POSTER # 2228

TREATMENT OF COMMUNITY ACQUIRED BACTERIAL PNEUMONIA (CABP) IN PATIENTS WITH DIABETES: OUTCOMES FROM A GLOBAL PHASE 3 STUDY OF DELAFLOXACIN (DLX)

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

Igor Kaidashev[1], Floarea-Mimi Nitu[2], Monica Popescu[3], Megan Quintas[4], Laura Lawrence[4], Yang Li[5] ,Sue Cammarata[4]

[1]Ukranian Medical Stomatological Academy, Poltava, Ukraine, [2]University of Medicine and Pharmacy, Craiova, Romania, [3]Saint Pantelimon Emergency Clinical Hospital, Bucharest, Romania, [4]Melinta Therapeutics, Lincolnshire, IL, US, [5]Firma Clinical, Hunt Valley, MD, US.

1-844-MED-MLNT
medinfo@melinta.com

INTRODUCTION

Delafloxacin is a novel fluoroquinolone that is approved in the US as an IV and oral formulation for the treatment of serious skin infections. Delafloxacin has 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 selection in diabetic patients[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 inpatient (non-ICU) and outpatient settings as a single agent, or in combination with an anti-pneumococcal β-lactam in ICU inpatient setting when *P. aeruginosa* is not a concern. This report focuses on results of patients with Diabetes.

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.

MATERIALS AND METHODS

Endpoints (*continued*)

- 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.

Analysis & Populations

- Confidence intervals (CI) 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.
- *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.
- *CE populations*: ITT patients who met key inclusion/exclusion criteria and minimal dosing requirements and did not have indeterminate or missing assessments at various study visits.

RESULTS

TABLE 1. OVERALL PATIENT BASELINE CHARACTERISTICS IN DIABETIC PATIENTS (ITT POPULATION)

Characteristic	Diabetic Total (N=131)	Non-Diabetic Total (N=728)	ALL (N=859)
Age, years			
Mean (SD)	66.2 (11.02)	58.9 (16.9)	60.0 (16.33)
Median (min, max)	67.0 (35, 66)	61 (18, 93)	62.0 (18, 93)
Sex, n (%)			
Male	77 (58.8)	427 (58.7)	504 (58.7)
Female	54 (41.2)	301 (41.3)	355 (41.3)
Race, n (%)			
Black	6 (4.6)	49 (6.7)	55 (6.4)
White	120 (91.6)	666 (91.5)	786 (91.5)
Other	5 (3.8)	13 (17.9)	18 (2.1)
PORT Class, n (%)			
II	10 (7.6)	101 (13.9)	111 (12.9)
III	69 (52.7)	449 (61.7)	518 (60.3)
IV	47 (35.9)	171 (23.5)	218 (25.4)
V	5 (3.8)	7 (1.0)	12 (1.4)
BMI, mean (SD)	30. 5 (5.8)	26.3 (5.2)	26.9 (5.5)
Bacteremia present, n (%)	1 (0.8)	12 (1.6)	13 (1.5)
Pre-existing Pulmonary Condition w/in 2 yrs, n (%)	20 (15.3)	107 (14.7)	127 (14.8)
Multilobar Pneumonia	38 (29.0)	207 (28.5)	245 (28.5)

RESULTS

DEMOGRAPHICS AND EFFICACY

In the overall ITT population, 783 patients (91.2%) completed the study with participation through TOC, 91.4% in the DLX group and 90.9% in the MOX group. Overall, median total drug exposure was 9.0 days (6.0 days for IV and 2.0 days for oral) and for diabetic patients was 8.0 days for DLX (6.0 days IV and 1.8 oral) and 9.5 for MOX (7 days IV and 2.0 oral). Overall, diabetic, and non-diabetic study demographics are presented in **Table 1**. As in recent pivotal CABP trials, enrollment was primarily from Europe (85.7%). Overall primary endpoint outcomes for the study are presented in **Table 2** and by diabetics in **Table 3**.

TABLE 2. OVERALL OUTCOMES FOR CABP STUDY (ITT AND CE POPULATIONS)

Key Endpoints			
Outcome	**DLX**	**MOX**	**Difference (95% CI)**
ITT Population			
Objective Responder, n/N (%)	383/431 (88.9)	381/428 (89.0)	−0.2 (−4.4, 4.1)
Clinical Success at TOC, n/N (%)	390/431 (90.5)	384/428 (89.7)	0.8 (−3.3, 4.8)
CE Population			
Objective Responder, n/N (%)	381/418 (91.1)	380/414 (91.8)	-0.6 (-4.5, 3.2)
Clinical Success at TOC, n/N (%)	376/397 (94.7)	373/394 (94.7)	0.0 (-3.2, 3.3)

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

TABLE 3. ECR AND CLINICAL OUTCOME FOR DIABETIC PATIENTS (ITT AND CE POPULATIONS)

Key Endpoints						
	Diabetic			**Non-Diabetic**		
Outcome, n/N (%)	**DLX**	**MOX**	**Difference (95% CI)**	**DLX**	**MOX**	**Difference (95% CI)**
ITT Population						
Objective Responder	63/70 (90.0)	54/61 (88.5)	1.5 (-9.6, 13.2)	320/361 (88.6)	327/367 (89.1)	-0.5 (-5.1, 4.2)
Clinical Success at TOC	61/70 (87.1)	53/61 (86.9)	0.3 (-11.6, 12.7)	329/361 (91.1)	331/367 (90.2)	0.9 (-3.4, 5.3)
CE Population						
Objective Responder	61/67 (91.0)	54/58 (93.1)	-2.1 (-12.4, 8.7)	320/351 (91.2)	326/356 (91.6)	-0.4 (-4.6, 3.8)
Clinical Success at TOC	59/63 (93.7)	51/52 (98.1)	-4.4 (-13.7, 4.5)	317/334 (94.9)	322/342 (94.2)	0.8 (-2.8, 4.3)

