common associated CNS adverse reactions are anxiety, restlessness, nervousness, euphoria, and dizziness with an incidence of up to 2%.[16] QT interval prolongation is also a notable adverse reaction to quinolones.[17] Other rare serious adverse events such as *Clostridium difficile*-associated diarrhea and hepatitis have also been observed with varying degrees of causation evidence.[18,19]

Thus, this integrated safety summary of nemonoxacin clinical trial data was prepared to evaluate the drug's safety profile, focusing on the safety concerns associated with quinolones.

Methods

Nemonoxacin clinical studies

Safety data were obtained from three multicenter, randomized, double-blind, parallel, comparative clinical trials. These studies were conducted from December 2006 to August 2012 in Taiwan, South Africa, and China. The objectives were to evaluate the efficacy and safety of nemonoxacin by comparing with those of levofloxacin, a frequently prescribed fluoroquinolone. Subjects meeting the eligibility criteria provided informed consent and were randomized into study groups (nemonoxacin 500 mg, nemonoxacin 750 mg, and levofloxacin 500 mg in two of the studies; nemonoxacin 500 mg and levofloxacin 500 mg in the remaining study). Study treatments were administered orally once daily for 7–10 days in 2 of the studies and only 7 days for the remaining study. The subjects were monitored for an additional 14 days after completing the study treatment period. For detailed study designs, please refer to the previously published reports.[8–10]

Study designs for all studies were approved by institutional review boards at participating sites and the studies were conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice (ICH-GCP) and the Declaration of Helsinki and its amendments. All patients provided written informed consent before participation.

Subject eligibility

Men and women aged ≥18 years with a clinical diagnosis of CAP and suitable to be treated as outpatients were eligible for enrollment. A chest radiograph demonstrating new or persistent/progressive infiltrates obtained within 48 h prior to the first dose of treatment was required. Exclusion criteria were as follows: subjects with active or chronic lung disease other than CAP, subjects with clinically significant hepatic/renal disease, CNS disorders, uncontrolled psychiatric illnesses, malignancies, or immunodeficiency; subjects with cardiovascular diseases that may result in abnormal QT intervals or abnormal protocol-defined electrocardiography (ECG) at screening; pregnant or lactating women; subjects who received antibiotics up to 7 days before randomization; subjects who received the investigational drug 1 month prior to randomization; and subjects with a history of hypersensitivity or drug reactions to quinolones.

Safety evaluations and statistics

For the integrated safety analysis, all randomized subjects who received at least one dose of the study drug (nemonoxacin or levofloxacin) were included in the safety population and only adverse events (AEs) that were reported after study drug treatment were analyzed. The relationship between each AE and the study drug was evaluated by the investigators. Data were collected from safety evaluations, including physical examinations, vital signs, urinalysis, blood biochemistry, hematology, chest X-rays, and 12-lead ECG. AEs reported were summarized using MedDRA System Organ Class (SOC), and Preferred Term (PT) and data are presented as numbers and percentages of subjects.

Safety data were summarized by treatment groups and descriptive statistics were applied to the safety analysis. Safety data regarding hematological, gastrointestinal, or hepatic disorders; ECG abnormalities; and other reported clinical concerns associated with quinolones were included in this analysis.

Results

Demographics and subject baseline characteristics

Subject demographics and baseline characteristics are summarized in Table 1. The subjects (995) were randomized to receive at least one dose of nemonoxacin 500 mg (NEMO-500MG [520 subjects]), nemonoxacin 750 mg (NEMO-750MG [155 subjects]), or levofloxacin 500 mg (LEVO [320 subjects]). The treatment groups were balanced with respect to race, sex, age, weight, BMI, baseline renal function, and baseline liver function, although baseline aspartate aminotransferase (AST) levels were slightly higher in the NEMO-750MG group than in the other groups.

Treatment duration

The majority of the subjects in the NEMO-500MG group (51.7%), NEMO-750MG group (69.7%), and LEVO group (55.3%) received the study treatment for at least 7 days but no longer than 10 days. The treatment duration was the shortest in the NEMO-750MG group with approximately 70% subjects receiving treatment for 7−10 days (Table 2).

