Chapter

Nemonoxacin (Taigexyn®): A New Non-Fluorinated Quinolone

Li-Wen Chang, Ming-Chu Hsu and Ying-Yuan Zhang

Abstract

Nemonoxacin (Taigexyn®), a novel C-8-methoxy non-fluorinated quinolone, has been approved for use in community-acquired pneumonia (CAP) in Taiwan (2014) and mainland China (2016). The FDA granted nemonoxacin 'qualified infectious disease product' and 'fast-track' designations for CAP and acute bacterial skin and skin structure infection in December 2013. It possesses a broad spectrum of bactericidal activity against typical and atypical respiratory pathogens. In particular, nemonoxacin has activity against resistant Gram-positive cocci, including penicillin-resistant *Streptococcus pneumoniae* and methicillin-resistant *Staphylococcus aureus*. Oral nemonoxacin was compared with oral levofloxacin for efficacy and safety in three randomized, double-blinded, controlled Phase II–III clinical trials for the treatment of CAP. This article will review the microbiological profile of nemonoxacin against respiratory pathogens including *S. pneumoniae* and *S. aureus*, and microbiological outcome data from the three Phase II–III studies.

Keywords: community-acquired pneumonia, Gram-positive bacteria, levofloxacin, nemonoxacin, novel antimicrobial, resistant pathogens

1. Introduction

Lower respiratory tract infections (LRTIs), which include community-acquired pneumonia (CAP), are the fourth leading cause of death worldwide and the first leading cause of death in low-income countries, causing 3.0 million deaths worldwide in 2016 [1]. CAP is a common condition that causes a significant disease burden for the community, particularly in children younger than 5 years, the elderly and immunocompromised people [2].

Most studies about aetiology show that *Streptococcus pneumoniae* (*S. pneumoniae*) remains the most frequently isolated pathogen in CAP patients [3, 4]. The relative frequency of other typical pathogens include *Haemophilus influenzae* (*H. influenzae*), *Moraxella catarrhalis* (*M. catarrhalis*), and *Klebsiella pneumoniae* (*K. pneumoniae*) [1, 4, 5], as well as atypical organisms include *Mycoplasma pneumoniae* (*M. pneumoniae*), *Chlamydia pneumoniae* (*C. pneumoniae*), and *Legionella pneumophila* (*L. pneumophila*) [6–10]. Recently, methicillin-resistant *Staphylococcus aureus* (MRSA) is becoming a major pathogen of CAP and causing a rapidly fatal pneumonia characterized as pulmonary haemorrhage and rapid progression to respiratory failure [11–13]. The increasing prevalence of antibiotic resistance in CAP caused by penicillin-intermediate *S. pneumoniae* (PISP) and penicillin-resistant *S. pneumoniae* (PRSP) are also of great concern [13].

All patients with CAP should initially be treated with empirical antibiotic(s) because specific pathogens are typically not identified at the time that antibiotic therapy is initiated. Several retrospective studies have shown that pathogens were not isolated or identified in more than 50% of patients exhibiting clinical signs and symptoms of pneumonia [14–17]. Furthermore, increasing incidence of antibiotic resistance (major in penicillin, cephalosporin, and macrolide resistance) observed in bacteria causing CAP has resulted in higher treatment failures and poorer medical outcomes for many patients with CAP [15]. A retrospective analysis indicated that the treatment failure of penicillin-based therapy was higher than that of fluoroquinolone-based therapy for CAP in an outpatient clinic basis [18]. The current recommendations for the management of community acquired pneumonia indicated that monotherapy with a respiratory fluoroquinolone as an appropriate empirical treatment for adult CAP inpatients and complicated CAP outpatients with risk factors, more severe disease, or recent use of antibiotics [19].

