International Journal of COPD

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ORIGINAL RESEARCH

Zabofloxacin versus moxifloxacin in patients with COPD exacerbation: a multicenter, double-blind, double-dummy, randomized, controlled, Phase III, non-inferiority trial

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This article was published in the following Dove Press journal:
International Journal of COPD
22 October 2015
Number of times this article has been viewed

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Abstract: A new quinolone, zabofloxacin, has now been developed; hence, a non-inferiority trial is needed to compare this new compound with another widely used quinolone to examine its efficacy and safety for the treatment of chronic obstructive pulmonary disease (COPD) exacerbations. This was a prospective, multicenter, double-blind, double-dummy, randomized, controlled, parallel-group, Phase III, non-inferiority clinical trial designed to compare oral zabofloxacin (367 mg once daily for 5 days) with moxifloxacin (400 mg once daily for 7 days) for the treatment of patients with COPD exacerbation. In all, 345 COPD patients with a moderate COPD exacerbation were enrolled in the study via the outpatient clinics at 31 university hospitals. Clinical per protocol analysis revealed that the clinical cure rate for zabofloxacin was 86.7% and that for moxifloxacin was 86.3% (the rate difference, 0.4%; 95% confidence interval, –7.7%–8.6%). Intention-to-treat analysis revealed clinical cure rates of 77.1% and 77.3% (difference, –0.2%; 95% confidence interval, –9.0%–8.8%), respectively. These results confirm that zabofloxacin is not inferior to moxifloxacin. The favorable microbiological response rate for zabofloxacin was 67.4% and that for moxifloxacin was 79.5% (P=0.22). Patients in the zabofloxacin group showed better patient-oriented outcomes, as measured by EXAcerbations of Chronic Pulmonary Disease Tool-Patient-Reported Outcome and the COPD assessment test scores, than patients in the moxifloxacin group. Adverse drug reactions related to zabofloxacin occurred in 9.7% of cases and those related to moxifloxacin occurred in 9.6% of cases (P=0.97). The dropout rate due to adverse events was 0% (0/175) in the zabofloxacin group and 1.8% (3/167) in the moxifloxacin group (P=0.12). Oral zabofloxacin (367 mg once daily for 5 days) was not inferior to oral moxifloxacin (400 mg once daily for 7 days) for the treatment of patients with COPD exacerbation.

Keywords: chronic obstructive pulmonary disease, exacerbation, zabofloxacin, quinolone, EXACT-PRO, CAT

Introduction

Exacerbation of chronic obstructive pulmonary disease (COPD) is characterized by a worsening of respiratory symptoms. The condition is important because it can negatively affect the quality of life of COPD patients. Moreover, exacerbation can be associated with significant mortality. Thus, adequate treatment of COPD exacerbation is mandatory. Most incidences of exacerbation are caused by respiratory tract infections;[1,2] thus, antibiotics are a key component of any treatment regimen. Antibiotics are indicated when there is evidence of an increase in either the purulence or volume of sputum.[3]

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http://dx.doi.org/10.2147/COPD.S90948

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Zabofloxacin is a new fluoroquinolone antibiotic. Previous studies show that zabofloxacin has excellent activity against both Gram-negative and Gram-positive pathogens;[4–6] however, no study has examined its effect on COPD exacerbation. Other fluoroquinolone antibiotics such as levofloxacin[7] and moxifloxacin[8] show good efficacy and safety profiles when used to treat patients with COPD exacerbation.

Therefore, the aim of the present study was to compare the efficacy and safety of oral zabofloxacin (367 mg once daily for 5 days) with that of moxifloxacin (400 mg once daily for 7 days) for the treatment of patients with COPD exacerbation.

Materials and methods

Study design

This was a prospective, multicenter, double-blind, double-dummy, randomized, controlled, parallel-group, Phase III, non-inferiority clinical trial designed to compare oral zabofloxacin (367 mg once daily for 5 days) with moxifloxacin (400 mg once daily for 7 days) for the treatment of patients with COPD exacerbation. The study was conducted between September 2012 and February 2014. This study was approved by all relevant ethical committees at each participating institution.

Study subjects

The enrollment criteria were as follows: 1) patients with COPD; 2) age ≥40 years; 3) patients experiencing moderate (patients who did not need hospitalization) exacerbation of COPD (worsening of the respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication); 4) a post-bronchodilator forced expiratory volume in 1 second/forced vital capacity <0.7; and 5) purulent sputum or increased volume of sputum. The exclusion criteria were as follows: 1) pregnant women; 2) patients who received systemic antibiotics and/or antifungal agents within the last 72 hours; 3) confirmed pneumonia (on chest X-ray) within 48 hours; 4) patients with underlying septic shock, bronchiectasis, lung abscess, active tuberculosis, pulmonary malignancy, cystic fibrosis, empyema, or asthma; 5) patients with kidney or liver disease with abnormal laboratory test results (creatinine clearance <50 mL/min/1.73 m^2; blood urea nitrogen >30 mg/dL; aspartate aminotransferase or alanine aminotransferase >3 times the upper limit of normal; total bilirubin >2 times upper limit of normal; or alkaline phosphatase >2 times upper limit of normal); 6) patients with an organic gastrointestinal disorder (such as active Crohn's disease or active ulcerative colitis) within 6 months; 7) an absolute neutrophil count <1,000 cells/mm^3; 8) patients with chronic hepatitis B or C; 9) immunocompromised patients (human immunodeficiency virus-positive, acquired immune deficiency syndrome, bone marrow transplantation, or leukemia); 10) a history of hypersensitivity to fluoroquinolone antibiotics; 11) a history of seizure or anti-seizure medications; 12) a history of ventricular arrhythmia; and 13) a history of corrected QT prolongation or treatment with medication that prolongs the corrected QT interval.

Randomization

Patients were randomized on a 1:1 basis and stratified according to the presence of chronic bronchitis (presence of cough and sputum production for at least 3 months in two consecutive years). Subjects were allocated via a blocked randomization protocol that was prepared beforehand; the ratio for each group was 1:1. The randomization list was applied independently via random numbers, which were generated by the randomization program within the SAS System. Numbers were generated according to the order in which the subjects were enrolled by each investigational institution. The randomization list was derived prior to the clinical study by a statistician employed by a contract research organization specified by the study sponsor.