Summary of AEs

An overview of AEs is shown in Table 3. The NEMO-750MG group was found to have a higher incidence of AEs, AEs that led to study discontinuation, and serious AEs (SAEs). However, the incidences of drug-related AEs and drug-related AEs resulting in discontinuation of the study drug were similar between the treatment groups. Events that led to study drug discontinuation differed between the groups. In the NEMO-500MG group, one subject had nausea and vomiting, the other showed increased blood bilirubin and conjugated bilirubin levels. In the NEMO-750MG group, one subject had muscle twitching, and in LEVO group, one subject had rash and another had nausea. All AEs were graded based on severity assessed by investigators as mild, moderate, or severe. Overall, there was no significant difference between the distribution of AEs based on severity within the treatment groups. Most of the subjects reported mild AEs (NEMO-500MG, 84.6%; NEMO-750MG, 80.2%; LEVO 84.5%); 14.7%, 14.8%, and 15.2% of the subjects in the NEMO-500MG, NEMO-750MG, and LEVO groups reported moderate AEs, respectively. Severe AEs were only reported in the nemonoxacin groups (NEMO-500MG 0.7% and NEMO-750MG 5.0%). Only one drug-related SAE, second-degree atrioventricular block, was reported in the NEMO-500MG group. The subject was asymptomatic throughout the AE and recovered 1.5 months later. Two deaths (1 due to sepsis and 1 due to pulmonary tuberculosis) were reported, one in each of the nemonoxacin groups, but neither was drug related. Both subjects were enrolled into the study by error. The baseline liver and renal function blood test Results of the subject who had sepsis were significantly out of range at the time of enrollment; however, the investigator became aware of the subject's condition only on day 2 of the study. The subject passed away 3 days later. The other subject who died had completed pulmonary tuberculosis treatment 7 months before enrollment, but was diagnosed with advanced pulmonary tuberculosis and immunosuppression when she was hospitalized on day 6 of the study. The subject passed away 2 days later.

Gastrointestinal, hematologic, and hepatic disorders were the most commonly reported drug-related AEs (Table 4). The NEMO-750MG group had a higher frequency of nausea, neutropenia, leukopenia, thrombocytosis, prolonged QT interval, and abnormal liver function. The incidence of increased alanine aminotransferase (ALT) was higher in the NEMO-500MG group. The prevalence of common (≥1%) drug-related AEs was comparable between the treatment groups.

Hematologic AEs

Hematologic abnormalities were major AEs and included neutropenia, leukopenia, and thrombocytosis. The incidence of leukopenia was the highest in the NEMO-750MG

Table 1 Subject demographics and baseline characteristics.

	Nemonoxacin 500 mg (N = 520)	Nemonoxacin 750 mg (N = 155)	Nemonoxacin total (N = 675)	Levofloxacin 500 mg (N = 320)
Sex (%)				
Male	283 (54.4)	78 (50.3)	361 (53.5)	188 (58.8)
Female	237 (45.6)	77 (49.7)	314 (46.5)	132 (41.3)
Race (%)				
Caucasian	18 (3.5)	20 (12.9)	38 (5.6)	17 (5.3)
Black	55 (10.6)	53 (34.2)	108 (16.0)	56 (17.5)
Asian	445 (85.6)	81 (52.3)	526 (77.9)	243 (75.9)
Other	2 (0.4)	1 (0.6)	3 (0.4)	4 (1.3)
Age (years)				
Mean (SD)	42.0 (14.87)	41.0 (16.12)	41.7 (15.16)	42.8 (15.35)
Median	41.0	39.0	41.0	42.0
Min - Max	17.0—71.0	18.0—86.0	17.0—86.0	17.0—87.0
Weight (kg)				
N	519	155	674	320
Mean (SD)	62.2 (12.53)	65.5 (17.56)	62.9 (13.91)	63.7 (12.33)
Median	60.0	61.0	60.0	62.0
Min - Max	37.0—111.7	25.0—133.6	25.0—133.6	37.0—123.9
BMI (kg/m^2)				
N	518	155	673	320
Mean (SD)	22.7 (3.79)	23.7 (5.47)	22.9 (4.25)	23.0 (3.71)
Median	22.0	22.5	22.1	22.2
Min - Max	15.8—42.2	10.4—44.7	10.4—44.7	15.2—35.5
ALT (IU/L)				
N	481	146	627	295
Mean (SD)	26.2 (20.72)	27.8 (24.93)	26.6 (21.76)	25.4 (18.43)
AST (IU/L)				
N	485	146	631	293
Mean (SD)	27.6 (18.82)	36.3 (52.40)	29.7 (30.29)	27.3 (15.76)
Creatinine clearance (mL/min)				
N	520	155	675	320
≤50	15 (2.9)	11 (7.1)	26 (3.9)	19 (5.9)
50-90	203 (39.0)	52 (33.5)	255 (37.8)	117 (36.6)
≥90	300 (57.7)	92 (59.4)	392 (58.1)	184 (57.5)