Nemonoxacin (NEMO), a novel C-8-methoxy non-fluorinated quinolone, exhibits the bactericidal action by inhibition of the topoisomerase II (DNA gyrase) and topoisomerase IV which are required for bacterial DNA replication, repair, transcription, and recombination. The mechanism of action for quinolones, including NEMO, is different from that of aminoglycosides, beta-lactams, macrolides or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to NEMO. Resistance to fluoroquinolones occurs majorly by a mutation in DNA gyrase and/or topoisomerase IV genes, altered drug permeation through efflux transporter [20]. Mutations in two quinolone resistance-determining regions (QRDR) of genes encoding DNA gyrase (gyrA and gyrB) and topoisomerase IV (parC and parE) cause resistance to fluoroquinolones [21, 22]. However, bacteria resistance to NEMO only occurred when three different mutations was found in their QRDR genes [23]. Thus, NEMO has a higher barrier for generating resistant pathogens compared to other fluoroquinolones. *In vitro* resistance to NEMO develops slowly and difficultly via multiple-step mutations [24, 25].

NEMO has shown broad spectrum activity both *in vitro* and *in vivo* against Gram-positive and Gram-negative bacteria [25–30], particularly multi-drug resistant Gram-positive bacteria such as PRSP and MRSA. NEMO also exhibits potent antibacterial activity against Gram-negative bacteria and atypical pathogens such as *H. influenzae*, *M. catarrhalis*, *M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila in vitro* [26, 31]. Oral NEMO (500 mg) has been approved for treatment of adult CAP patients in Taiwan (2014) and mainland China (2016) [32, 33]. In December 2013, the U.S. Food and Drug Administration (FDA) granted NEMO with 'qualified infectious disease product (QIDP)' and 'fast-track' designations for CAP and acute bacterial skin and skin structure infection [34]. NEMO (intravenous formulation) also submitted its new drug application (NDA) in May 2017, and granted priority review by the China FDA in February 2018 [35, 36].

An integrated analysis of one Phase III (registration number: NCT01529476) and two Phase II studies (registration numbers: NCT00434291 and NCT01537250) was conducted to compare the commercial dose of oral NEMO 500 mg vs. oral levofloxacin (LEVO) 500 mg for CAP treatment [37–39]. This article will review the integrated efficacy results of NEMO vs. LEVO against the common respiratory pathogens isolated from the three Phase II–III trials. LEVO was chosen as the comparator because it is commonly prescribed worldwide and it is recommended in guidelines for the treatment of CAP.

2. Materials and methods

2.1 Ethical approval

One Phase III study was conducted between March 2011 and August 2012 at 53 centres in China and Taiwan [study number: TG-873870-C-4 (study C4)]; one Phase II study was conducted from August 2009 to August 2010 at 26 centres in China [study number: TG-873870-C-3 (study C3)]; the other Phase II study was conducted from December 2006 to September 2007 at 19 centres in the Republic of South Africa and Taiwan [study number: TG-873870-02 (study 02)]. Three studies were conducted in accordance with International Conference on Harmonization Guidelines, the Declaration of Helsinki, and the Good Clinical Practice. The protocols and sample informed consent form were approved by the Institutional Review Board of each participating study site. Written informed consent was provided by all patients or their legally authorized representatives prior to screening/study enrollment.

2.2 Study design

All three studies were designed as multicenter, randomized, double-blind, double-dummy, active comparator-controlled trials to assess the non-inferiority of NEMO vs. LEVO for the treatment of CAP in adult patients.

Eligible patients were randomized assigned in a 2:1 ratio to receive either NEMO 500 mg or LEVO 500 mg in the phase III trial, and in a 1:1:1 ratio to receive either NEMO 500 mg or 750 mg, or LEVO 500 mg in the two phase II trials. All drugs were orally administered once daily for 7–10 days. To be evaluable, the test-of-cure (TOC) assessments had to occur between 7 and 21 days after administration of the last dose of study medication. This article will review the integrated efficacy results of three Phase II–III trials comparing the commercial dose of NEMO 500 mg vs. LEVO 500 mg for CAP treatment.

2.3 Eligibility criteria

Adult subjects were eligible if they had a clinical diagnosis of CAP (defined as fever, elevated white blood cell count, cough, purulent sputum, dyspnoea or tachypnoea, chest pain, pulmonary consolidation, etc.), had a chest radiograph demonstrating new or persistent/progressive infiltrate, and suitable for outpatient therapy with an oral antimicrobial agent.