Investigational drugs

The test drug was manufactured by Dongwha Pharm. Co., Ltd. (Chungju City, Seoul, Korea). The placebo for the test drug was also manufactured by Dongwha Pharm. Co., Ltd. The placebo preparation was identical to that of the drug but lacked the active ingredient, zabofloxacin D-aspartate. The comparator, Avelox® 400 mg (Bayer Korea Ltd., Seoul, Korea), was purchased from Bayer Korea Ltd. The placebo for the comparator was manufactured by NextPharma Allphamed PHARBIL Arzneimittel GmbH (Göttingen, Germany). Again, the placebo lacked the active ingredient, moxifloxacin hydrochloride. The test drug, the test drug placebo, the comparator, and the comparator placebo were packaged by Dongwha Pharm. Co., Ltd. in accordance with a previously-prepared randomization list. The drugs were then kept in the investigational products storage facility.

Blinding

The test drug, comparator, and placebos were indistinguishable in terms of appearance. The allocation information was blinded from all site investigators and subjects.

Study protocol

Patients were randomized to receive oral zabofloxacin (367 mg once daily for 5 days) and placebo (once daily for 2 days),

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or moxifloxacin (400 mg once daily for 7 days) during seven consecutive days. History taking, physical examination, laboratory tests, an electrocardiogram, and a chest X-ray were performed on Day 1 (inclusion visit, visit 1). Sputum samples were also collected. Patients who met the enrollment criteria and provided written informed consent were randomized and given the drugs. Patients were assessed over the telephone on treatment Day 4±1 (visit 2). Clinical response, microbiological response, and drug safety were assessed on the test of cure (TOC) visit on Day 10±3 (visit 3). These parameters were reassessed at the end of study (EOS) visit on Day 36±7 (visit 4).

Clinical assessment

Clinical failure was defined as a lack of improvement in dyspnea or sputum purulence/volume at TOC compared with the inclusion visit coupled with a requirement for additional antibiotic therapy. Clinical cure was defined as an improvement in dyspnea or sputum purulence/volume at TOC compared with the inclusion visit. Clinical response, microbiological response, and safety were assessed again at the EOS visit. Relapse was defined as a worsening of dyspnea or sputum purulence compared with the TOC visit (ie, the patient met the definition of "clinical cure" at the TOC visit but required additional antibiotic therapy between the TOC and EOS visits).

Microbiological assessment

Microbiological responses were classified as follows: eradication, presumed eradication, persistence, presumed persistence, recurrence, indeterminate, and emergent infection. Eradication and presumed eradication were favorable microbiological responses whereas persistence, presumed persistence, recurrence, indeterminate, and emergent infection were unfavorable microbiological responses. Eradication was defined as confirmed pathogen-free after the initial pathogen had been identified. The definition of presumed eradication was that additional samples were either uncollectable or non-culturable after the initial pathogen was identified and there were no clinical signs of persistent infection. Persistence was defined as the detection of pathogen after the initial pathogen was identified. The definition of presumed persistence was that additional samples were either uncollectable or non-culturable after the initial pathogen had been identified and there were clinical signs of persistent infection. Recurrence was defined as detection of the same pathogen (initially confirmed) at the EOS visit, even though the patient had been classified into the eradication or presumed eradication groups at the TOC visit. Indeterminate response was defined as the lack of a confirmed pathogen coupled with an unclear clinical response. Emergent infection was defined as the detection of any pathogen (other than the initial pathogen) in a patient showing clinical signs of infection.

Symptom scores

Symptom severity was determined by examining the EXAcerbations of Chronic Pulmonary Disease Tool (EXACT)-Patient-Reported Outcome (PRO) and COPD assessment test (CAT) scores obtained on Days 1–7 and on Day 36.

Primary and secondary endpoints

The primary endpoint was the clinical response rate at the time of the TOC visit in the per protocol (PP) group. The secondary endpoints were as follows: 1) clinical response rate at the EOS visit; 2) clinical response rate in the microbiological PP group at the TOC and EOS visits; 3) microbiological response rate in the microbiological PP group at the TOC and EOS visits; 4) changes in the EXACT-PRO score at the TOC and EOS visits; and 5) changes in the CAT score at the TOC and EOS visits.

Safety assessments

Drug safety was assessed in all study subjects who received at least one dose of the investigational product. Data related to adverse events, vital signs, and laboratory tests, as well as findings from physical examinations, were reviewed. All collected data were evaluated in terms of severity, changes from baseline values, and relationships to treatment with the investigational products.

Statistical analysis

All statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC, USA). The primary aim of the study was to reject the null hypothesis that zabofloxacin therapy was >10% less effective than moxifloxacin therapy. To examine the difference in the clinical cure rate, the 95% confidence interval (CI) for zabofloxacin minus that of moxifloxacin was calculated using Mantel–Haenszel weights. For zabofloxacin to be considered no less effective than moxifloxacin, the lower limit of this CI had to be greater than −10%. The clinical cure rate of moxifloxacin in a previous study was 91%[8] and the clinical cure rate of the test drug and the comparator were presumed as 91%. Level of significance (α) was 0.05 and type 2 error (β) was set as 0.2 to maintain the power of the test as 80%. The number of cases required for the clinical trial was 129 subjects per group. Dropout rate was expected as 25% and

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calculated number of subjects in each group was 172. Both intention-to-treat (ITT) and PP analyses were performed. Differences between groups were assessed using the chi-squared test or Fisher's exact test (categorical variables) and Student's *t*-test or the Mann–Whitney *U*-test (continuous variables). A paired *t*-test was used to compare changes in the EXACT-PRO and CAT scores between Day 1 and the other test days. To compare changes in the EXACT-PRO and CAT scores between the zabofloxacin- and moxifloxacin-treated groups, the delta values (differences between score on Day 1 and other test days) for each group were compared using Student's *t*-test. Data are expressed as the mean ± standard deviation throughout the paper except in the figures. Data are expressed as mean ± standard error of mean in figures.