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

group (NEMO-500MG, 2.3%; NEMO-750MG, 4.5%; LEVO, 3.1%). However, when hematological test Results were reviewed, the number of subjects whose white blood cell counts were normal at baseline and decreased to a clinically significant value of $\leq 2.8 \times 10^3/mm^3$ during the study was comparable between the treatment groups (NEMO-500MG, 2.3%; NEMO-750MG, 1.7%; LEVO, 1.8%) (Table 5). The incidence of thrombocytosis was the highest in the NEMO-750MG group (NEMO-500MG, 0.8%; NEMO-750MG, 2.6%; LEVO, 0.6%), and the number of subjects whose platelet count reached $\geq 700 \times 10^3/mm^3$ during the study were also in the highest in the NEMO-750MG group (NEMO-500MG, 0.2%; NEMO-750MG, 1.5%; LEVO, 0%). Anemia was reported only by 1 subject (0.2%) in the NEMO-500MG group; however, 1.7%—5.6% of the male subjects and 1.8% of the female subjects in the NEMO-500MG group had clinically significant decreased hemoglobin or hematocrit levels.

Table 2 Treatment durations.

Treatment duration (days)	Nemonoxacin 500 mg (N = 520), n (%)	Nemonoxacin 750 mg (N = 155), n (%)	Nemonoxacin total (N = 675), n (%)	Levofloxacin 500 mg (N = 320), n (%)
<3	22 (4.2)	6 (3.9)	28 (4.1)	8 (2.5)
≥3 to < 7	22 (4.2)	6 (3.9)	28 (4.1)	21 (6.6)
≥7 to < 10	269 (51.7)	108 (69.7)	377 (55.9)	177 (55.3)
≥10	207 (39.8)	35 (22.6)	242 (35.9)	114 (35.6)

Table 3 Overview of adverse events.

	Nemonoxacin 500 mg (N = 520), n (%)	Nemonoxacin 750 mg (N = 155), n (%)	Nemonoxacin total (N = 675), n (%)	Levofloxacin 500 mg (N = 320), n (%)
All AEs	192 (36.9)	85 (54.8)	277 (41.0)	127 (39.7)
Drug-related AEs	119 (22.9)	48 (31.0)	167 (24.7)	72 (22.5)
AEs led to study drug discontinuation	9 (1.7)	6 (3.9)	15 (2.2)	6 (1.9)
Drug-related AEs led to study drug discontinuation	2 (0.4)	1 (0.6)	3 (0.4)	2 (0.6)
SAEs	13 (2.5)	7 (4.5)	20 (3.0)	4 (1.3)
Drug-related SAEs	1 (0.2)	0	1 (0.1)	0
Deaths	1 (0.2)	1 (0.6)	2 (0.3)	0
Drug-related deaths	0	0	0	0

AEs = treatment-emergent adverse events; SAEs = serious adverse events.

Hepatic AEs

ALT levels were slightly higher in the NEMO-500MG group. A review of changes in hepatic parameters for the prediction of potential hepatotoxicity is shown in Table 6. The NEMO-500MG and LEVO groups seemed to show a ≥3-fold increase above the upper limit of normal (ULN) in ALT levels, whereas the NEMO-750MG group showed a ≥3-fold or ≥5-fold increase above the ULN in AST levels. investigation revealed that there was only one subject in the NEMO-750MG group who met the criteria for Hy's Law (an increase in ALT or AST level of ≥3-fold above the ULN, a <2-fold increase in alkaline phosphatase level, and a ≥2-fold increase in total bilirubin level above the ULN). The subject had an ALT level of 2.7-fold above the ULN, an AST level of 8.7-fold above the ULN, total bilirubin level of 3.7-fold above the ULN, creatinine level of 6.5-fold above the ULN, and calculated creatinine clearance of 11 ml/min at screening. These parameters showed that the subject was critically ill and was mistakenly enrolled into the study. The subject died of sepsis and the investigator considered the event to be possibly unrelated to the study drug.