Patients were excluded if they had any of the following conditions: severe CAP (e.g. requiring invasive endotracheal ventilation or vasoconstrictor due to septic shock), other pneumonia infection (e.g. hospital-acquired pneumonia, viral pneumonia, aspiration pneumonia), history of lung diseases (e.g. active tuberculosis, bronchiectasis, cystic fibrosis, lung abscess, lung cancer, post-obstructive pneumonia), history of hypersensitivity or allergic reactions to any quinolone, history of cardiac diseases (e.g. QTc prolongation, clinically significant abnormality on a 12-lead electrocardiogram at screening), clinically significant renal, hepatic or mental disease, malabsorption syndrome, and received prohibited medications prior enrollment (e.g. other investigational drug, systemic antibacterial agent, chemotherapeutic agents or oncolytics).

Subjects could be withdrawn from the study at any time, for any reason, and without prejudice to further treatment. The criteria for enrollment were to be followed explicitly. If a patient who did not meet enrollment criteria was inadvertently enrolled, that patient was withdrawn from the study. An exception could

have been granted in rare circumstances where there was a compelling safety or ethical reason to allow the patient to continue. In these rare cases, the Investigator was required to obtain documented approval from Sponsor to allow the subject to continue in the study.

2.4 Efficacy assessment

Clinical response at the TOC visit was the primary efficacy endpoint for the three CAP studies. Clinical response was defined as cure (complete resolution or improvement of all pneumonia-related signs and symptoms that existed during enrollment, with chest radiographs improved or not worse, no further antibiotic therapy required, and no new sign and symptoms occurred), failure (persistence or worsening of sign and symptoms of pneumonia, additional treatment with a non-study antibiotic for pneumonia, or progression of chest radiograph abnormalities) or unevaluable (lost to follow-up or withdrew consent which made it lost post-treatment information, failed to complete at least 3 days of treatment, or had an infection other than pneumonia judged by the investigator).

Microbiological response at the TOC visit was the secondary efficacy endpoint for the three CAP studies. 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). Microbiological failure was defined as persistence and presumed persistence of the baseline pathogen.

2.5 Microbiological evaluations

Baseline bacterial cultures were taken from the primary site of infection (e.g. sputum expectoration), together with 2 sets of blood cultures obtained within 24 h before patients received the 1st dose of study drugs.

Sputum samples were collected by expectoration after deep coughing. Fresh specimens collected under the supervision of the investigator were immediately transported to a local laboratory for Gram stain. Cultures were only performed on specimens if the Gram stain revealed <10 squamous epithelial cells and >25 leukocytes per low-power field. All isolates identified at the local laboratory from such specimens were then sent to the central laboratory for re-identification and susceptibility testing using CLSI methodology. Only the central laboratory microbiology results were utilized in the database. The only exception was if a local laboratory specimen had become unavailable. MICs of NEMO and LEVO were determined for all isolates.

Serology tests for *M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila* were performed at both baseline and TOC visits. Urine samples were also collected to identify *L. pneumophila* by antigen testing at the baseline visit.

2.6 Statistics

Non-inferiority (NI) of NEMO to LEVO was evaluated for clinical response by using 2-sided 95% confidence interval (CI) for the true difference in clinical cure rate (NEMO minus LEVO), with clinical cure or failure determined at the TOC visit. NI was concluded if the lower limit of the 2-sided 95% CI was not lower than −10% for the phase III study (lower limit of 95% CI $\geq -10\%$), and not lower than −15% for the two phase II studies (lower limit of 95% CI $\geq -15\%$).

3. Integrated results

3.1 Clinical responses

The clinical responses at the TOC visit for NEMO 500 mg compared to LEVO 500 mg are outlined in **Table 1**. The integrated analysis of clinical cure rate for NEMO was 93.0% compared with 91.9% for LEVO.

All three studies met its clinical endpoint by confirming the non-inferiority of NEMO 500 mg compared with LEVO 500 mg. In the primary population with evaluable assessment at TOC visit, the clinical cure rates for NEMO and LEVO were 94.3% (300/318) and 93.5% (143/153), respectively, in study C4; 93.3% (56/60) and 88.5% (46/52), respectively, in study C3; and 87.0% (67/77) and 91.1% (72/79), respectively, in study 02. The treatment differences (95% CI) between NEMO and LEVO were 0.9% (−3.8%, 5.5%) in study C4, 4.9% (−5.9%, 15.6%) in study C3, and −4.1% (−13.9%, 5.7%) in study 02. Thus, in the three studies, NEMO was found to be non-inferior to LEVO because the lower limit of the 95% CI of the treatment difference was ≥ −10% in the phase III study and ≥ −15% in both phase II studies. Non-inferiority of NEMO 500 mg to LEVO 500 mg was demonstrated.

