Efficacy of Delafloxacin Versus Moxifloxacin Against Bacterial Respiratory Pathogens in Adults with Community-Acquired Bacterial Pneumonia (CABP): Microbiology Results from the Delafloxacin Phase 3 CABP Trial

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Key words: Community acquired bacterial pneumonia, clinical trial, fluoroquinolone, delafloxacin

Abstract: Delafloxacin is a novel fluoroquinolone with activity against Gram-positive, Gram-negative and atypical pathogens, including fluoroquinolone non-susceptible MRSA. The microbiological results of a phase 3 clinical trial in community acquired pneumonia comparing delafloxacin [300 mg IV with option to switch to 450 mg orally every 12h to moxifloxacin 400 mg IV with option to switch to 400 mg orally QD] were determined. Patients from 4 continents, predominately Europe but also South America, and Asia, were enrolled. The microbiological intent-to-treat (MITT) population included 520 patients and 60.5% of these patients had a bacterial pathogen identified. Multiple diagnostic methods were employed including culture,
serology, PCR, and urinary antigen. Based on baseline MIC₉₀ values, delafloxacin exhibited at least 16-fold greater activity than moxifloxacin for Gram-positive and fastidious Gram-negative pathogens. Delafloxacin retained activity against resistant phenotypes found in *S. pneumoniae* (penicillin-, macrolide-, multiple-drug resistant), *Haemophilus* species (β-lactamase producing, macrolide-non-susceptible) and *S. aureus* (MRSA, fluoroquinolone-non-susceptible MSSA). The microbiological success rates were: 92.7% for *S. pneumoniae* (87.5% for PRSP), 92.6% for *S. aureus* (100% for MRSA), 100% for *E. coli*, 82.4% for *K. pneumoniae*, 100% for *K. oxytoca*, 100% for *M. catarrhalis*, 91.7% for *H. influenzae*, 88.6% for *H. parainfluenzae*, 96.7% for *M. pneumoniae*, 93.1% for *L. pneumophila*, and 100% for *C. pneumoniae*. There was little correlation between MIC and outcome with a high proportion of favorable outcomes observed across all delafloxacin baseline MIC values. Delafloxacin may be considered a treatment option as monotherapy for CAP in adults, where broad spectrum coverage including MRSA activity is desirable.

**Introduction:**

Each year 5-10 million patients are treated for community-acquired pneumonia (CAP) in the US (1), with medical costs exceeding $10 billion in 2011 (2). According to the Centers for Disease Control and Prevention (CDC), there were 49,157 deaths and 257,000 visits to the emergency department with pneumonia as the primary diagnosis (3). In the Etiology of Pneumonia in the Community (EPIC) study, certain pathogens were isolated with increased frequency in intensive care unit (ICU) patients over non-ICU patients: *S. pneumoniae* (8% vs. 4%), *S. aureus* (5% vs. 1%), and Enterobacteriaceae (3% vs. 1%) (4). A follow-up analysis of the EPIC data revealed that among 2,259 adults hospitalized for community-acquired pneumonia, 37 (1.6%) had *S. aureus* identified, including 15 (0.7%) with
MRSA and 22 (1.0%) with MSSA, while 115 (5.1%) had *S. pneumoniae*. In addition, patients with CAP caused by *S. aureus*, especially MRSA, tended to have higher severity scores than patients with non-*S. aureus* and pneumococcal CAP (5). The EPIC study demonstrated that while MRSA is an infrequent pulmonary pathogen, it is important to detect because it can be associated with severe disease and may be resistant to standard antibiotics for CAP.

Delafloxacin is a novel fluoroquinolone antibiotic that possesses activity against Gram-positive, Gram-negative and atypical pathogens, including activity against fluoroquinolone non-susceptible MRSA isolates (6). It is FDA approved for treatment of patients with acute bacterial skin and soft tissue infections (ABSSSI) and community acquired bacterial pneumonia (CABP) (7). In a recently completed Phase 3 CABP study, delafloxacin was non-inferior to moxifloxacin in the primary endpoint, early clinical response (88.9 vs 89.0; 95% CI: -4.4, 4.1). A detailed analysis of the microbiology from the Phase 3 study (ML-3341-306; ClinicalTrials.gov identifier: NCT02679573) was conducted and is presented herein.