ECG assessments

QT interval represents the time from onset of ventricular depolarization to completion of depolarization and is corrected for heart rate (QTc). QTc prolongation indicates

Table 4 Summary of drug-related AEs (≥1%).

	Nemonoxacin 500 mg (N = 520), n (%)	Nemonoxacin 750 mg (N = 155), n (%)	Nemonoxacin total (N = 675), n (%)	Levofloxacin 500 mg (N = 320), n (%)
Abnormal liver function	0	4 (2.6)	4 (0.6)	1 (0.3)
Increased γ-glutamyl transferase	7 (1.3)	0	7 (1.0)	4 (1.3)
Increased alanine aminotransferase	23 (4.4)	0	23 (3.4)	8 (2.5)
Increased aspartate aminotransferase	10 (1.9)	1 (0.6)	11 (1.6)	3 (0.9)
Electrocardiogram - prolonged QT [a]	4 (0.8)	4 (2.6)	8 (1.2)	5 (1.5)
Headache	5 (1.0)	2 (1.3)	7 (1.0)	3 (0.9)
Dizziness	10 (1.9)	3 (1.9)	13 (1.9)	3 (0.9)
Rash	2 (0.4)	0	2 (0.3)	4 (1.3)
Abdominal pain (upper abdomen)	0	2 (1.3)	2 (0.3)	0
Abdominal discomfort	5 (1.0)	2 (1.3)	7 (1.0)	1 (0.3)
Diarrhea	7 (1.3)	2 (1.3)	9 (1.3)	3 (0.9)
Vomiting	6 (1.2)	4 (2.6)	10 (1.5)	7 (2.2)
Nausea	13 (2.5)	11 (7.1)	24 (3.6)	8 (2.5)
Neutropenia [b]	13 (2.5)	13 (8.4)	26 (3.9)	14 (4.4)
Thrombocytosis [c]	4 (0.8)	4 (2.6)	8 (1.2)	2 (0.6)
Leukopenia [d]	12 (2.3)	7 (4.5)	19 (2.8)	10 (3.1)

[a] Includes prolonged QT and prolonged corrected QT intervals.
[b] Includes decreased neutrophil percentage or count and neutropenia.
[c] Includes increased platelet count and thrombocytosis.
[d] Includes decreased white blood cells count and leukopenia.

Table 5 Clinically significant hematological changes.

Clinically significant changes[a]	Nemonoxacin 500 mg (N = 520), n/N (%)	Nemonoxacin 750 mg (N = 155), n/N (%)	Nemonoxacin total (N = 675), n/N (%)	Levofloxacin 500 mg (N = 320), n/N (%)
White blood cells				
$\leq 2.8 \times 10^3$ cells/mm^3	8/349 (2.3)	2/119 (1.7)	10/468 (2.1)	4/218 (1.8)
Platelets				
$\geq 700 \times 10^3$/mm^3	1/424 (0.2)	2/131 (1.5)	3/555 (0.5)	0
Hemoglobin				
≤11.5 g/dL (male)	4/234 (1.7)	1/56 (1.8)	5/290 (1.7)	3/150 (2.0)
≤9.5 g/dL (female)	0	0	0	0
Hematocrit				
≤37% (male)	12/213 (5.6)	6/54 (11.1)	18/267 (6.7)	8/144 (5.6)
≤32% (female)	3/167 (1.8)	0	3/222 (1.4)	4/96 (4.2)

[a] Denominator represents the number of subjects with normal test Results at baseline.

prolonged repolarization and thus increased risk of cardiac events, including ventricular arrhythmias such as torsade de pointes, and cardiac arrest. A prolonged QT interval is a notable adverse reaction to quinolones, including moxifloxacin, and was observed in 0.8%, 2.6%, and 1.5% of the subjects in the NEMO-500MG, NEMO-750MG, and LEVO groups, respectively (Table 7).

