POSTER # 2232

A GLOBAL PHASE 3 STUDY OF DELAFLOXACIN (DLX) COMPARED TO MOXIFLOXACIN (MOX) IN PATIENTS WITH COMMUNITY ACQUIRED BACTERIAL PNEUMONIA (CABP)

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

Robert A. Salata[1], Rodolfo Álvarez-Sala[2], Juan P. Horcajada[3], Megan Quintas[4], Laura Lawrence[4], Yang Li[5], Sue Cammarata[4]

[1]Case Western Reserve University, Cleveland, OH, US, [2] La Paz University Hospital, Madrid, Spain, [3]Hospital del Mar, Barcelona Spain, [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 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 pathogens including fluoroquinolone or macrolide-resistant strains and MRSA[1,2]. Delafloxacin has good activity against levofloxacin susceptible Gram-negative organisms. 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[3]. Empiric treatment of CABP is based on many 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 in ICU inpatient setting when *P. aeruginosa* is not a concern.

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 and respiratory specimen was collected for Gram stain and culture and susceptibility testing if applicable.
- Men and women, 18 and above, who had evidence of acute onset of CABP were eligible with:
  - at least 2 of the following clinical signs and symptoms (new or worsening): cough, purulent sputum, difficulty breathing (dyspnea) and chest pain due to pneumonia
  - at least 2 of the following findings: 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. Enrollment was stratified by PORT Risk Class, 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. Baseline pathogens were detected by culture of blood and respiratory specimens, PCR-based assays, serological assessments, and urinary antigen detection.

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 any of the 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

- 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.

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.
- *MITT populations*: ITT patients who had a baseline bacterial pathogen identified, either by culture of a respiratory or blood specimen(s) or a nonculture method of detection (i.e., urinary antigen test, PCR, or serologic testing) that was known to cause CABP and against which the study drug had antibacterial activity.
- *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.
- *ME populations:* subset of patients that met both MITT and CE criteria at various study visits.

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)	26.81 (5.6)	26.97 (5.5)	26.89 (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)

RESULTS

DEMOGRAPHICS AND EFFICACY

In the 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. For both groups median total drug exposure was 9.0 days (6.0 days for IV and 2.0 days for oral). Study demographics are presented in **Table 1.** As in recent pivotal CABP trials, enrollment was primarily from Europe (85.7%). Primary endpoint outcomes for the study are presented in **Figures 1-2.**

FIGURE 1. ECR OUTCOME BY POPULATION AND SUBGROUP

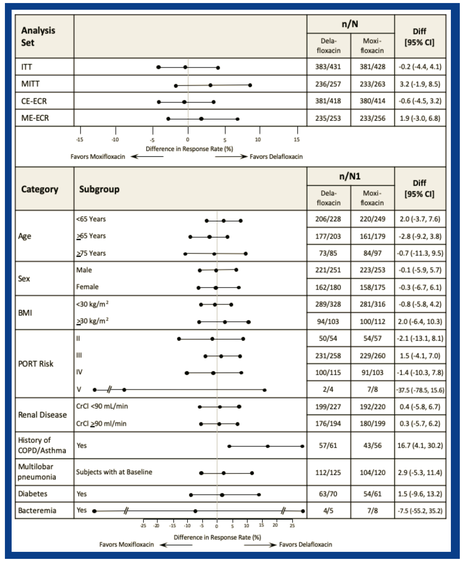
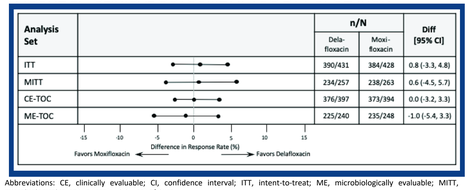


FIGURE 2. CLINICAL OUTCOME AT TOC BY POPULATION



Abbreviations: CE, clinically evaluable; CI, confidence interval; ITT, intent-to-treat; ME, microbiologically evaluable; MITT, microbiological intent-to-treat; TOC, Test of Cure.

MICROBIOLOGICAL FINDINGS

Of 859 patients in the ITT population, 520 (60.5%) had at least 1 pathogen detected at baseline by any method (including culture, serology, PCR, and urinary antigen), and thus comprising the MITT population. By pathogen, the rates of microbiological success (documented or presumed eradicated) at TOC were similar between the DLX and MOX groups for the most common pathogens in the ME-TOC population (**Table 2**). The most common pathogens isolated at baseline were *S. pneumoniae* (43.5%), *H. parainfluenzae* (14.6%), *M. pneumoniae* (12.5%), *L. pneumophila* (11.9%), *H. influenzae* (11.9%), and *S. aureus* (11.0%). Two patients had MRSA at baseline in the DLX treatment group and were successes.

