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ANALYSIS OF THE MICROBIOLOGICAL DATA FROM THE DELAFLOXACIN PHASE 3 COMMUNITY ACQUIRED BACTERIAL PNEUMONIA (CABP)

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INTRODUCTION

- CABP is a major health concern associated with poor outcomes, high mortality and significant healthcare expenditures due to treatment failures, ED visits, hospitalizations, and readmissions.
- Delafloxacin (DLX) is a novel FQ with potent in vitro activity against Gram-positive, Gram-negative and atypical pathogens commonly identified in patients with CABP and influenza-related co/secondary bacterial pneumonia, including macrolide, PCN, FQ-resistant, MDR *Streptococcus pneumoniae* and FQ-resistant MRSA.
- In CABP, DLX IV/oral monotherapy is comparable to moxifloxacin. DLX has FQ class warnings but has no QT restrictions or phototoxicity, no food effect or major drug-drug interactions.
- A detailed analysis of the microbiology from the Phase 3 study (ClinicalTrials.gov identifier: NCT02679573) is presented.

METHODS

Study Design and Efficacy Endpoints.

- Delafloxacin was studied in one phase 3, multicenter, stratified, randomized, double-blind trial designed using the guidelines of FDA.
- 859 patients with CABP were randomly assigned in a 1:1 ratio to receive either delafloxacin at 300 mg IV with an option to switch to 450 mg orally every 12h or moxifloxacin 400 mg IV or oral QD.

Analysis sets.

- MITT-1 consisted of baseline pathogens detected by all methods (i.e., including culture, serology, PCR, and urinary antigen).
- MITT-2 included baseline pathogens isolated by culture only.
- ME analysis data set included all patients in the MITT analysis data set who also met the criteria for the corresponding clinically evaluable (CE) analysis data set (CE=ITT subjects who met key inclusion/exclusion criteria and minimal dosing requirements without indeterminate or missing assessments).

Microbiologic outcomes.

- By-pathogen microbiological responses were based upon follow-up cultures performed at TOC that documented eradication or persistence of baseline pathogens. Baseline pathogens identified by a test method other than routine culture of a blood or lower respiratory tract sample could only have a presumed or indeterminate microbiological response, unless persistence was demonstrated by culture.

Other Definitions.

- For documented eradicated: the respiratory and/or blood culture specimen at TOC showed the pathogen(s) present at enrollment was eradicated and there was no use of additional antimicrobial therapy for the current infection.
- For presumed eradicated: no respiratory and/or blood culture specimen was available at TOC with a clinical assessment of success.
- For documented persistence: The respiratory and/or blood culture specimen collected at TOC was positive for the causative pathogen(s) present at enrollment. Persistence of the baseline pathogen at EOT was carried forward to TOC.
- For presumed persistence: no respiratory or blood culture specimen was available for a case classified as clinical failure (including failures carried forward to TOC).
- Pathogens were classified as *definitive* or *probable* based on method of detection (See Table). If a pathogen was detected or identified from multiple sources and there was at least 1 definitive diagnosis, the pathogen was considered definitive; if all diagnoses were probable, then the pathogen was considered probable.

RESULTS

Pathogen Identification and Level of Microbiological Evidence of CABP by Detection Method