Incidence of other ECG or cardiac abnormalities was <1% in all treatment groups. ECG abnormalities, second-degree atrioventricular block, nodal rhythm, bundle branch block, and sinus bradycardia were reported in the NEMO-500MG group, whereas ventricular extrasystoles, tachycardia, palpitations, sinus bradycardia, and sinus arrhythmia were reported in the LEVO group (Table 7).

A summary of clinically significant QT changes using Fridericia's correction formula (QTcF) is shown in Table 8. In the treatment groups, most of the subjects reported QT prolongation of QTcF >450 ms (ms). One subject in the NEMO-750MG group and two subjects in the LEVO group had QTcF >500 ms; there were no such subjects in the NEMO-500MG group. The subjects who had QTcF >500 ms were asymptomatic and no syncopal or ventricular-related arrhythmias were reported. The majority of the QTcF changes were changes of more than 30 ms from baseline. Nevertheless, there were no clinically relevant differences observed in the rates of the QTcF changes from baseline among the treatment groups.

Discussion

Quinolones are antimicrobial agents indicated for treating a wide range of bacterial infections. Ciprofloxacin,

Table 6 Clinically significant changes in hepatic parameters.

Clinically significant changes[a]	Nemonoxacin 500 mg (N = 520), n/N (%)	Nemonoxacin 750 mg (N = 155), n/N (%)	Nemonoxacin total (N = 675), n/N (%)	Levofloxacin 500 mg (N = 320), n/N (%)
ALT				
$\geq 3 \times$ ULN	5/520 (1.0)	0	5/675 (0.7)	4/320 (1.3)
$\geq 5 \times$ ULN	0	0	0	0
AST				
$\geq 3 \times$ ULN	1/520 (0.2)	1/155 (0.6)	2/675 (0.3)	3/320 (0.9)
$\geq 5 \times$ ULN	1/520 (0.2)	1/155 (0.6)	2/675 (0.3)	0
Total bilirubin				
$> 2 \times$ ULN	1/518 (0.2)	2/155 (1.3)	3/673 (0.4)	1/319 (0.3)
ALP				
$> 1.5 \times$ ULN	6/517 (1.2)	5/155 (3.2)	11/672 (1.6)	5/319 (1.6)
Hy's law				
ALT $> 3 \times$ ULN and ALP $< 2 \times$ ULN and total bilirubin $\geq 2 \times$ ULN	0	0	0	0
AST $> 3 \times$ ULN and ALP $< 2 \times$ ULN and total bilirubin $\geq 2 \times$ ULN	0	1/155 (0.6)	1/670 (0.1)	0

[a] Denominator represents the number of subjects with normal laboratory test Results at baseline.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; ULN = upper limit of normal.

Table 7 Drug-related ECG adverse events and cardiac abnormalities.

Drug-related adverse events	Nemonoxacin 500 mg (N = 520), n (%)	Nemonoxacin 750 mg (N = 155), n (%)	Nemonoxacin total (N = 625), n (%)	Levofloxacin 500 mg (N = 320), n (%)
Electrocardiogram - QT prolonged[a]	4 (0.8)	4 (2.6)	8 (1.2)	5 (1.5)
Electrocardiogram - abnormal	1 (0.2)	0	1 (0.1)	0
Atrioventricular block (second degree)	1 (0.2)	0	1 (0.1)	0
Nodal rhythm	1 (0.2)	0	1 (0.1)	0
Ventricular extrasystoles	0	0	0	1 (0.3)
Bundle branch block	2 (0.4)	0	2 (0.3)	0
Tachycardia	0	0	0	1 (0.3)
Palpitations	0	0	0	1 (0.3)
Sinus bradycardia	2 (0.4)	0	2 (0.3)	1 (0.3)
Sinus arrhythmia	0	0	0	1 (0.3)

[a] Includes "Electrocardiogram - QT corrected interval prolonged".

levofloxacin, and moxifloxacin are the most widely used quinolones.[16] AEs commonly associated with fluoroquinolones include gastrointestinal and CNS toxicity (headache and dizziness). ECG abnormalities (such as QT interval prolongation), disrupted glucose metabolism, phototoxicity, tendon and joint disorders, hypersensitivity and skin disorders, peripheral neuropathy, retinal detachment, and hepatic toxicity were also reported.[16,17]

This report presents the safety profile of nemonoxacin by integrating the data of two phase II and one phase III clinical study data. In general, nemonoxacin taken orally once daily was found to be safe and well tolerated in patients with CAP. Similar to that with other quinolones, gastrointestinal disorders and abnormal levels of hepatic enzymes (increased levels of ALT, AST, and γ-glutamyl transferase) were the most frequently reported drug-related AEs in the nemonoxacin group. CNS and skin disorders were also reported in this group.