This study is registered with ClinicalTrials.gov number NCT01658020 and Clinical Research Information Service registry number KCT0000532.

Results

Study subjects

A total of 345 COPD patients with moderate exacerbation were enrolled in the study via the outpatient clinics at 31 university hospitals. Patients were randomly assigned to receive zabofloxacin (n=176) or moxifloxacin (n=169). In all, 342 subjects (175 zabofloxacin and 167 moxifloxacin) were included in the ITT analysis (three patients were excluded in the ITT because the drug was not administered). A total of 274 subjects (143 zabofloxacin and 131 moxifloxacin) were included in the clinical PP analysis and 82 subjects (43 zabofloxacin and 39 moxifloxacin) were included in the microbiological PP analysis (Figure 1).

Baseline characteristics are described in Table 1. There were no significant differences in the baseline characteristic of the two groups, except sex and smoking history.

Clinical response

The clinical cure rates in the PP analysis at the time of the TOC visit were 86.7% (124/143) for zabofloxacin and 86.3% (113/131) for moxifloxacin. The difference in the clinical cure rate between the two antibiotics (zabofloxacin minus moxifloxacin) was 0.4% (95% CI, −7.7%–8.6%). ITT analysis revealed the clinical cure rates to be 77.1% (135/175) and 77.3% (129/167), respectively, with a difference of −0.1% (95% CI, −9.0%–8.8%) (Table 2). These results confirm that zabofloxacin was not inferior to moxifloxacin in terms of clinical efficacy at TOC. Clinical PP analysis showed that the clinical cure rate for zabofloxacin at the time of the EOS visit was 76.2% (109/143), whereas that for moxifloxacin was 71.0% (93/131, *P*=0.28). Clinical ITT analysis showed that the clinical cure rate for zabofloxacin at the time of the EOS visit was 68.6% (120/175), whereas that for moxifloxacin was 64.7% (108/167, *P*=0.67).

Clinical PP analysis of the subgroup of patients with chronic bronchitis showed that at the time of the TOC visit, the clinical cure rate for zabofloxacin was 88.2% (45/51) and that for moxifloxacin was 89.1% (49/55, *P*=0.89). The clinical cure rates for the subgroup of patients without chronic bronchitis were 85.9% (79/82) and 84.2% (64/76), respectively (*P*=0.76). ITT analysis showed that the clinical cure rates for the subgroup of patients with chronic bronchitis were 80% (52/65) and 77.5% (55/71, *P*=0.64), respectively, and those for the subgroup of patients without chronic bronchitis were 75.5% (83/110) and 77.1% (74/96), respectively (*P*=0.87).

Microbiological response

The antimicrobial susceptibilities of pathogens isolated at visit 1 are described in Table 3. Microbiological PP analysis of the microbiological response rates at the TOC visit revealed that 29 subjects (67.4%) in the zabofloxacin group and 31 subjects (79.5%) in the moxifloxacin group presented with a favorable microbiological response (eradication or presumed eradication) (*P*=0.22). Microbiological PP analysis at EOS revealed that 27 subjects (62.8%) in the zabofloxacin group and 25 subjects (64.1%) in the moxifloxacin group showed a favorable microbiological response (*P*=0.90, Table 4).

Changes in the CAT and EXACT-PRO scores

Clinical PP analysis revealed that the EXACT-PRO scores on Days 2, 3, 4, 5, 6, 7, and 36 decreased significantly when compared with the scores on Day 1 for both the zabofloxacin and moxifloxacin groups (Figure 2A). However, the decline of EXACT-PRO scores for the zabofloxacin group on Days 6 and 7 were significantly greater than those of the moxifloxacin group (Figure 2C). PP analysis showed that the CAT scores on Days 3, 4, 5, 6, 7, and 36 were significantly lower than those on Day 1 for both the zabofloxacin and moxifloxacin groups (Figure 2B). Again, the decline in the CAT scores on Days 5, 6, and 7 was significantly greater in the zabofloxacin than moxifloxacin groups (Figure 2D).

Clinical ITT analysis of the EXACT-PRO scores showed that the scores on Days 2, 3, 4, 5, 6, 7, and 36 were significantly lower than those on Day 1 for both the zabofloxacin and moxifloxacin groups (Figure 3A). However, the decline