TABLE 2. PER PATHOGEN MICROBIOLOGICAL SUCCESS RATE AT TOC (ME TOC POPULATION)

Organism	DLX (N=240)	MOX (N=248)
Streptococcus pneumoniae	102/110 (92.7)	93/99 (93.9)
PSSP	46/49 (93.9)	44/47 (93.6)
PISP	16/17 (94.1)	6/7 (85.7)
PRSP	7/8 (87.5)	11/11 (100.0)
MRSP	15/17 (88.2)	17/18 (94.4)
Haemophilus parainfluenzae	31/35 (88.6)	32/37 (86.5)
Mycoplasma pneumoniae	29/30 (96.7)	29/29 (100.0)
Legionella pneumophila	27/29 (93.1)	32/32 (100.0)
H. influenzae	22/24 (91.7)	31/35 (88.6)
Staphylococcus aureus	25/27 (92.6)	28/30 (93.3)
MRSA	2/2 (100.0)	0
MSSA	23/25 (92.0)	28/30 (93.3)
Chlamydia pneumoniae	24/24 (100)	15/15 (100)
Klebsiella pneumoniae	14/17 (82.4)	16/16 (100.0)
Escherichia coli	13/13 (100.0)	9/9 (100.0)
Pseudomonas aeruginosa	11/12 (91.7)	11/11 (100.0)

Microbiological Success rate = Documented or presumed eradicated. MRSA = Methicillin Resistant *Staphylococcus aureus*, MSSA = Methicillin Susceptible *Staphylococcus aureus*. PSSP = Penicillin-Susceptible *Streptococcus pneumoniae*, PISP = Penicillin-Intermediate *Streptococcus pneumoniae*, PRSP = Penicillin-Resistant *Streptococcus pneumoniae*, MRSP = Macrolide-Resistant *Streptococcus pneumoniae*.

TABLE 3. OVERALL SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS (TEAE) (SAFETY POPULATION)

Category	DLX (N=429)	MOX (N=427)
Any TEAE, n (%)	131 (30.5)	112 (26.2)
TEAE related to study drug, n (%)	65 (15.2)	54 (12.6)
TEAE with severe intensity, n (%)	19 (4.4)	14 (3.3)
Any TEAE leading to premature study drug discontinuation (DC), n (%)	15 (3.5)	7 (1.6)
Any related TEAE leading to premature study drug DC, n (%)	9 (2.1)	4 (0.9)
Any SAE (Serious Adverse Event), n (%)	23 (5.4)	20 (4.7)
Any SAE related to study drug, n (%)	2 (0.5)*	0
TEAE leading to death, n (%)	9 (2.1)	7 (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 patient with 1 or more reported TEAEs was counted only once. *The related SAEs were hypersensitivity and *C difficile* colitis, both resulted in discontinuation of study drug. DC = Discontinuation

SAFETY

- TEAE rates were comparable between DLX and MOX, as were drug-related TEAEs (**Table 3**).
- Similar rates of SAEs in both groups were noted. DLX had two potentially related SAEs as determined by the investigator (Hypersensitivity and *C difficile* colitis).
- Diarrhea was the most common TEAE in both treatment arms (**Table 4**) and no TEAE was reported in ≥ 5% of patients in either treatment group.
- There were no significant differences in laboratory hepatic enzymes between the two treatment groups. Abnormal labs were generally considered unrelated by the investigator to delafloxacin treatment, were associated with other medical conditions, events, or social circumstances, or did not require treatment and were reversible (**Table 5**). There were no reports of cases meeting the Hy's law definition in either treatment group.

TABLE 4. ALL TEAES IN >2% OF PATIENTS, REGARDLESS OF CAUSALITY (SAFETY POPULATION)

Category	DLX (N=429)	MOX (N=427)
Patients with at least 1 TEAE, n (%)	131 (30.5)	112 (26.2)
Diarrhea, n (%)	20 (4.7)	14 (3.3)
Transaminases increased, n (%)	13 (3.0)	6 (1.4)
Headache, n (%)	8 (1.9)	11 (2.6)

Note: At each level of subject summarization, a patient with 1 or more reported TEAEs was counted only once.

TABLE 5. INCIDENCE OF ELEVATED TRANSAMINASES (SAFETY POPULATION)

Overall Worst Post-Baseline	DLX (N=429)	MOX (N=427)
>5x ULN ALT, n (%)	6 (1.4)	7 (1.6)
>5x ULN AST, n (%)	4 (0.9)	2 (0.5)

Note: ALT = Alanine Aminotransferase, AST = Aspartate Aminotransferase, ULN = Upper limit of normal range. For Overall Worst Post-Baseline, all laboratory assessments including those obtained from unscheduled visits are included, and the patient is included in the numerator if he/she met the criterion at least once.

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 and clinical outcome (success) results for DLX were comparable to MOX, regardless of population.
- DLX showed greater efficacy in ECR for the History of COPD/asthma subgroup which warrants further investigation.
- Microbiologic response by patient and pathogen were comparable between DLX and MOX including common CABP organisms that were gram-positive, gram-negative, and atypical.
- DLX was well tolerated in this study; the most common TEAEs among DLX-treated patients.

REFERENCES

1. Flamm RK, Rhomberg PR, Huband MD, *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, Quintas M, *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, Anzueto A, *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.

Refer to full prescribing information at www.baxdela.com