**Materials and Methods**

**Study design and efficacy endpoints.** Delafloxacin was studied in patients with CABP in one phase 3, multicenter, stratified, randomized, double-blind trial designed using the guidelines of FDA (8) and the European Medicines Agency (9). A total of 859 adult patients from sites on 4 continents, including sites in the United States (0.7%), Europe (85.7%), Latin America (5.4%), and South Africa (8.3%), were enrolled. The enrollment period spanned from December 2016 to July 2018. 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 with an option to switch to 400 mg orally QD. The mean duration of treatment with delafloxacin was 8.4 (± 1.93) days and the mean duration of treatment with moxifloxacin was 8.5
In order to be enrolled, patients had to meet entry criteria and have radiological evidence as well as ≥ 2 clinical signs and symptoms of CABP including cough, production of purulent sputum consistent with a bacterial infection, difficulty breathing (dyspnea), and chest pain due to pneumonia. Additional enrollment criteria were consistent with FDA guidance (8).

Efficacy was evaluated through assessments of signs and symptoms of infection at 96 (± 24) hours after the first dose of study drug (Early Clinical Response [ECR]), with response defined as improvement in least 2 of the following symptoms: pleuritic chest pain, frequency or severity of cough, amount and quality of productive sputum, and dyspnea (difficulty breathing); and no worsening of the other symptoms. A key efficacy endpoint was the clinical and microbiological assessment at Test-of-Cure (TOC; 5-10 days after EOT).

Analysis sets. Various subsets of data were used to evaluate the clinical response and the microbiological response. Details of the data sets used for analysis of the microbiological response are included here. The intent-to-treat (ITT) analysis data set included all patients who signed consent and were randomly assigned to a treatment. The microbiological intent-to-treat (MITT) analysis data set included all patients in the ITT analysis data set who had a baseline bacterial pathogen identified that was known to cause CABP and against which the study drug had antibacterial activity. The MITT population had 2 subgroups, MITT-1 and MITT-2, depending upon methods of detection of baseline pathogens. The MITT-1 consisted of baseline pathogens detected by all methods (i.e., including culture, serology, PCR, and urinary antigen) while the MITT-2 included baseline pathogens isolated by culture only (blood or any respiratory source, including organisms cultured from oropharyngeal and nasopharyngeal swabs). The microbiologically evaluable (ME) analysis data set included all subjects in the MITT analysis data set who also met the criteria for the corresponding clinically evaluable (CE) analysis data.
Microbiological outcomes. By-patient microbiological responses at TOC were determined by consideration of the microbiological response(s) for each baseline pathogen at TOC. By-patient microbiological success was defined as eradication or presumed eradication of all baseline pathogens. By-patient microbiological responses for patients in the microbiological intent-to-treat (MITT-1) and microbiologically evaluable at Test of Cure (ME-1TOC) populations were based upon by-pathogen microbiological responses of baseline pathogens identified by all test methods. By-patient microbiological responses for patients in the MITT-2 and ME-2TOC populations were based upon by-pathogen microbiological responses of baseline pathogens identified by culture methods. By-pathogen microbiological responses were based upon follow-up cultures performed at TOC that documented eradication or persistence of pathogens detected at baseline. When post-baseline culture results were missing, the microbiological response was determined by the clinical outcome assigned by the Investigator. Pathogens identified at baseline by a test method other than routine culture of a blood or lower respiratory tract sample (i.e., all atypical pathogens, and \textit{S. pneumoniae} detected by NP swab culture/PCR or UAT) could only have a presumed or indeterminate microbiological response, unless persistence (\textit{S. pneumoniae} only) was demonstrated by traditional culture at EOT or microbiological TOC. The definitions of documented eradicated, presumed eradicated, and documented persisted were as follows: 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).

**Pathogen Detection Methods and Level of Diagnostic Certainty:** Pathogens were classified as definitive or probable based on the method of detection (Table 1). 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. Patients with at least 1 definitive diagnosis were considered as having a definitive microbiological diagnosis, and if all diagnoses were probable, the patient was categorized as having a probable microbiological diagnosis. All sputum and endotracheal or transtracheal aspirate (ETA) samples were evaluated by Gram stain to determine specimen quality. All efforts were made to obtain an adequate specimen, defined in this study as having < 10 squamous epithelial cells (SEC) and/or > 25 polymorphonuclear neutrophils (PMN) per low-power field. Gram-stain quality was used in the evaluation of diagnostic certainty (Table 1).