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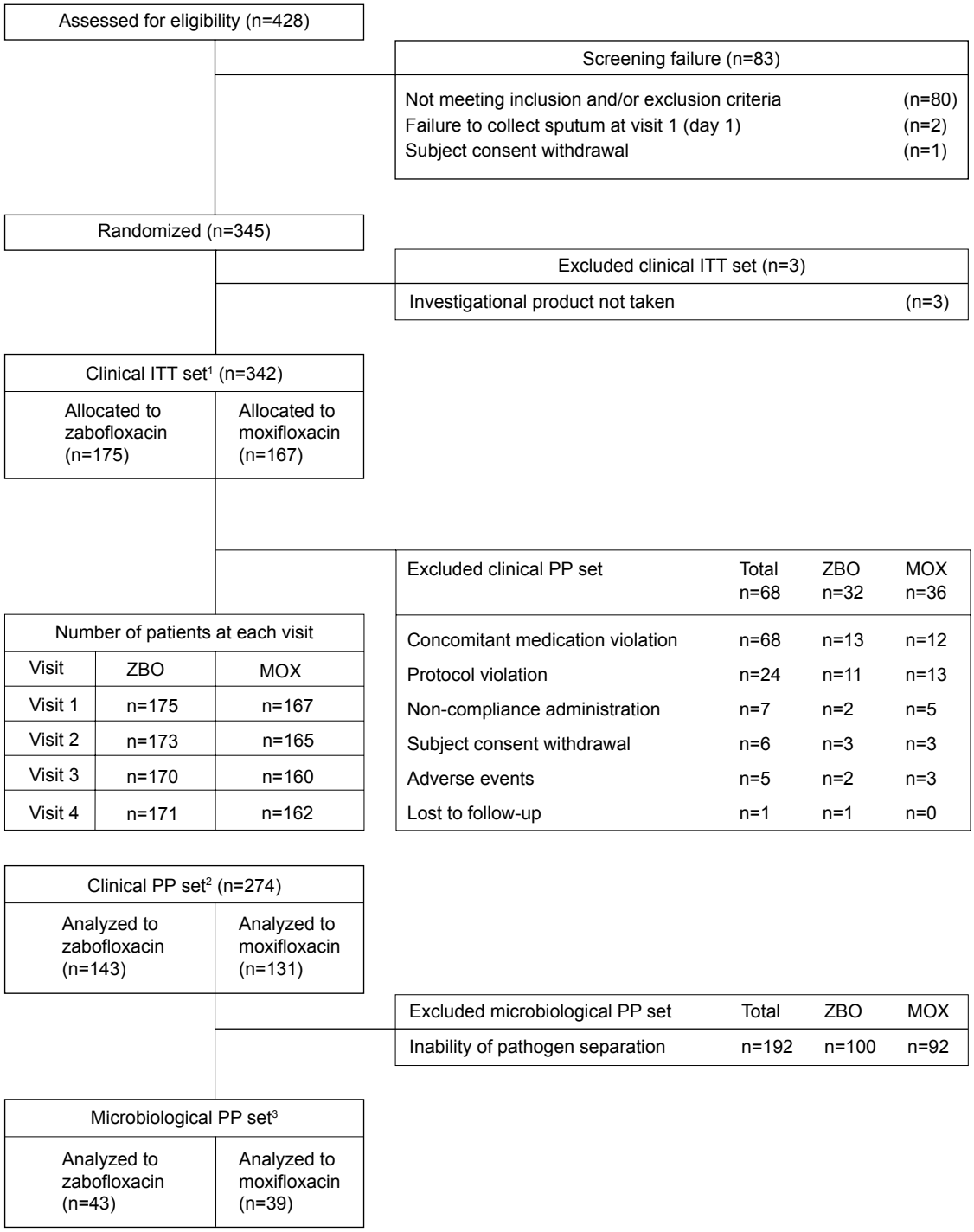

Figure 1 Disposition of patients during study.

Notes: [1]Clinical ITT set: This population consisted of all randomized subjects who received at least one dose of the investigational product. [2]Clinical PP set: This population consisted of all randomized subjects who met the study inclusion and/or exclusion criteria, who received an adequate course of therapy, for whom sufficient information was available to determine the subject's outcome, and who had no confounding factors that interfered with the assessment of the outcome. [3]Microbiological PP set: This population consisted of a subset of the clinical PP subjects who had a baseline pathogen identified.

Abbreviations: ZBO, zabofloxacin; MOX, moxifloxacin; ITT, intention-to-treat; PP, per protocol.

in the scores for the zabofloxacin group on Days 6 and 7 was significantly greater than those for the moxifloxacin group (Figure 3C). Clinical ITT analysis of the CAT scores showed that the scores for the zabofloxacin group on Days 2, 3, 4, 5, 6, 7, and 36 were significantly lower than those on Day 1; however, the scores for the moxifloxacin group were significantly lower on Days 3, 4, 5, 6, 7, and 36 than on Day 1 (Figure 3B). The decline in the CAT scores for the zabofloxacin group on Days 5, 6, 7, and 36 was significantly greater than that in the moxifloxacin group (Figure 3D).

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Table 1 Baseline characteristics of the patients

Characteristics	Zabofloxacin (n=175) (%)	Moxifloxacin (n=167) (%)	*P*-value
Age, years	67.8±7.8	68.4±8.0	0.46
Sex, male	153 (87.4)	159 (95.2)	0.01
Height, cm	162.9±6.5	164.1±6.3	0.10
Weight, kg	59.8±11.1	58.7±9.6	0.33
Smoking history			<0.01
Current	50 (28.6)	38 (22.8)	
Ex	107 (61.1)	126 (75.5)	
Never	18 (10.3)	3 (1.8)	
Alcohol			0.29
Never	26 (14.9)	21 (12.6)	
Ex	91 (52.0)	101 (60.5)	
Current	58 (33.1)	45 (27.0)	
Chronic bronchitis	65 (37.1%)	71 (42.5%)	0.31
PFT (post-BD)			
FVC (L)	2.9±0.8	3.1±0.7	0.10
FVC (%)	74.9±17.0	76.5±16.7	0.40
FEV_1 (L)	1.4±0.5	1.4±0.5	0.93
FEV_1 (%)	50.5±18.1	49.1±17.2	0.51
FEV_1/FVC (%)	47.8±12.7	45.2±12.6	0.07
Dyspnea			0.60
Mild	27 (15.4)	25 (15.0)	
Moderate	113 (64.6)	101 (60.5)	
Severe	35 (20.0)	41 (24.6)	
Comorbidity			
Ischemic heart disease	13 (7.4)	14 (8.4)	0.74
Congestive heart failure	12 (6.9)	7 (4.2)	0.28
Cerebrovascular disease	7 (4.0)	3 (1.8)	0.34
Diabetes mellitus	15 (8.6)	18 (10.8)	0.49
Hypertension	50 (28.6)	48 (28.7)	0.97
Osteoporosis	11 (6.3)	6 (3.6)	0.25
Hyperlipidemia	14 (8.0)	9 (5.4)	0.34
Concomitant medication			
Systemic steroid during exacerbation	81 (46.3)	85 (50.9)	0.39
LABA	17 (9.7)	28 (16.8)	0.05
LAMA	116 (66.3)	118 (70.7)	0.38
ICS	9 (5.1)	9 (5.4)	0.92
ICS + LABA	99 (56.6)	89 (53.3)	0.54
Theophylline	29 (16.6)	21 (12.6)	0.30
PDE4I	9 (5.1)	12 (7.2)	0.43
Symptom score on Day 1			
EXACT-PRO	45.5±9.6	46.7±11.9	0.31
CAT	22.6±7.0	23.2±7.6	0.45

Note: Data are expressed as mean ± standard deviation or as number (percentage) of patients.

