POSTER # 2234

OUTCOMES BY AGE AND GENDER FROM A GLOBAL PHASE 3 STUDY OF DELAFLOXACIN (DLX) IN COMMUNITY ACQUIRED BACTERIAL PNEUMONIA (CABP)

IDWeek 2019™
Washington, D.C.
October 2-6, 2019

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INTRODUCTION

Delafloxacin is a novel fluoroquinolone approved in the US as an IV and oral formulation for the treatment of serious skin infections, and with excellent *in vitro* activity against Gram-positive, Gram-negative, and atypical pathogens including fluoroquinolone or macrolide-resistant strains and MRSA[1,2]. Delafloxacin has good activity against Gram-negative organisms that are susceptible to levofloxacin. Delafloxacin has FQ class labelling but has no QT restrictions or phototoxicity, no food effects and no significant drug-drug interactions which may be a consideration in antibiotic choice especially in the older patient[3]. Empiric treatment of CABP is based on an array of factors, including likely pathogens and the possibility of resistance, patient comorbidities, pharmacokinetic (PK) properties, drug safety profiles, and treatment setting. Clinical situations in which fluoroquinolones are considered to have an appropriate role in treatment, according to Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) Guidelines (2007)[4] include the outpatient and inpatient (non-ICU) settings as a single agent, or in combination with an anti-pneumococcal β-lactam in ICU inpatient settings when *P. aeruginosa* can be excluded. This report focuses on results of patients by age and gender.

MATERIALS AND METHODS

Study Design:

- Phase 3, randomized, double-blind, comparator-controlled, multicenter, global study.
- Baseline characteristics including chest radiography within 48 hours before first dose of study drug, and blood cultures (24 hours before dose) were performed.
- Patients were classified as Pneumonia Patient Outcomes Research Team (PORT) Risk Class II, III, IV, or V.
- Men and women, 18 and above, were eligible with:
  - at least 2 of the following: new or worsening cough, purulent sputum, difficulty breathing (dyspnea) and chest pain due to pneumonia
  - at least 2 of the following: fever, hypothermia, tachycardia, tachypnea AND at least 1 of the following findings: hypoxemia, clinical evidence of pulmonary consolidation and/or presence of pulmonary rales, elevated white blood cell count (WBC) > 10,000/mm^3 or 15% immature neutrophils
  - lobar, multi-lobar, or patchy parenchymal infiltrate(s) consistent with acute bacterial pneumonia on a pulmonary imaging study.
- Patients received at least 6 IV 300 mg delafloxacin doses (BID), with an option for oral 450 mg delafloxacin (BID) for up to 20 total doses, OR at least 3 IV 400 mg moxifloxacin doses (QD), with an option for oral 400 mg moxifloxacin (QD), for up to 10 total doses.
- Patients were evaluated at screening, Early Clinical Response (ECR, 96 [± 24] hours after the start of the first dose of study drug), End of Treatment (EOT, last dose [+ 28 hours]), and Test of Cure (TOC, 5 to 10 days after last dose).
- Enrollment was limited to ≤25% PORT Risk Class II, and ≤25% of patients receiving 1 dose of a short-acting antimicrobial drug or drug regimen within 24 hours of enrollment and was stratified by PORT, medical history of chronic obstructive pulmonary disease (COPD) or asthma, and prior single dose/regimen systemic antimicrobial use.
- Efficacy was evaluated through assessment of clinical signs and symptoms of pneumonia and microbiological assessments and susceptibility testing of bacterial isolates.

Endpoints

- The primary efficacy endpoint for the FDA was ECR: improvement at 96 (±24 hrs), in at least 2 of the following : pleuritic chest pain, frequency/severity of cough, amount/quality of productive sputum and dyspnea, and no worsening of other symptoms.
- For the EMA, the primary efficacy endpoint was the investigator-assessed clinical outcome at TOC. Clinical success criteria were resolution/near resolution of CABP symptoms present at study entry, no use of additional antimicrobial therapy, and no new symptoms associated with the current CABP.

MATERIALS AND METHODS

Analysis

- CIs were calculated using the Miettinen-Nurminen method, without stratification. If the lower bound of the CI was greater than −12.5%, noninferiority of delafloxacin was concluded.