The US FDA has issued warnings and precautions regarding all fluoroquinolones and related disabling and potentially irreversible SAEs that occur together, including tendinitis, tendon rupture, peripheral neuropathy, and CNS-related AEs.[20] None of these adverse reactions was reported in the three clinical trials analyzed in this study, except CNS disorders, such as dizziness and headache, which were reported in all treatment groups (NEMO-500MG: 1.9% and 1%; NEMO-750MG: 1.9% and 1.3%; LEVO 0.9% and 0.9%, respectively). Even so, the rates were lower than those reported for frequently used quinolones.[21–23]

Hematologic abnormalities including neutropenia and leukopenia were also observed, but did not seem to cause any concern. These adverse reactions have previously been reported for frequently used quinolones with varying incidence.[21–23]

In 2011, the Pharmacovigilance Working Party of the European Medicines Agency released a report on the risk of QTc prolongation for different fluoroquinolones, classifying moxifloxacin and levofloxacin as drugs with potential and low potential for causing QTc prolongation, respectively.[24] In this report, prolonged QT interval was observed in 0.8%, 2.6%, and 1.5% of the subjects in the NEMO-500MG, NEMO-750MG, and LEVO groups, respectively. Occurrences of QTcF with changes of >500 ms and >60 ms from baseline were similar between the treatment groups. No patient experienced torsade de pointes. These data suggested that the potential for nemonoxacin to cause QT prolongation might be similar to that associated with levofloxacin.

Table 8 Summary of clinically significant ECG changes.

Clinically significant changes in QTc ms (Fridericia)[a]	Nemonoxacin 500 mg (N = 520), n/N (%)	Nemonoxacin 750 mg (N = 155), n/N (%)	Nemonoxacin total (N = 675), n/N (%)	Levofloxacin 500 mg (N = 320), n/N (%)
QTcF >450 ms	20/507 (3.9)	5/146 (3.4)	25/653 (3.8)	6/302 (2.0)
QTcF >480 ms	5/507 (1.0)	0	5/653 (0.8)	1/302 (0.3)
QTcF >500 ms	0	1/146 (0.7)	1/653 (0.2)	2/302 (0.7)
QTcF >30 ms change from baseline	85/507 (16.8)	25/146 (17.1)	110/653 (16.8)	41/302 (13.6)
QTcF >60 ms change from baseline	17/507 (3.4)	7/146 (4.8)	24/653 (3.7)	9/302 (3.0)

[a] Subjects with normal test Results at baseline.
QTcF = corrected QT interval (Fridericia formula); ms = milliseconds.

Previous *in vitro* studies have shown that nemonoxacin has superior antibacterial activity against methicillin-resistant *S. aureus* (MRSA), penicillin-resistant *S. pneumoniae* (PRSP), and multidrug-resistant *S. pneumoniae* (MDRSP).[25–27] Furthermore, compared to other quinolones, nemonoxacin has a lower propensity to develop resistant *S. pneumoniae* strains.[28] An *in vitro* study suggested that *Mycobacterium tuberculosis* is less susceptible to nemonoxacin compared to its susceptibility to levofloxacin or moxifloxacin.[29] Consequently, nemonoxacin treatment is less likely to delay the diagnosis of tuberculosis since tuberculosis may sometimes be mistaken for CAP. Clinical studies have also shown high clinical and bacteriological success rates associated with nemonoxacin in patients with CAP.[8–10] No new safety signals were found for nemonoxacin in this analysis and all subjects tolerated the study drug well, indicating that nemonoxacin has a desirable safety and tolerability profile, comparable to that of levofloxacin. These findings further suggest that nemonoxacin, a non-fluorinated quinolone, may be a suitable alternative to fluoroquinolones for treating patients with CAP.

Conflicts of interest

Y.C., L.C., and M.H are employees of TaiGen Biotechnology Co., Ltd. All other authors declare no conflicts of interest.

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