Abbreviations: PFT, pulmonary function test; BD, bronchodilator; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroid; PDE4I, phosphodiesterase 4 inhibitor; EXACT-PRO, EXAcerbations of Chronic Pulmonary Disease Tool-Patient-Reported Outcome; CAT, chronic obstructive pulmonary disease assessment test.

Adverse events

Adverse events occurred in 36.6% (64/175; 108 events) of patients in the zabofloxacin group and in 38.9% (65/167; 105 events) of patients in the moxifloxacin group (*P*=0.65). The rate of adverse drug reactions to zabofloxacin was 9.7% (17/175; 25 events) and that to moxifloxacin was 9.6% (16/167; 23 events); the difference was not statistically significant (*P*=0.97, Table 5). Serious adverse events occurred in 4% (7/175; seven events: COPD exacerbation in four cases, influenza like illness in one, pneumonia in one, acute pyelonephritis in one) of patients in the zabofloxacin group and in 4.8% (8/167; eight events: COPD exacerbation in four cases, pneumonia in two, variant angina in one, urethral stenosis in one) of patients in the moxifloxacin group; again, the difference was not statistically significant (*P*=0.72). There was no incidence of serious adverse drug reaction. The dropout rate due to adverse events was 0% (0/175) in the zabofloxacin group and 1.8% (3/167) in the moxifloxacin group (*P*=0.12).

Discussion

The present study compared the efficacy and safety of zabofloxacin with that of moxifloxacin for the treatment of COPD patients with exacerbation. Both drugs showed comparable efficacy and a good safety profile. Also, there were no significant differences in the microbiological response rates. Interestingly, analysis of the EXACT-PRO and CAT scores revealed that zabofloxacin seemed to be superior to moxifloxacin.

There have been several randomized clinical trials to compare the effect of moxifloxacin with other antibiotics on exacerbation of chronic bronchitis. Moxifloxacin was not inferior to clarithromycin,[9,10] azithromycin,[11,12] ceftriaxone,[13] and amoxicillin/clavulanic acid.[14] In a meta-analysis,[15] moxifloxacin was clinically equivalent and bacteriologically superior to the antibiotic regimens routinely used in patients with exacerbation of chronic bronchitis. This comparison was made between moxifloxacin and non-quinolone antibiotics.

Urueta-Robledo et al[8] showed that a 5-day course of moxifloxacin was clinically and bacteriologically equivalent to a 7-day course of levofloxacin for the treatment of patients with an acute exacerbation of chronic bronchitis. Here, we found that a 5-day course of zabofloxacin was clinically and bacteriologically equivalent to a 7-day course of moxifloxacin for the treatment of patients with an acute exacerbation of COPD. Because levofloxacin, moxifloxacin, and zabofloxacin are all quinolone antibiotics, the clinical efficacy may be similar. The main purpose of this study is to prove the non-inferiority of zabofloxacin to moxifloxacin. However, we also aimed to see whether a shorter period of administration of zabofloxacin results in comparable clinical

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Table 2 Clinical response rates

	Clinical PP		Clinical ITT	
	Zabofloxacin (n=143) (%)	Moxifloxacin (n=131) (%)	Zabofloxacin (n=175) (%)	Moxifloxacin (n=167) (%)
Test of cure				
Clinical cure	124 (86.7)	113 (86.3)	135 (77.1)	129 (77.3)
95% CI of clinical cure	(81.2, 92.3)	(80.4, 92.2)	(71.9, 84.2)	(72.9, 85.4)
Clinical failure	19 (13.3)	18 (13.7)	20 (11.4)	18 (10.8)
Indeterminate	0 (0.0)	0 (0.0)	20 (11.4)	20 (12.0)
End of study				
Clinical cure	109 (76.2)	93 (71.0)	120 (68.6)	108 (64.7)
95% CI of clinical cure	(69.3, 83.2)	(63.2, 78.8)	(62.5, 76.2)	(59.0, 73.5)
Clinical failure	33 (23.1)	34 (26.0)	34 (19.4)	34 (20.4)
Relapse	14 (9.8)	16 (12.2)	14 (8.0)	16 (9.6)
Indeterminate	1 (0.7)	4 (3.1)	21 (12.0)	25 (15.0)

Abbreviations: PP, per protocol; ITT, intention-to-treat; CI, confidence interval.

Table 3 Antimicrobial susceptibility of pathogens isolated at visit 1 (enrollment day)

Pathogen	n	Zabofloxacin			Moxifloxacin		
		MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range
Haemophilus influenzae	54	0.004	0.008	0.002–0.25	0.016	0.016	0.004–0.5
Pseudomonas aeruginosa	28	1	8	≤0.125–32	2	16	≤0.125–64
Streptococcus pneumoniae	27	0.031	0.125	0.008–0.25	0.25	1	0.125–>2
Moraxella catarrhalis	16	0.016	0.016	0.004–0.016	0.063	0.063	0.016–0.063

Notes: n, number of patients with pathogen in sputum. MIC_{50}, MIC_{90}, and range values are expressed as μg/mL.
Abbreviation: MIC, minimum inhibitory concentration.

Table 4 Microbiological response according to the microbiological per protocol analysis

	Zabofloxacin n=43 (%)	Moxifloxacin n=39 (%)	*P*-value
Test of cure			0.22
Favorable bacteriological response	29 (67.4)	31 (79.5)	
Eradication	11 (25.6)	11 (28.2)	
Presumed eradication	18 (41.9)	20 (51.3)	
Unfavorable bacteriological response	14 (32.6)	8 (20.5)	
Persistence	11 (25.6)	5 (12.8)	
Presumed persistence	1 (2.3)	0 (0.0)	
Recurrence	0 (0.0)	0 (0.0)	
Indeterminate	0 (0.0)	0 (0.0)	
Emergent infection	2 (4.7)	3 (7.7)	
End of study			0.90
Favorable bacteriological response	27 (62.8)	25 (64.1)	
Eradication	10 (23.3)	8 (20.5)	
Presumed eradication	17 (39.5)	17 (43.6)	
Unfavorable bacteriological response	16 (37.2)	14 (35.9)	
Persistence	5 (11.6)	3 (7.7)	
Presumed persistence	2 (4.7)	2 (5.1)	
Recurrence	4 (9.3)	2 (5.1)	
Indeterminate	0 (0.0)	0 (0.0)	
Emergent infection	5 (11.6)	7 (18.0)	

Abbreviation: n, number of patients.