3.2 Microbiological response

3.2.1 Overall recovery rate

The overall recovery rate of pathogens (typical and atypical combined) in all randomized patients was 57.0% (504/989). This included pathogens identified in

Population	Clinical response	NEMO n (%)	LEVO n (%)	Differences % (95% CI)
Integrated analysis				
Integrated-primary population	Cure[a]	423 (93.0%)	261 (91.9%)	—
	Failure	32 (7.0%)	23 (8.1%)	
	Unevaluable	22 (–)	18 (–)	
Phase III Study-C4				
Primary population[b]	Cure[a]	300 (94.3%)	143 (93.5%)	0.9 (−3.8, 5.5)
	Failure	18 (5.7%)	10 (6.5%)	
	Unevaluable	10 (–)	7 (–)	
Phase II Study-C3				
Primary population[b]	Cure[a]	56 (93.3%)	46 (88.5%)	4.9 (−5.9,15.6)
	Failure	4 (6.7%)	6 (11.5%)	
	Unevaluable	0 (–)	0 (–)	
Phase II Study-02				
Primary population[b]	Cure[a]	67 (87.0%)	72 (91.1%)	−4.1 (−13.9,5.7)
	Failure	10 (13.0%)	7 (8.9%)	
	Unevaluable	12 (–)	11 (–)	

[a]*Clinical cure rate = 100 × number of patients with clinical cure/(number of patients with clinical cure + number of patients with clinical failure). Unevaluable response was excluded.*
[b]*Primary populations were modified intention-to-treat (mITT), full analysis set (FAS), and intention-to-treat (ITT) for TG-873870-C4, TG-873870-C3, and TG-873870-02 studies, respectively [35–37].*

Table 1.
Clinical response at TOC in primary population.

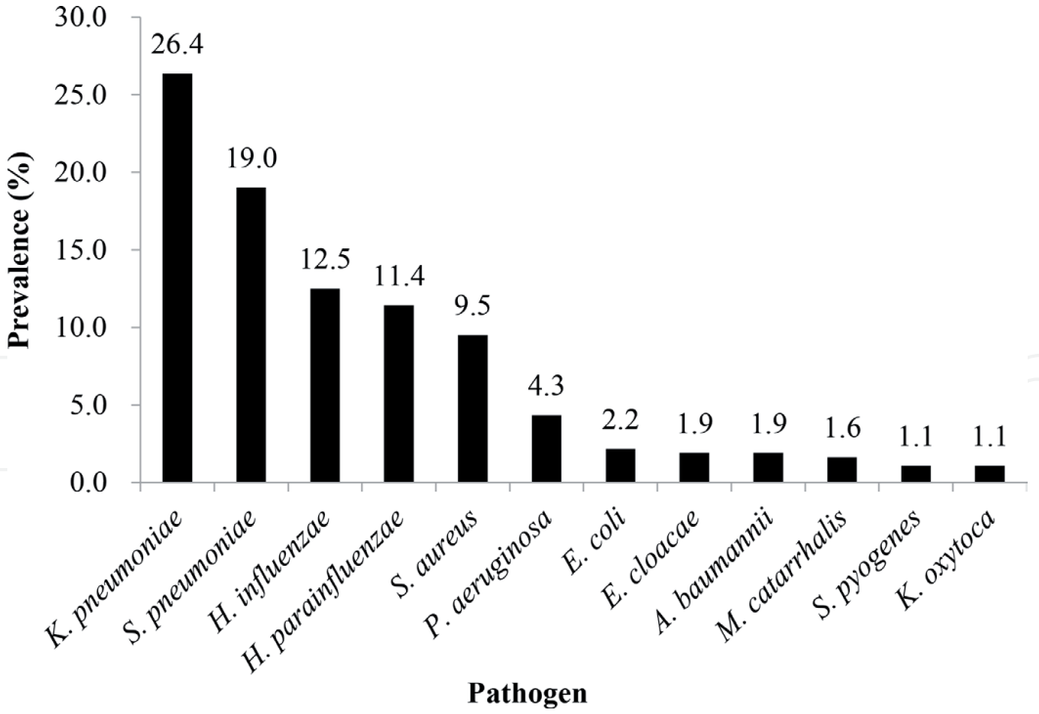

Figure 1.
Identification and prevalence of baseline pathogens in three CAP studies.