In Study ML-3341-306, 78/520 [15%] patients in the MITT-1 analysis set had a probable diagnosis. For the microbiological outcome analyses presented herein, only the most conservative definitive diagnosis data is presented.

**Microbiology methods.** Causative pathogens were identified by culture and non-culture methods as described in Table 1. For *S. pneumoniae* cultured from NP swabs, a concomitant lytA PCR value of ≥ 1000 gene copies/mL was required to be considered a pathogen (10). All isolates
underwent susceptibility testing, and a subset of isolates underwent molecular or phenotypic
characterization including whole genome sequencing for fluoroquinolone resistance
mechanisms, PCR for PVL/mecA genes (S. aureus-all isolates were PVL negative), β-lactamases
(Haemophilus/Moraxella spp), and serotyping (S. pneumoniae). Details regarding these methods
are described herein:
(i) **Susceptibility testing.** Isolates were submitted to the central laboratory (Covance
Laboratories, Indianapolis, IN, USA) for identification and susceptibility testing per CLSI
guidelines (11). The comparator fluoroquinolone antibiotics included levofloxacin,
ciprofloxacin and moxifloxacin. Nonsusceptibility to these antibiotics was determined using
CLSI interpretative criteria (12). For analysis tables prepared using patient outcome and isolate
microbiological data, fluoroquinolone susceptibility/nonsusceptibility was based upon
levofloxacin and ciprofloxacin data. The designation of S. aureus isolates as MRSA or MSSA
was based upon oxacillin susceptibility and cefoxitin disk diffusion results, determined using
CLSI interpretative criteria (12). For M. catarrhalis, CLSI M45 (13) was used. For H.
influenzae and H. parainfluenzae, MIC interpretations for moxifloxacin, levofloxacin, and
azithromycin were derived according to CLSI M100-S28 (14).
(ii) **Mycoplasma pneumoniae culture.** Oropharyngeal (OP) swabs obtained at baseline were
forwarded frozen (-60°C) in SP4M transport media to the University of Alabama (UAB),
Birmingham, AL, USA for M. pneumoniae culture, identification and antibiotic susceptibility
testing. Cultures were performed according to previously described methods (15). Positive
mycoplasma broth cultures were subjected to real-time repMp1 qPCR analysis, to differentiate
M. pneumoniae from commensal mycoplasma species. Cultures were held for 6 weeks before
reported out as negative.
(iii) **Mycoplasma pneumoniae susceptibility testing.** Antibiotic susceptibility testing for delafloxacin and comparator antibiotics (levofloxacin, moxifloxacin, tetracycline, erythromycin, azithromycin and clindamycin) was determined using broth microdilution in accordance with CLSI guideline M43-A (16). Microdilution plates were incubated aerobically at 37°C and examined daily for color change in the growth control wells. MIC values were recorded as the lowest concentration of antimicrobial inhibiting color change in SP4 broth at the time the growth control well demonstrated a color change from pink to yellow. Assay QC was performed each day of antimicrobial susceptibility testing using *M. pneumoniae* M129 (ATCC 29342). Since there are no delafloxacin *M. pneumoniae* QC ranges, *S. aureus* ATCC 29213, *E. coli* ATCC 25922, and *P. aeruginosa* ATCC 49247 QC ranges were used according to CLSI document M100S28 (14). All results were within acceptable QC ranges.

(iv) **Legionella pneumophila culture.** Respiratory samples obtained at baseline were forwarded frozen (-70°C) to the Special Pathogens Laboratory, Pittsburgh, PA, USA for *L. pneumophila* culture, identification, antibiotic susceptibility testing and serotyping. All respiratory specimens were plated on buffered charcoal yeast extract media containing L-cysteine (BCYE), BCYE Selective agar with PAC (polymyxin B, anisomycin, and cefamandole; Remel, San Diego, CA, USA) and BCYE Selective agar with PAV (polymyxin B, anisomycin, vancomycin; Remel, San Diego, CA, USA). Some respiratory samples that grew heavy normal flora without Legionella species were pretreated with acid (0.2M KCl-HCl, pH 2.2 acid treatment solution) and re-cultured. Plates were incubated at 35±2°C for up to 7 days and were examined with the aid of a dissecting microscope. Identification of colonies that resembled those of *L. pneumophila* was confirmed by using latex agglutination (Legionella
Latex Test, Oxoid, Hampshire, UK) and direct immunofluorescence (Monofluo L. pneumophila IFA Test kit, BioRad, Hercules, CA, USA).