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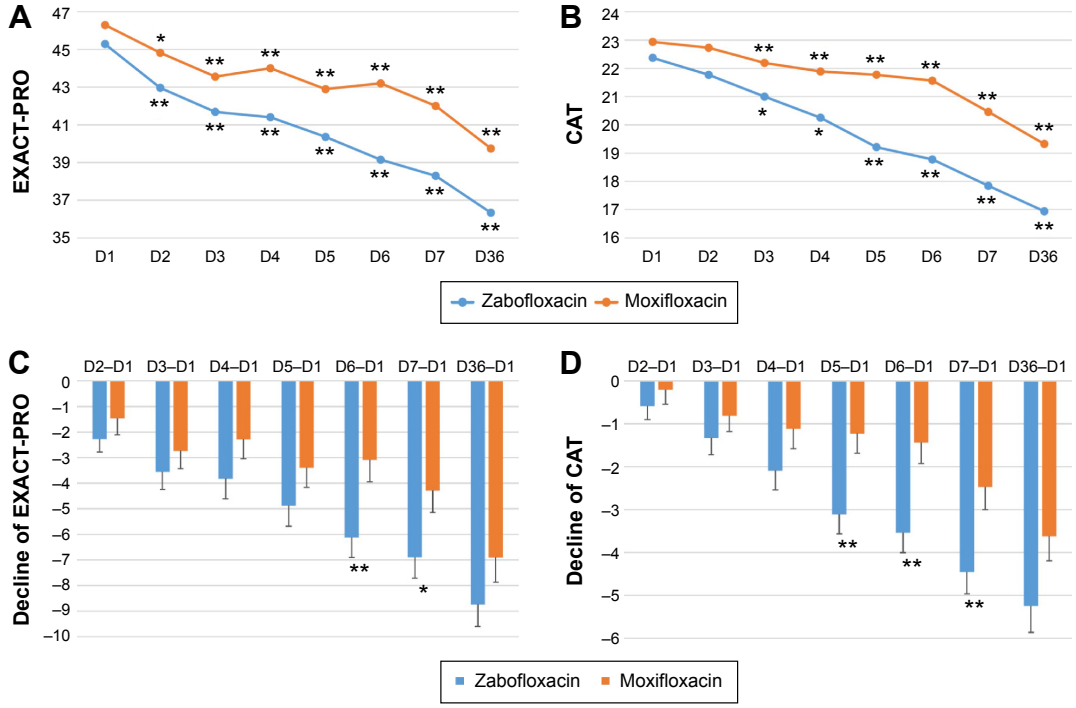

Figure 2 Clinical per protocol analysis of changes in the EXACT-PRO and CAT scores.
Notes: The EXACT-PRO (**A**) and CAT scores (**B**) decreased significantly compared with those on D1 (*$P<0.05$, **$P<0.01$ vs D1) in both the zabofloxacin and moxifloxacin groups. The decline in the EXACT-PRO (**C**) scores on D6 and D7 and the decline in the CAT scores (**D**) on D5, D6, and D7 were significantly greater in the zabofloxacin than in the moxifloxacin group (*$P<0.05$ and **$P<0.01$ between the zabofloxacin and moxifloxacin groups).
Abbreviations: EXACT-PRO, EXAcerbations of Chronic Pulmonary Disease Tool-Patient-Reported Outcome; CAT, chronic obstructive pulmonary disease assessment test; D, day.