appropriate sputum specimen, blood, or other test such as urinary antigen test and atypical pathogen serology testing. The recovery rate for typical pathogens was 29.3% (290/989). These results were consistent with those observed in other CAP studies [38–42]. The most commonly identified pathogens in all randomized patients were *K. pneumoniae*, *S. pneumoniae*, *Haemophilus species*, and *S. aureus* (**Figure 1**).

3.2.2 Microbiological responses to individual pathogens

The per-pathogen responses of NEMO 500 mg and LEVO 500 mg for the most prevalent pathogens are outlined in **Table 2**. High clinical and microbiological response rates were achieved against the common CAP pathogens, with similar success rates between the two treatment groups.

The microbiological responses were evaluated in the primary populations who had at least one typical bacterial pathogen identified at baseline from an appropriate specimen. Microbiological eradication and presumed eradication were considered to be success responses. The microbiological success rates for the common baseline CAP pathogens (NEMO vs. LEVO) were 95.6% (22/23) vs. 90.0% (18/20) for *S. pneumoniae*, 95.2% (20/21) vs. 88.9% (8/9) for *S. aureus*, 92.9% (39/42) vs. 86.1% (31/36) for *K. pneumoniae*, and 90.7% (39/43) vs. 91.3% (21/23) for Haemophilus species.

Among the *S. pneumoniae* isolates, four were penicillin non-susceptible (PRSP and PISP), with three isolates identified in the NEMO group and one isolate in the LEVO group. The microbiological responses for penicillin non-susceptible *S. pneumoniae* were all success for both groups.

As expected in CAP, the isolation of MRSA was rare, with only 4 isolates identified in the NEMO group. Three out of four patients infected with MRSA had successful responses after receiving NEMO.

Overall, the clinical and microbiological responses for the most commonly identified pathogens were almost concordant. High clinical cure rates were achieved

Baseline pathogen	Clinical cure rate[a]		Microbiological success rate[b]	
	NEMO n1/n2 (%)	LEVO n1/n2 (%)	NEMO n1/n2 (%)	LEVO n1/n2 (%)
Gram-positive bacteria				
Streptococcus pneumoniae	22/24 (91.7%)	19/20 (95.0%)	22/23 (95.6%)	18/20 (90.0%)
PRSP	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)
PISP	2 (100.0%)	—	2 (100.0%)	—
Staphylococcus aureus	20/21 (95.2%)	8/9 (88.9%)	20/21 **(95.2%)**	8/9 (88.9%)
MRSA	3/4 (75.0%)	—	3/4 (75.0%)	—
Gram-negative bacteria				
Klebsiella pneumoniae	40/42 (95.2%)	32/36 (88.9%)	39/42 (92.9%)	31/36 (86.1%)
Haemophilus species	39/43 (90.7%)	21/23 (91.3%)	39/43 (90.7%)	21/23 (91.3%)
Escherichia coli	5/5 (100.0%)	1/1 (100.0%)	5/5 (100.0%)	1/1 (100.0%)
Moraxella catarrhalis	2/2 (100.0%)	3/3 (100.0%)	2/2 (100.0%)	3/3 (100.0%)
Pseudomonas aeruginosa	6/7 (85.7%)	5/5 (100.0%)	6/7 (85.7%)	4/5 (80.0%)
Acinetobacter baumannii	5/5 (100.0%)	1/1 (100.0%)	5/5 (100.0%)	1/1 (100.0%)
Atypical pathogens				
Mycoplasma pneumoniae	90/97 (92.8%)	63/66 (95.5%)	—	—
Chlamydia pneumoniae	22/23 (95.7%)	16/16 (100.0%)	—	—
Legionella pneumophila	19/21 **(90.5%)**	8/8 (100.0%)	—	—