Analysis Populations

- *ITT population:* all randomized patients with a signed informed consent form (ICF).
- *Safety population:* all randomized patients who received at least 1 dose of the study drug.

RESULTS

TABLE 1. PATIENT BASELINE CHARACTERISTICS (ITT POPULATION)

Characteristic	DLX (N=431)	MOX (N=428)	Total (N=859)
Age, years			
Mean (SD)	60.7 (16.06)	59.3 (16.58)	60.0 (16.33)
Median (min, max)	63.0 (18, 89)	61.0 (18, 93)	62.0 (18, 93)
Sex, n (%)			
Male	251 (58.2)	253 (59.1)	504 (58.7)
Female	180 (41.8)	175 (40.9)	355 (41.3)
Race, n (%)			
Black	22 (5.1)	33 (7.7)	55 (6.4)
White	398 (92.3)	388 (90.7)	786 (91.5)
Other	11 (2.6)	7 (1.6)	18 (2.1)
PORT Class, n (%)			
II	54 (12.5)	57 (13.3)	111 (12.9)
III	258 (59.9)	260 (60.7)	518 (60.3)
IV	115 (26.7)	103 (24.1)	218 (25.4)
V	4 (0.9)	8 (1.9)	12 (1.4)
BMI, mean (SD)	26.8 (5.6)	27.0 (5.5)	26.9 (5.5)
Patients with diabetes, n (%)	70 (16.2)	61 (14.3)	131 (15.3)
Bacteremia present, n (%)	5 (1.2)	8 (1.9)	13 (1.5)
Smoking Status, n (%)			
Current	103 (23.9)	94 (22.0)	197 (22.9)
Former	76 (17.6)	98 (22.9)	174 (20.3)
Pre-existing Pulmonary Condition, 2 yr, n (%)	65 (15.1)	62 (14.5)	127 (14.8)
COPD/Asthma	61 (14.2)	56 (13.1)	117 (13.6)
Multilobar Pneumonia	125 (29.0)	120 (28.0)	245 (28.5)

TABLE 2. OVERALL OUTCOMES FOR CABP STUDY (ITT POPULATION)

Key Endpoints	DLX n/Total (%)	MOX n/Total (%)	Difference (95% CI)
ECR at 96 ± 24 hrs (ITT)	383/431 (88.9)	381/428 (89.0)	−0.2 (−4.4, 4.1)
Clinical Success at TOC (ITT)	390/431 (90.5)	384/428 (89.7)	0.8 (−3.3, 4.8)

Difference = Difference in responder rates (DLX treatment group minus MOX treatment group). Confidence intervals are calculated using Miettinen and Nurminen method without stratification.

RESULTS

DEMOGRAPHICS AND EFFICACY

In the ITT population, 783 subjects (91.2%) completed the study with participation through TOC, 91.4% in the DLX group and 90.9% in the MOX group. For both groups median total drug exposure was 9.0 days (6.0 days for IV and 2.0 days for oral). Overall study demographics are presented in **Table 1**. As in recent pivotal CABP trials, enrollment was primarily from Europe (85.7%). Mean (SD) age were 49 (12.6), 74 (6.3) and 80 (4.0) years for categories <65, ≥65, and ≥75 year categories. Overall primary endpoint outcomes for the study are presented in **Table 2** and by age/gender in **Table 3A** and **B.**

TABLE 3A. ECR AND CLINICAL OUTCOME BY AGE GROUP (ITT POPULATION)

Efficacy Endpoint	Outcome	Age Category	DLX (N=431)	MOX (N=428)	Difference (95% CI)
ECR	Objective Responder, n/N1 (%)	<65 years	N1 = 228	N1 = 249	-
			206 (90.4)	220 (88.4)	2.0 (-3.7, 7.6)
		≥65 years	N1 = 203	N1 = 179	-
			177 (87.2)	161 (89.9)	-2.8 (-9.2, 3.8)
		≥75 years	N1 = 85	N1 = 97	-
			73 (85.9)	84 (86.6)	-0.7 (-11.3, 9.5)
Clinical Outcome at TOC	Success, n/N1 (%)	<65 years	N1 = 228	N1= 249	-
			209 (91.7)	221 (88.8)	2.9 (-2.5, 8.4)
		≥65 years	N1 = 203	N1 = 179	-
			181 (89.2)	163 (91.1)	-1.9 (-8.0, 4.3)
		≥75 years	N1 = 85	N1 = 97	-
			77 (90.6)	87 (89.7)	0.9 (-8.5, 9.9)

Difference = Difference in responder rates (DLX treatment group minus MOX treatment group). Confidence intervals are calculated using Miettinen and Nurminen method without stratification. Abbreviations: CE, clinically evaluable; CI, confidence interval; ITT, intent-to-treat; TOC, Test of Cure.