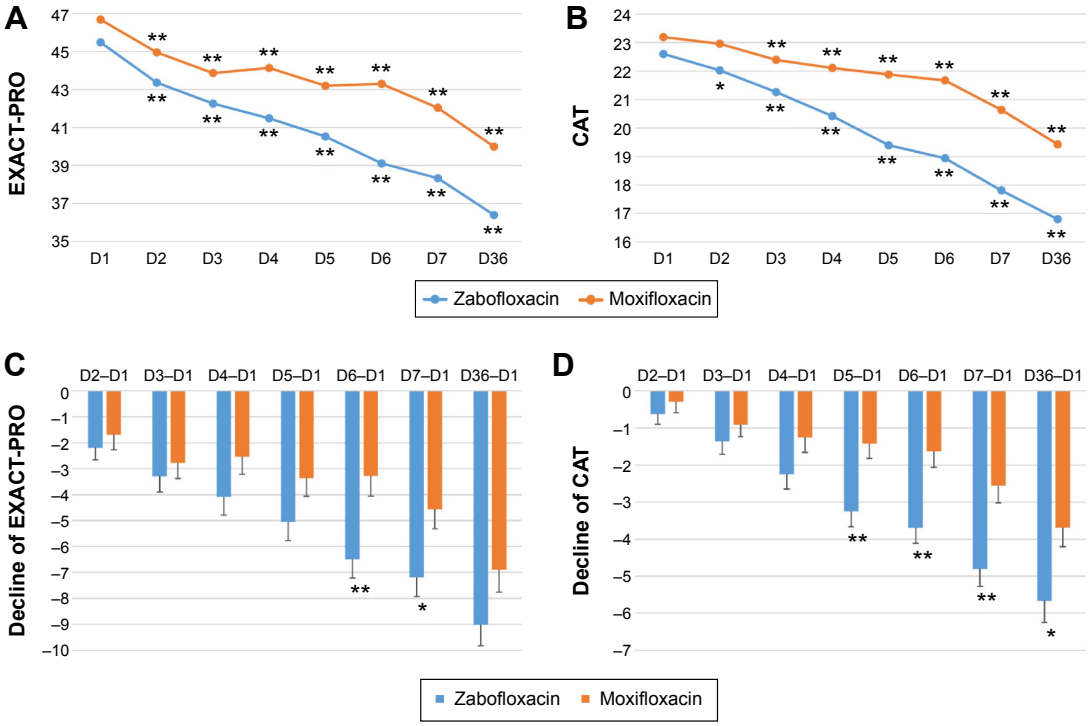

Figure 3 Clinical intention-to-treat analysis of the changes of EXACT-PRO and CAT scores.
Notes: The EXACT-PRO (**A**) and CAT scores (**B**) decreased significantly compared with those on D1 (*$P<0.05$, **$P<0.01$ vs D1) in both the zabofloxacin and moxifloxacin groups. The decline in the EXACT-PRO (**C**) scores on D6 and D7 and the decline in the CAT scores (**D**) on D5, D6, D7, and D36 were significantly greater in the zabofloxacin than in the moxifloxacin group (*$P<0.05$ and **$P<0.01$ between the zabofloxacin and moxifloxacin groups).
Abbreviations: EXACT-PRO, EXAcerbations of Chronic Pulmonary Disease Tool-Patient-Reported Outcome; CAT, chronic obstructive pulmonary disease assessment test; D, day.

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Table 5 Adverse drug reactions

Adverse drug reaction	Number (%) of cases	
	Zabofloxacin n=175 (%)	Moxifloxacin n=167 (%)
Gastrointestinal disorder		
Nausea	3 (1.7)	4 (2.4)
Dry mouth	0 (0.0)	1 (0.6)
Diarrhea	4 (2.3)	1 (0.6)
Dyspepsia	1 (0.6)	0 (0.0)
Vomiting	1 (0.6)	0 (0.0)
Abdominal discomfort	1 (0.6)	0 (0.0)
Abdominal pain	0 (0.0)	1 (0.6)
Epigastric discomfort	0 (0.0)	1 (0.6)
Stomatitis	0 (0.0)	1 (0.6)
Respiratory, thoracic, and mediastinal problems		
Chronic obstructive pulmonary disease	1 (0.6)	0 (0.0)
Sputum retention	0 (0.0)	1 (0.6)
Nervous system disorders		
Dizziness	3 (1.7)	1 (0.6)
Headache	1 (0.6)	1 (0.6)
Tremor	0 (0.0)	1 (0.6)
Paresthesia	1 (0.6)	0 (0.0)
Somnolence	0 (0.0)	1 (0.6)
General disorders and administration site conditions		
Chest discomfort	2 (1.1)	0 (0.0)
Face edema	1 (0.6)	0 (0.0)
Fatigue	0 (0.0)	1 (0.6)
Peripheral edema	0 (0.0)	1 (0.6)
Infections and infestations		
Nasopharyngitis	0 (0.0)	1 (0.6)
Investigations		
Glucose urine present	1 (0.6)	0 (0.0)
Red blood cell microcytes present	0 (0.0)	1 (0.6)
Skin and subcutaneous tissue disorders		
Pruritus	1 (0.6)	1 (0.6)
Rash	1 (0.6)	0 (0.0)
Drug eruption	0 (0.0)	1 (0.6)
Erythema	1 (0.6)	0 (0.0)
Cardiac disorders		
Palpitations	1 (0.6)	0 (0.0)
Renal and urinary disorders		
Hematuria	0 (0.0)	1 (0.6)
Musculoskeletal and connective tissue disorders		
Flank pain	1 (0.6)	0 (0.0)
Eye disorders		
Vision blurred	0 (0.0)	1 (0.6)
Vascular disorders		
Flushing	0 (0.0)	1 (0.6)
Total	17/175 (9.7)	16/167 (9.6)

efficacy. Since a previous study[8] compared a 5-day course of study drug (moxifloxacin) with a 7-day course of reference drug (levofloxacin), we also performed this study in a similar manner. In this study, in spite of the shorter period of drug administration, zabofloxacin showed comparable clinical effect on COPD exacerbation. Moreover, in spite of the shorter period of drug administration, symptom improvement was significantly faster in the zabofloxacin group.

This study is interesting when compared with the previous studies in that we focused on COPD rather than chronic bronchitis. Thus, this study can provide evidence that zabofloxacin is suitable for the treatment of patients with an acute exacerbation of COPD. Moreover, we stratified patients according to the type of chronic bronchitis. Subgroup analysis revealed that the efficacy of zabofloxacin was comparable with that of moxifloxacin in patients with and without chronic bronchitis. Thus, zabofloxacin can be used to treat patients with COPD exacerbation regardless of whether a patient has the phenotype of chronic bronchitis or not.

There are no clear guidelines regarding the period of antibiotic therapy for acute COPD exacerbations. The present study is valuable in that it is the first to show that a 5-day course of zabofloxacin yields a good clinical response to COPD exacerbations. PP analysis revealed that the clinical cure rate at the time of the TOC visit was 86.7%. Considering that the study was limited to patients with moderate exacerbation (ie, patients who did not require hospitalization), this favorable result may be expected. However, the results provide valuable information regarding the period of antibiotic therapy required to manage COPD exacerbations.

To the best of our knowledge, this is the first study to measure EXACT-PRO and CAT scores for COPD patients during and after treatment with antibiotics. Interestingly, the results showed that zabofloxacin may be better than moxifloxacin in terms of symptom reduction during the treatment of exacerbations. The reason for this remains unclear. Further studies of CAT and EXACT-PRO scores during antibiotic treatment of exacerbations are needed to validate and support our results. However, we cautiously suggest that zabofloxacin may be more favorable than moxifloxacin. This is supported by other previous studies. For example, Kosowska-Shick et al[6] showed that compared with other quinolones (including moxifloxacin), zabofloxacin was the most effective against both quinolone-susceptible and -resistant pneumococci. Park et al[4] also showed that zabofloxacin was the most effective quinolone antibiotic against infections caused by *Streptococcus pneumoniae*. Zabofloxacin also shows rapid bactericidal activity and a long post-antibiotic effect against *S. pneumoniae*.[16] This efficacy against *S. pneumoniae* can be explained by the finding that that DNA gyrase and DNA topoisomerase IV in *S. pneumoniae* are both targets for zabofloxacin.[17] Zabofloxacin also shows good activity against atypical bacterial respiratory pathogens.[18] Taken together,

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these results suggest that zabofloxacin has good clinical efficacy against respiratory pathogens. A Phase II, double-blind, multicenter study showed that zabofloxacin was comparable with moxifloxacin in terms of efficacy against community-acquired bacterial pneumonia.[19]

Zabofloxacin and moxifloxacin showed similar adverse event profiles in the present study. Gastrointestinal problems, including nausea and diarrhea, were the most common drug-related adverse events. There were no serious adverse events that were related to both drugs. Both drugs were generally well tolerated, and few patients (none in the zabofloxacin group and three in the moxifloxacin group) dropped out due to adverse events. This result is compatible with that of a previous study comparing moxifloxacin with levofloxacin.[8] Although gastrointestinal problems were the most common adverse events in that study, the discontinuation rate was also very low (approximately 2%).