[a]*Clinical cure rate = 100 × number of patients with clinical cure/(number of patients with clinical cure + number of patients with clinical failure). Unevaluable response was excluded.*
[b]*Microbiological success rate = 100 × number of patients with success response/(number of patients with success response + number of patients with failure response). Unevaluable response was excluded.*

Table 2.
Per-pathogen clinical and microbiological response at TOC in the integrated-primary population.

against not only typical bacteria but also atypical pathogens after NEMO treatment, with 92.8% (90/97), 95.7% (22/23), and 90.5% (19/21) for *M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila*, respectively.

3.2.3 Antimicrobial susceptibility

The susceptibility of baseline pathogens isolated from the three CAP studies are outlined in **Table 3**. All isolates of *S. pneumoniae*, including PRSP and LEVO-resistant strains, were inhibited by NEMO at concentrations of ≤1 mg/L. The MIC_{90} for *S. pneumoniae* were 0.125 mg/L for NEMO and 1 mg/L for LEVO.

NEMO was active against *S. aureus*, with MIC_{90} of 0.25 mg/L compared with an MIC_{90} of 2 mg/L for LEVO. Among the *S. aureus*, 5 isolates were MRSA, with MIC ranges of 0.03–1 mg/L for NEMO and 0.12–32 mg/L for LEVO. All isolates of *S. aureus*, including MRSA, were inhibited by NEMO at concentrations of ≤1 mg/L.

The *in vitro* activity of NEMO was comparable to that of LEVO against Gram-negative bacteria. But for Gram-positive bacteria including MRSA, the MIC_s of NEMO were 8-fold lower than that of LEVO, supporting its utility in the treatment of patients with CAP.

Baseline pathogen (number of isolates)	NEMO (mg/L)			LEVO (mg/L)		
	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range
Gram-positive bacteria						
S. pneumoniae (70)	0.12	0.12	≤0.015–1	1	1	0.03–8
PRSP (2)	—	—	0.12–1		—	1
LEVO-resistant (1)	—	—	0.5	—	—	8
S. aureus (35)	0.03	0.25	≤0.015–1	0.25	2	0.12–32
MRSA (5)	0.25	—	0.03–1	2	—	0.12–32
Gram-negative bacteria						
K. pneumoniae (97)	0.25	8	≤0.06–>32	0.06	4	≤0.03–>32
H. influenzae (46)	0.03	0.12	≤0.008–1	0.015	0.06	≤ 0.008–1
H. parainfluenzae (42)	0.12	2	≤0.008–4	0.06	1	≤ 0.008–8
E. coli (8)	1	—	≤0.06–>32	0.5	—	≤0.03–32
M. catarrhalis (6)	0.06	—	0.015–0.06	0.06	—	≤0.008–0.06
P. aeruginosa (16)	1	8	0.25–16	0.5	16	0.12–>32
A. baumannii (7)	0.25	—	0.12–1	0.12	—	≤0.06–1

MIC_{50} = concentration of antibiotic (mg/L) required to inhibit 50% of bacteria;
MIC_{90} = concentration of antibiotic (mg/L) required to inhibit 90% of bacteria.

Table 3.
In vitro *activity of NEMO and LEVO against baseline isolates from patients enrolled in the three CAP studies.*

4. Conclusion

Efficacy data reported herein from the individual and integrated analyses of the three CAP trials demonstrate that oral NEMO 500 mg administered once daily for 7–10 days is an efficacious treatment for adult CAP. Non-inferiority of NEMO 500 mg to LEVO 500 mg, a widely used agent in the clinical setting, was demonstrated in the three CAP studies. NEMO was effective in eradicating the typical pathogens associated with CAP, including high cure rates for atypical pathogens. Furthermore, the *in vitro* activity of NEMO against bacterial pathogens isolated from patients enrolled in the CAP clinical trials demonstrated a susceptibility profile that supports its utility in the treatment of patients with CAP.

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Conflict of interest

Li-Wen Chang and Ming-Chu Hsu are employees of TaiGen Biotechnology Co., Ltd.

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