TABLE 3B. ECR AND CLINICAL OUTCOME BY GENDER (ITT POPULATION)

Efficacy Endpoint	Outcome	Category	DLX (N=431)	MOX (N=428)	Difference (95% CI)
ECR	Objective Responder, n/N1 (%)	Female	N1 = 180	N1 = 175	-
			162 (90.0)	158 (90.3)	-0.3 (-6.7, 6.1)
		Male	N1 = 251	N1 = 253	-
			221 (88.0)	223 (88.1)	-0.1 (-5.9, 5.7)
Clinical Outcome at TOC	Success, n/N1 (%)	Female	N1 = 180	N1 = 175	-
			167 (92.8)	159 (90.9)	1.9 (-3.9, 8.0)
		Male	N1 = 251	N1 = 253	-
			223 (88.8)	225 (88.9)	-0.1 (-5.7, 5.5)

Difference = Difference in responder rates (DLX treatment group minus MOX treatment group). Confidence intervals are calculated using Miettinen and Nurminen method without stratification. Abbreviations: CE, clinically evaluable; CI, confidence interval; ITT, intent-to-treat; TOC, Test of Cure.

TABLE 4. OVERALL SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS (TEAE) BY AGE AND GENDER (SAFETY POPULATION)

Category	Overall		<65 years		≥65 years		≥75 years		Female		Male	
	DLX (N=429)	MOX (N=427)	DLX (N=227)	MOX (N=248)	DLX (N=202)	MOX (N=179)	DLX (N=84)	MOX (N=97)	DLX (N=179)	MOX (N=174)	DLX (N=250)	MOX (N=253)
Any TEAE, n (%)	131 (30.5)	112 (26.2)	66 (29.1)	59 (23.8)	65 (32.2)	53 (29.6)	25 (29.8)	29 (29.9)	56 (31.3)	46 (26.4)	75 (30.0)	66 (26.1)
TEAE related to study drug, n (%)	65 (15.2)	54 (12.6)	38 (16.7)	33 (13.3)	27 (13.4)	21 (11.7)	10 (11.9)	8 (8.2)	25 (14.0)	26 (14.9)	40 (16.0)	28 (11.1)
TEAE with severe intensity, n (%)	19 (4.4)	14 (3.3)	8 (3.5)	5 (2.0)	11 (5.4)	9 (5.0)	5 (6.0)	6 (6.2)	7 (3.9)	5 (2.9)	12 (4.8)	9 (3.6)
Any TEAE leading to premature study drug DC, n (%)	15 (3.5)	7 (1.6)	7 (3.1)	4 (1.6)	8 (4.0)	3 (1.7)	3 (3.6)	1 (1.0)	5 (2.8)	3 (1.7)	10 (4.0)	4 (1.6)
Any related TEAE leading to premature study drug DC, n (%)	9 (2.1)	4 (0.9)	4 (1.8)	3 (1.2)	5 (2.5)	1 (0.6)	2 (2.4)	0	3 (1.7)	2 (1.1)	6 (2.4)	2 (0.8)
Any SAE (Serious Adverse Event), n (%)	23 (5.4)	20 (4.7)	10 (4.4)	8 (3.2)	13 (6.4)	12 (6.7)	6 (7.1)	7 (7.2)	8 (4.5)	7 (4.0)	15 (6.0)	13 (5.1)
Any SAE related to study drug, n (%)	2 (0.5)	0	1 (0.4)	0	1 (0.5)	0	1 (1.2)	0	1 (0.6)	0	1 (0.4)	0
TEAE leading to death, n (%)	9 (2.1)	7 (1.6)	3 (1.3)	1 (0.4)	6 (3.0)	6 (3.4)	1 (1.2)	4 (4.1)	3 (1.7)	3 (1.7)	6 (2.4)	4 (1.6)