The present study has several limitations. First, although this was a randomized trial, there were some differences in baseline characteristics. Male sex and smoking status are both important factors in the management of COPD. We are unclear as to whether these two unmatched factors affected the clinical outcome. Second, the study was limited to patients suffering moderate exacerbations. Thus, the efficacy of zabofloxacin (orally for 5 days) applied only to this population. It is unclear whether such a protocol will be effective in hospitalized COPD patients with severe exacerbations. Further studies should examine the efficacy of zabofloxacin in hospitalized patients due to severe exacerbations. Third, 7 days of moxifloxacin instead of five may have affected the adverse effect of moxifloxacin. Fourth, bacteriologic eradication in this study was lower than two previous studies.[8,9] We do not know exact reason for this difference. However, it may be because of the difference in the characteristics of the enrolled patients. In the previous two studies, enrolled patients were mainly suffering from chronic bronchitis while in this study they were COPD patients. Thus, baseline severity of disease may have resulted in a lower bacteriologic response. In our study, the mean forced expiratory volume in 1 second of patients was about 50%.

Conclusion

Oral zabofloxacin (367 mg once daily for 5 days) was not inferior to oral moxifloxacin (400 mg once daily for 7 days) for the treatment of patients with COPD exacerbations. This treatment protocol may be a useful option for the treatment of COPD patients with exacerbations of moderate severity in the outpatient setting.

Acknowledgments

This study was supported by Dongwha Pharm. Co., Ltd., Seoul, Korea.

The members (other than authors) of this study are as follows: Sook Young Lee (Seoul St. Mary's Hospital, Seoul, Korea), Sung Hwan Jung, Jeong Woong Park (Gachon University Gil Medical Center, Incheon, Korea), Ju Sang Kim, Joong Hyun Ahn, Ah Young Shin, Hwa Young Lee (Incheon St. Mary's Hospital, Incheon, Korea), Woo Jin Kim, Yoonki Hong (Kangwon National University Hospital, Chencheon, Korea), Jong Deog Lee, Yi Young Jung (Gyeongsang National University, Jinju, Korea), Hee Joung Kim (Konkuk University Medical Center, Seoul, Korea), Chi Young Jung, Young June Jeon (Keimyung University Dongsan Medical Center, Daegu, Korea), Sang Yeub Lee, Kwang Ho In, Eun Joo Lee (Korea University Anam Hospital, Seoul, Korea), Sang-Do Lee, Sei Won Lee, Jae Seung Lee (Asan Medical Center, Seoul, Korea), Hun Gyu Hwang, Gune-Il Lim, Myung Shin Kim (Soonchunhyang University Hospital Gumi, Gumi, Korea), Ju Ock Na, Yong Hoon Kim, Jae Sung Choi, Ho Sung Lee (Soonchunhyang University Cheonan Hospital, Cheonan, Korea), Seung Soo Sheen, Keu Sung Lee (Ajou University Hospital, Suwon, Korea), Seung Won Ra, Kwang Won Seo, Yangjin Jegal, Jong-Joon Ahn (Ulsan University Hospital, Ulsan, Korea), Won Yeon Lee, Myoung Kyu Lee, Suk Joong Yong, Kye Chul Shin (Yonsei University Wonju Severance Christian Hospital, Wonju, Korea), Jin Hwa Lee, Yon Ju Ryu, Seok Jeong Lee (Ewha Womans University Mokdong Hospital, Seoul, Korea), Hang Jea Jang (Haeundae Paik Hospital, Busan, Korea), Yong Chul Lee, So Ri Kim, Seung Yong Park, Chi Ryang Chung (Chonbuk National University Hospital, Jeonju, Korea), Sung Soo Jung, Ju Ock Kim, Jeong Eun Lee (Chungnam National University Hospital, Daejeon, Korea), Kang Hyeon Choe, Ki Man Lee, Jin Young An (Chungbuk National University Hospital, Cheongju, Korea), Yong Bum Park, Changhwan Kim, Jae Young Lee, Eun Kyung Mo (Hallym University Kangdong Sacred Heart Hospital, Seoul, Korea), Seung Hun Jang, Ki Suck Jung (Hallym University Sacred Heart Hospital, Anyang, Korea), Tae-Hyung Kim, Ji-Young Moon (Hanyang University Guri Hospital, Guri, Korea), Hye Sook Choi (Dongguk University Gyeongju Hospital, Gyeongju, Korea), Young Sam Kim (Severance Hospital, Seoul, Korea), Kyeong-Cheol Shin (Yeungnam University Medical Center,

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Daegu, Korea), Sung Ho Yoon (Chosun University Hospital, Gwangju, Korea).

We express our special thanks to Cheol Hee Lim and Sun Hea Lee, Dongwha Pharm. Co., Ltd., Seoul, Korea.

Disclosure

CK Rhee received consulting/lecture fees from MSD Korea, AstraZeneca Korea, Novartis Korea, GSK Korea, Takeda Korea, Mundipharma Korea, Sandoz Korea and Boehringer-Ingelheim Korea. YM Oh received honoraria/consulting fees from DongWha, MSD Korea, AstraZeneca Korea, GlaxoSmithKline Korea, Novartis, and Boehringer-Ingelheim Korea. The other authors report no other conflicts of interest in this work.

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