Pathogen	Specimen Type	Method of Detection	Definitive Diagnosis	Probable Diagnosis
S. pneumoniae	Sputum, ETA	Culture and Gram-stain	Positive culture w/ Gram-stain of <10 SECs and/or >25 PMN/lpf	Positive culture w/out Gram-stain of <10 SECs and/or >25 PMN/lpf
	BAL, mini BAL, PSB, pleural fluid and blood	Culture	Positive Culture	-
	NP swab	PCR	-	Positive *lytA* PCR (≥ 1000 gene copies/mL)
	NP swab	Culture and PCR	Positive culture only with *lytA* PCR (≥ 1000 gene copies/mL)	-
	Urine	Urinary Antigen	Positive Urinary Antigen	-
Other CABP pathogens	Sputum, ETA	Culture and Gram-stain	Positive culture with Gram-stain of <10 SECs and/or >25 PMN/lpf	Positive culture w/out Gram-stain of <10 SECs and/or >25 PMN/lpf
	BAL, mini BAL, PSB, pleural fluid and blood	Culture	Positive Culture	-
M. pneumoniae	OP swab	Culture	Positive culture	-
	Serum	Serology	4-fold ↑ titer reaching ≥ 160	-
L. pneumophila	Sputum, BAL, mini-BAL), PSB, pleural fluid	Culture	Positive culture	-
	Urine	Urinary antigen	Positive urinary Antigen	-
	Serum	Serology	4-fold ↑ in titer reaching ≥ 128	-
C. pneumoniae	Serum	Serology	4-fold ↑in titer reaching ≥ 64	-

Distribution of Pathogens Identified by All Diagnostic Methods (MITT-1) by Definitive or Probable Diagnosis

	Delafloxacin N=257 n (%)		Moxifloxacin N=263 n (%)	
Organism	MITT-1 (Def Diag)	MITT-1 (Prob Diag)	MITT-1 (Def Diag)	MITT-1 (Prob Diag)
All patients, N1	231	39	238	39
S. pneumoniae	98 (38.1)	22 (8.6)	83 (31.6)	23 (8.7)
H. parainfluenzae	31 (12.1)	4 (1.6)	37 (14.1)	4 (1.5)
M. pneumoniae	35 (13.6)	0	30 (11.4)	0
L. pneumophila	29 (11.3)	0	33 (12.5)	0
H. influenzae	20 (7.8)	7 (2.7)	30 (11.4)	5 (1.9)
S. aureus	25 (9.7)	2 (0.8)	25 (9.5)	5 (1.9)
C. pneumoniae	25 (9.7)	0	16 (6.1)	0
K. pneumoniae	15 (5.8)	2 (0.8)	16 (6.1)	0
E. coli	16 (6.2)	0	8 (3.0)	3 (1.1)
P. aeruginosa	11 (4.3)	2 (0.8)	11 (4.2)	0
K. oxytoca	6 (2.3)	0	4 (1.5)	0
M. catarrhalis	4 (1.6)	2 (0.8)	5 (1.9)	1 (0.4)

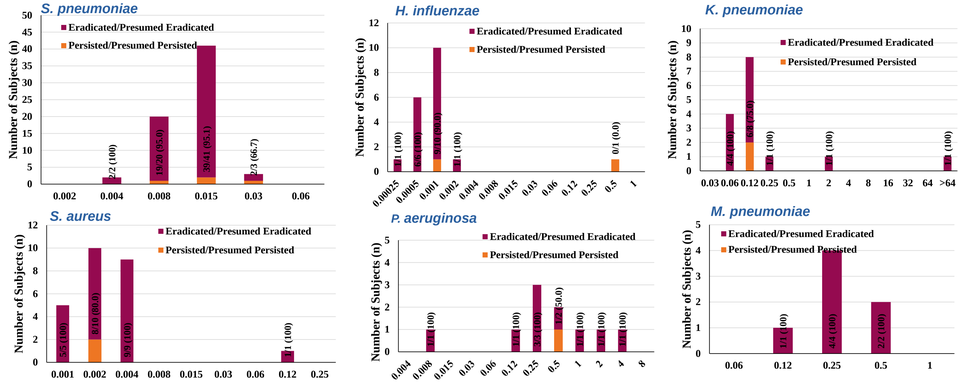
Baseline Pathogen MIC (MITT-2; Combined Treatment Groups)

