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

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ECOPY

METHODS

BACKGROUND AND PURPOSE

- Delafloxacin (DLX) is a novel FQ approved for IV/oral treatment of serious skin infections, active against many gram-positive FQ- or macrolide-resistant strains including MRSA. DLX has FQ class warnings but no QT restrictions, no phototoxicity, no food restrictions and no major DDIs.
- We report the outcomes in a Phase 3 global, randomized 1:1, double-blind, active-controlled study where DLX IV/oral was evaluated in comparison to moxifloxacin (MOX) in the treatment of CABP. This analysis focuses on patients with renal impairment (CrCl <90 mL/min based on Cockcroft Gault (CG) equation). The study design is based on FDA guidance.

MATERIALS AND METHODS

STUDY POPULATION (Planned N=860)

- 18+ years age, male and female
- Clinical and radiographic evidence of CABP: at least 2 symptoms of CABP: sputum, chest pain, dyspnea, or cough
- Patients were treated for minimum of 3 days with IV, then oral switch at the investigator discretion. Patients were treated for 5-10 days total therapy at physician discretion.
- Delafloxacin dosing: (based on MDRD)
  - Normal function or mild or moderate renal impairment: 300 mg IV q12h or 450 mg oral q12h
  - Severe renal impairment: 200 mg IV q12h or 450 mg oral q12h
  - ESRD: excluded from this study
- Moxifloxacin dosing: 400mg IV QD or 400mg oral QD

VISIT SCHEDULE

SCR/BASE	ECR	EOT	TOC	Follow Up
Day -1 to 1	96 h (±24) after first dose	24 h (±4) after last dose	5-10 days after last dose	Day 28 (±2)

SCR/BASE=screening/baseline; ECR=early clinical response; EOT=end of treatment; TOC=test of cure

Average Days of treatment ~8.5 in both groups; 6.3 days IV and 2.2 days oral

ANALYSIS SETS

Intent to Treat (ITT)
All randomized patients

Micro ITT (MITT)
Patients w/ baseline pathogen

Clinically Evaluable (CE)
Patients treated per protocol with efficacy assessments

Micro Evaluable (ME)
CE patients with pathogens

KEY ENDPOINTS

- **ECR at 96 h (±24) after first dose in ITT population (NI margin: 12.5%)**
  Responder = Improvement in ≥2 of the following: chest pain, frequency or severity of cough, sputum production, dyspnea, and no worsening
- **Investigator-assessed Clinical Outcome at TOC**

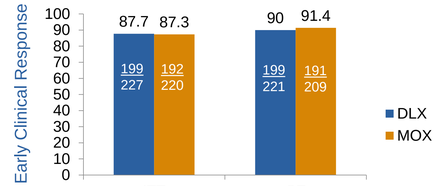
RESULTS IN PATIENTS WITH RENAL IMPAIRMENT

859 patients were randomized. The outcomes were comparable between treatment groups with ECR 88.9% DLX and 89.0% MOX as well as clinical response at TOC 90.5% DLX and 89.7% MOX.
52% of patients had renal impairment calculated by CG.

TABLE 1: DEMOGRAPHICS (ITT)

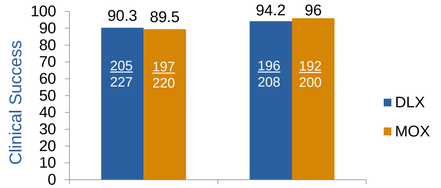
Results shown as n (%) unless otherwise noted	DLX (N=227)	MOX (N=220)
Age, Mean (SD)	69.5 (11.1)	69.0 (12.1)
Age ≥65	164 (72.2)	150 (68.2)
Sex		
Male	122 (53.7)	122 (55.5)
Female	105 (46.3)	98 (44.5)
Race		
Black or African American	11 (4.8)	13 (5.9)
Caucasian	209 (92.1)	203 (92.3)
Other	7 (3.0)	4 (1.8)
Level of Renal Impairment		
Mild (CrCl 60-90 mL/min)	142 (62.6)	134 (60.9)
Mod (CrCl 30-<60 mL/min)	80 (35.2)	79 (35.9)
Severe (CrCl <30 mL/min)	5 (2.2)	7 (3.2)
History Diabetes	43 (18.9)	39 (17.7)
PORT CLASS		
II	20 (8.8)	16 (7.3)
III	118 (52.0)	123 (55.9)
IV	85 (37.4)	74 (33.6)
V	4 (1.8)	7 (3.2)
Bacteremia	2 (0.9)	5 (2.3)
Multi-lobar pneumonia	59 (26.0)	68 (31.1)
Presence pleural effusion	40 (17.6)	58 (26.5)

FIGURE 1 EARLY CLINICAL RESPONSE IN PATIENTS WITH RENAL IMPAIRMENT (ITT AND CE GROUPS)



Δ (95% CI) 0.4 (-5.8,6.7) -1.3 (-7, 4.3)

FIGURE 2 CLINICAL SUCCESS AT TOC IN PATIENTS WITH RENAL IMPAIRMENT (ITT AND CE GROUPS)



Δ (95% CI) 0.8 (-4.9, 6.5) -1.8 (-6.3, 2.6)

TABLE 5 WORST ALT AT ANY TIME IN STUDY n(%)

	DLX N=227	MOX N=219
ALT >2X ULN	23 (10.3)	22 (10.5)
ALT> 3X ULN	8 (3.5)	11 (5.1)
ALT >5X ULN	2 (0.9)	5 (2.3)

TABLE 3: PER PATHOGEN MICRO RESPONSE AT TOC (ME-TOC)

Documented or presumed eradication, n/N (%)	DLX ME Pts with pathogen=122	MOX ME Pts with pathogen=131
S. pneumoniae	55/60 (91.7)	57/58 (98.3)
H. parainfluenzae	19/19 (100)	13/18 (72.2)
S. aureus	12/14 (85.7)	14/16 (87.5)
MRSA	1/1 (100)	na
M. pneumoniae	11/11 (100)	11/11 (100)
H. influenzae	14/14 (100)	16/18 (88.9)
L. pneumophila	14/16 (87.5)	16/16 (100)
C. pneumoniae	9/9 (100)	9/9 (100)
K. pneumoniae	8/11 (72.7)	10/10 (100)
E. coli	5/5 (100)	6/6 (100)
P. aeruginosa	8/8 (100)	4/4 (100)

TABLE 4: SUMMARY OF ADVERSE EVENTS (AE)

% (#) patients with at least one:	DLX N=227	MOX N=219
Any AE	32.6% (74)	29.7% (65)
Related AE	16.7% (38)	13.7% (30)
Severe AE	4.0% (9)	4.1% (9)
AE leading to drug DC	3.5% (8)	2.3% (5)
AESI* regardless of causality	5.7% (13)	9.6% (21)
SAE	4.4% (10)	5.5% (12)
Deaths	1.3% (3)	2.3% (5)
Most frequent all-cause AEs		
Diarrhea	5.7% (13)	3.7% (8)
Headache	2.6% (6)	2.3% (5)
Transaminase Increase	1.3% (3)	1.8% (4)

*AESI=AE of special interest

CONCLUSIONS AND CLINICAL IMPLICATIONS

IV/oral DLX treatment provided comparable outcomes to MOX among patients with renal impairment regardless of subgroup or pathogen

DLX is well tolerated in CABP patients with renal impairment with low rates of treatment DC. The lack of QT restrictions or major DDIs may be a factor in antibiotic choice.

IV/oral DLX may be a useful treatment option in CABP including patients with renal impairment and gram-positive, gram-negative or atypical pathogens