Note: A treatment-emergent adverse event (TEAE) is defined as any AE that starts after the first dose of study drug or worsens in intensity after the first dose of study drug through Follow-up. Related includes possibly, probably, and definitely related. At each level of subject summarization, a subject with 1 or more reported TEAEs was counted only once. DC = Discontinuation

TABLE 5A. ALL TEAES IN >2% OF PATIENTS, REGARDLESS OF CAUSALITY BY AGE (SAFETY POPULATION)

Category	< 65 years		≥65 years		≥75 years	
	DLX (N=227)	MOX (N=248)	DLX (N=202)	MOX (N=179)	DLX (N=84)	MOX (N=97)
Patients with at least 1 TEAE, n (%)	66 (29.1)	59 (23.8)	65 (32.2)	53 (29.6)	25 (29.8)	29 (29.9)
Diarrhea, n (%)	11 (4.8)	8 (3.2)	9 (4.5)	6 (3.4)	6 (7.1)	2 (2.1)
Constipation, n (%)	2 (0.9)	1 (0.4)	1 (0.5)	3 (1.7)	0	2 (2.1)
Transaminases increased, n (%)	10 (4.4)	5 (2.0)	3 (1.5)	1 (0.6)	0	0
Headache, n (%)	2 (0.9)	9 (3.6)	6 (3.0)	2 (1.1)	2 (2.4)	0
Hypokalemia, n (%)	6 (2.6)	0	2 (1.0)	2 (1.1)	1 (1.2)	1 (1.0)
Insomnia, n (%)	0	0	3 (1.5)	4 (2.2)	1 (1.2)	1 (1.0)
COPD, n (%)	0	0	2 (1.0)	0	2 (2.4)	0
Anaemia, n (%)	0	1 (0.4)	3 (1.5)	1 (0.6)	2 (2.4)	0
Atrial fibrillation, n (%)	0	0	1 (0.5)	3 (1.7)	1 (1.2)	2 (2.1)
Cardiac failure, n (%)	2 (0.9)	0	1 (0.5)	2 (1.1)	1 (1.2)	2 (2.1)
Oedema peripheral	0	1 (0.4)	1 (0.5)	2 (1.1)	0	2 (2.1)

TABLE 5B. ALL TEAES IN >2% OF PATIENTS, REGARDLESS OF CAUSALITY BY GENDER (SAFETY POPULATION)

Category	Female		Male	
	DLX (N=179)	MOX (N=174)	DLX (N=250)	MOX (N=253)
Patients with at least 1 TEAE, n (%)	56 (31.3)	46 (26.4)	75 (30.0)	66 (26.1)
Diarrhea, n (%)	10 (5.6)	7 (4.0)	10 (4.0)	7 (2.8)
Transaminases increased, n (%)	13 (3.0)	6 (1.4)	11 (4.4)	5 (2.0)
Headache, n (%)	4 (2.2)	6 (3.4)	4 (1.6)	5 (2.0)
Hypokalemia, n (%)	5 (2.8)	1 (0.6)	3 (1.2)	1(0.4)

SAFETY

- TEAE rates were generally comparable between DLX and MOX, as were drug-related TEAEs, and were comparable across age groups and gender (**Table 4**).
- Severe AEs were slightly higher for both treatment groups in ≥ 65 and ≥75 yr age groups.
- TEAEs causing study drug DCs were similar between treatment groups, and between age groups and gender.
- The most common AEs varied with age group, except for diarrhea and headache which were common for all groups (**Table 5A**).
- No differences in common AEs were noted between gender groups and treatment groups (**Table 5B**).

CONCLUSIONS

- IV/oral DLX is noninferior to IV/oral MOX in the primary efficacy analysis of ECR (improvement at 96 [±24] hours after first dose of study drug) and clinical success at TOC in the ITT population.
- ECR responders and clinical outcome (success) results for DLX were comparable to MOX, regardless of age or gender groups, and were comparable to overall efficacy results.
- DLX was well tolerated in this study; the most common TEAE among DLX-treated patients were diarrhea, increased transaminases, headache, and hypokalemia.

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