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

SAFETY

- TEAE rates (drug-related or not) were generally comparable between DLX and MOX and in overall and non-diabetic groups (**Table 4**).
- AE rates (any, related, and severe) for diabetic groups were slightly higher than overall and non-diabetic groups.
- TEAEs causing study drug DCs were similar between treatment groups and diabetic and non-diabetic patients.
- SAE rates and AEs leading to death were higher in diabetics in both treatment groups.
- Most common AEs were dependent on the group (**Table 5**). Diarrhea and hypokalemia rates were slightly higher in the DLX diabetic group compared to MOX.

TABLE 4. OVERALL SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS (TEAE) IN DIABETIC PATIENTS (SAFETY POPULATION)

Category	Overall		Diabetic		Non-Diabetic	
	DLX (N=429)	**MOX (N=427)**	**DLX (N=70)**	**MOX (N=60)**	**DLX (N=359)**	**MOX (N=367)**
Any TEAE, n (%)	131 (30.5)	112 (26.2)	34 (48.6)	20 (33.3)	97 (27.0)	92 (25.1)
TEAE related to study drug, n (%)	65 (15.2)	54 (12.6)	13 (18.6)	7 (11.7)	52 (14.5)	47 (12.8)
TEAE with severe intensity, n (%)	19 (4.4)	14 (3.3)	4 (5.7)	5 (8.3)	15 (4.2)	9 (2.5)
Any TEAE leading to premature study drug DC, n (%)	15 (3.5)	7 (1.6)	2 (2.9)	1 (1.7)	13 (3.6)	6 (1.6)
Any related TEAE leading to premature study drug DC, n (%)	9 (2.1)	4 (0.9)	1 (1.4)	1 (1.7)	8 (2.2)	3 (0.8)
Any SAE (Serious Adverse Event), n (%)	23 (5.4)	20 (4.7)	6 (8.6)	7 (11.7)	17 (4.7)	13 (3.5)
Any SAE related to study drug, n (%)	2 (0.5)	0	0	0	3 (0.8)	0
TEAE leading to death, n (%)	9 (2.1)	7 (1.6)	4 (5.7)	2 (3.3)	5 (1.4)	5 (1.4)

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 5. ALL TEAES IN ≥3% OF PATIENTS, REGARDLESS OF CAUSALITY (SAFETY POPULATION) IN DIABETIC PATIENTS

Category	Overall		Diabetes		Non-Diabetes	
	DLX (N=429)	**MOX (N=427)**	**DLX (N=70)**	**MOX (N=60)**	**DLX (N=359)**	**MOX (N=367)**
Patients with at least 1 TEAE, n (%)	131 (30.5)	112 (26.2)	34 (48.6)	20 (33.3)	97 (27.0)	92 (25.1)
Diarrhea, n (%)	20 (4.7)	14 (3.3)	8 (11.4)	2 (3.3)	12 (3.3)	12 (3.3)
Constipation, n (%)	3 (0.7)	4 (0.9)	2 (2.9)	2 (3.3)	1 (1.3)	2 (0.5)
Transaminases increased, n (%)	13 (3.0)	6 (1.4)	1 (1.7)	2 (3.3)	12 (3.3)	4 (1.1)
Headache, n (%)	8 (1.9)	11 (2.6)	2 (2.9)	0	6 (1.7)	11 (3.0)
Cardiac failure, n (%)	3 (0.7)	2 (0.5)	1 (1.4)	2 (3.3)	2 (0.6)	0
Septic Shock, n (%)	2 (0.9)	0	3 (4.3)	0	0	1 (0.3)
Hypokalemia, n (%)	8 (1.9)	2 (0.5)	4 (5.7)	0	4 (1.1)	2 (0.5)
Hyperglycaemia, n (%)	2 (0.5)	6 (1.4)	2 (2.9)	3 (5.0)	0	3 (0.8)
Infusion site phlebitis, n (%)	4 (0.9)	0	3 (4.3)	0	1 (0.3)	0

CONCLUSIONS

- IV/oral DLX is noninferior to IV/oral MOX in the primary efficacy analysis of ECR and clinical success at TOC in the ITT population.
- ECR responders and clinical success results for DLX were comparable to MOX, regardless of diabetic status of patients, and were comparable to overall efficacy results.
- In general, AE rates were higher overall in diabetic groups in both treatment groups compared to non-diabetic patients.
- DLX was well tolerated in this study; the most common TEAE among DLX-treated patients was diarrhea.

REFERENCES

1. Flamm RK, Rhomberg PR, *et al. In vitro* activity of delafloxacin tested against isolates of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. AAC, 2016;60(10):6381-5.
2. McCurdy S, Lawrence L, *et al. In vitro* activity of delafloxacin and microbiological response against fluoroquinolone-susceptible and non-susceptible Staphylococcus aureus isolates from two phase 3 studies of acute bacterial skin and skin structure infections. AAC. 2017; 61(9).
3. Melinta Therapeutics; 2019 Baxdela (delafloxacin) [package insert]. US Food and Drug Administration website: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208610s000,208611s000lbl.pdf. June 2017.
4. Mandell LA, Wunderink RG, *et al.* Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44(suppl 2):S27-72.