	Delafloxacin			
Organism	n	MIC Range (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
S. pneumoniae	142	0.004-0.03	0.015	0.015
PRSP	19	0.004-0.015	0.015	0.015
MDR	12	0.004-0.015	0.015	0.015
Macrolide NS	34	0.004-0.015	0.015	0.015
S. aureus	57	0.001-0.12	0.002	0.004
MSSA	55	0.001-0.12	0.002	0.004
MRSA	2	0.002-0.004	-	-
FQ-NS	3	0.12	-	-
H. parainfluenzae	75	0.0005-4	0.008	0.5
Macrolide NS	8	0.002-2	-	-
H. influenzae	61	0.00025-0.5	0.001	0.002
Macrolide NS	2	0.001-0.002	-	-
M. catarrhalis	12	0.002-0.015	0.004	0.004
K. pneumoniae	33	0.03->256	0.12	0.25
E. coli	27	0.015-4	0.06	4
P. aeruginosa	24	0.008-16	0.5	4
M. pneumoniae	19	0.125-0.5	0.25	0.5
Macrolide-R	2	0.125-0.25	-	-
L. pneumophila	5	0.00025-0.001	-	-

Per-Pathogen Micro Response at TOC (ME1-TOC)

	ME-1 TOC (All Diagnoses) Success n/N (%)		ME1-TOC (Definitive Diagnosis) Success n/N (%)	
Organism	Delafloxacin (N =240)	Moxifloxacin (N=248)	Delafloxacin (N =219)	Moxifloxacin (N=225)
S. pneumoniae	102/110 (92.7)	93/99 (93.9)	85/91 (93.4)	72/77 (93.5)
PRSP	7/8 (87.5)	11/11 (100)	7/8 (87.5)	11/11 (100)
MDR	4/4 (100.0)	8/8 (100.0)	4/4 (100.0)	8/8 (100.0)
Macrolide-R	15/17 (88.2)	17/18 (94.4)	15/16 (93.8)	17/18 (94.4)
S. aureus	25/27 (92.6)	28/30 (93.3)	23/25 (92.0)	23/25 (92.0)
MSSA	23/25 (92.0)	28/30 (93.3)	21/23 (91.3)	23/25 (92.0)
FQ-R MSSA	1/1 (100.0)	0	1/1 (100.0)	0
MRSA	2/2 (100.0)	0	2/2 (100.0)	0
H. parainfluenzae	31/35 (88.6)	32/37 (86.5)	27/31 (87.1)	30/34 (88.2)
H. influenzae	22/24 (91.7)	31/35 (88.6)	17/19 (89.5)	27/30 (90.0)
M. catarrhalis	6/6 (100.0)	6/6 (100.0)	4/4 (100.0)	5/5 (100.0)
K. pneumoniae	14/17 (82.4)	16/16 (100.0)	13/15 (86.7)	16/16 (100.0)
E. coli	13/13 (100.0)	9/9 (100.0)	13/13 (100.0)	6/6 (100.0)
P. aeruginosa	11/12 (91.7)	11/11 (100.0)	9/10 (90.0)	11/11 (100.0)
M. pneumoniae	29/30 (96.7)	29/29 (100.0)	29/30 (96.7)	29/29 (100.0)
L. pneumophila	27/29 (93.1)	32/32 (100.0)	27/29 (93.1)	32/32 (100.0)

Delafloxacin Microbiological Outcome by Delafloxacin MIC (µg/mL) for Select CABP Pathogens (ME2-TOC; Definitive)



CONCLUSIONS

- **There was a high degree of favorable microbiological response at TOC (eradication or presumed eradication) for delafloxacin treated patients.**
- **Delafloxacin retained potent activity against resistant phenotypes found in *S. pneumoniae* (PRSP, macrolide-resistant, MDR), *Haemophilus* species (macrolide-non-susceptible) and *S. aureus* (including MRSA and FQ-non-susceptible MSSA).**
- **Like LEAP and OPTIC, no FQ-non-susceptible *S. pneumoniae* isolates were recovered from this trial.**
- **These data demonstrated the overall microbiological efficacy of IV/oral delafloxacin monotherapy in the treatment of adult patients with CABP.**

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