(v) **Legionella pneumophila susceptibility testing.** MIC testing was conducted by broth microdilution according to CLSI guidelines for aerobic bacteria (17) using 96-well microtiter plates containing delafloxacin and comparator agents. The bacterial inoculum was prepared from an overnight culture grown on BCYE agar at 35±2°C in a humidified chamber. The adjusted broth culture was diluted to approximately 0.5 to 1x10⁶ CFU/mL in Legionella broth medium (buffered yeast extract broth not supplemented with charcoal) (18). Two-fold serial dilutions of antibiotics were prepared in broth (0.05 mL) and added to an equal volume of inoculum in each well. Final volume per well was 0.1 mL. After incubation at 35±2°C in a humidified chamber, the MIC was read as the first well showing no visible growth at 48 h. Since there are no delafloxacin L. pneumophila QC ranges, S. aureus ATCC 29213 and E. coli ATCC 25922 QC ranges were used according to CLSI document M100S28 (14). All results were within acceptable QC ranges.

(vi) **Molecular analysis.** A pathogen was considered fluoroquinolone-non-susceptible if the pathogen was non-susceptible to levofloxacin or ciprofloxacin or moxifloxacin based on CLSI and EUCAST interpretive criteria. At the time of the study, EUCAST fluoroquinolone breakpoints were lower than CLSI breakpoints, therefore, the analysis of fluoroquinolone-resistant pathogens based on EUCAST criteria were chosen for discussion. Whole genome sequencing was performed using total genomic DNA as input material for library construction. DNA libraries were prepared using the Nextera XT™ library construction protocol and index kit (Illumina, San Diego, CA, USA) and sequenced on a MiSeq Sequencer (Illumina) using a MiSeq Reagent Kit v3 (600 cycle) with a minimum of 20x coverage. For DNA assembly and
data analysis, FASTQ format sequencing files for each sample set were quality assured, error
corrected, and assembled independently using de novo assembler SPAdes 3.9.0. A JMI
Laboratories designed software pipeline was applied to the assembled sequences to align
against known plasmid-mediated fluoroquinolone resistance genes (data not shown). gyrA and
 gyrB (that encode for DNA gyrase) and parC and parE (that encode for topoisomerase IV)
sequences were extracted from assembled genomes and respective putative protein sequences
were screened for mutations in the quinolone-resistance determinant regions (QRDRs).
Reference sequences for each gene and species were used for comparison with query
sequences.

(vii) **Pulsed-Field Gel Electrophoresis.** Isolate genomic DNA of *H. parainfluenzae* was
prepared from agarose embedded cells. Clean extracted DNA was digested with the species-
specific restriction enzyme according to manufacturer instructions (New England Biolabs,
Ipswich, MA, USA). DNA fragments were resolved on CHEF DR II electrophoresis equipment
(BioRad, Hercules, CA, USA) along with appropriate molecular weight ladders. Gels were
stained with ethidium bromide and visualized and documented using the GelDocTM XR+
(BioRad).

(viii) **lytA PCR assay.** The *lytA* PCR assay is a laboratory-developed test that targets the
autolysin gene *lytA*, a single copy gene that is encoded by all pneumococcal strains (19, 20).
Sequence of primers and probe and assay conditions were performed as previously described
with NP swabs as specimen types (21).

(ix) **Streptococcal and Legionella urinary antigen:** The Alere BinaxNOW® *S. pneumoniae*
and *L. pneumophila* Urinary Antigen Cards (Alere, Inc, Scarborough, ME, USA) were
performed by Covance Laboratories according to the manufacturer’s directions.
(x) **S. pneumoniae serotyping**: All S. pneumoniae isolates cultured from NP swabs or received from Covance Laboratories were serotyped by Quellung reaction using Neufeld reagents (Statens Serum Institute, Copenhagen, Denmark) at Emory University. Non-typeable isolates were also tested by latex agglutination and confirmed as non-typeable using Quellung antisera (results not shown).

(xi) **Serological testing**: Serum samples were collected at baseline (acute sample) and at TOC or follow up (convalescent sample) and forwarded to the Covance Central Laboratory for serology testing to identify patients infected with atypical pathogens (C. pneumoniae, M. pneumoniae, and L. pneumophila). Serum was tested for anti-C. pneumoniae antibodies using the FOCUS Chlamydia MIF IgG Test System (Focus Diagnostics, Cypress, CA, USA). Serum was tested for anti-M. pneumoniae antibodies using MBL BION M. pneumoniae Antigen Substrate Slide, IgG Binding Reagent, and Reagents for IFA Testing (MBL, Woburn, MA, USA). Serum was tested for anti-L. pneumophila antibodies using the ZEUS IFA L. pneumophila (Group 1 - 6) Test System (Zeus Scientific, Branchburg, NJ, USA).

**Results**

**Diagnostic Yield**

Of 859 patients in the ITT population, 520 patients (60.5%) had at least 1 pathogen detected at baseline by any method (including respiratory or blood culture, PCR, serology, and urinary antigen), and thus comprised the MITT-1 population. 90.2% (469/520) of the MITT-1 had a definitive pathogen detected. **Table 2** presents comparisons of the yield for these pathogens by diagnostic method employed in the trial and by definitive diagnoses in the MITT-1 population. In the delafloxacin treatment group, for S. pneumoniae, the NP swab culture/PCR methodology yielded the highest number of S. pneumoniae diagnoses (21.8%) followed by urinary antigen
(17.1%) and sputum culture (11.7%). For *M. pneumoniae* (12.5%) and *L. pneumophila* (10.1%), serology yielded the highest number of diagnoses. Diagnostic yield was generally comparable between treatment groups except for *S. pneumoniae* diagnosis by urinary antigen where the delafloxacin treatment group had slightly more diagnoses using this method than the moxifloxacin arm (17.1% versus 11.8%).

**Monomicrobial versus Polymicrobial Infections.** The presence of monomicrobial Gram-positive, Gram-negative and atypical and polymicrobial infections was as follows: in the MITT-1 (definitive diagnoses) and ME-2TOC populations, in the delafloxacin arm, 26.4% (61/231) and 33.7% (64/190) of patients had a monomicrobial Gram-positive infection, respectively. In the MITT-1 (definitive diagnoses) and ME-2TOC populations in the delafloxacin arm, 20.3% (47/231) and 38.4% (73/190) had monomicrobial Gram-negative infections, 13.4% (31/231) and 4.7% (9/190) had atypical infections, and 39.8% (92/231) and 23.2% (44/190) had polymicrobial infections. There were no major differences in the percentage of patients with monomicrobial or polymicrobial infections between the two treatment arms.

**Antimicrobial susceptibility results.** The in vitro activity of delafloxacin against baseline pathogens is shown in Table 3. Based on MIC₉₀ values at baseline, delafloxacin exhibited at least 16-fold greater activity than moxifloxacin for all Gram-positive and fastidious Gram-negative pathogens in the MITT-2 population (supplemental index). Most of these isolates were fluoroquinolone-resistant, macrolide-susceptible, and penicillin-susceptible (PSSP), methicillin-susceptible (MSSA), or β-lactamase-negative (*Haemophilus* spp.). However, delafloxacin retained activity against resistant phenotypes found in *S. pneumoniae* (PRSP, PISP, macrolide-non-susceptible, multi-drug resistant), *Haemophilus* species (β-lactamase positive and
macrolide-non-susceptible) and *S. aureus* (MRSA, fluoroquinolone-non-susceptible MSSA) and *M. pneumoniae* (macrolide-resistant) (Table 3).

**Efficacy Analysis for Delafloxacin**

The analysis of the per-pathogen microbiological response observed for delafloxacin and moxifloxacin treated patients at baseline is presented in Table 4. Overall, there was a high degree of favorable response at TOC for delafloxacin treated patients. By pathogen, the rates of microbiological success (documented or presumed eradication) at TOC were similar between the delafloxacin group and the moxifloxacin group for the most common pathogens (occurring in > 5 patients in either treatment group) in the ME-1TOC population (Table 4). Similar findings were observed in the MITT-1, MITT-2, and ME-2TOC populations (data not shown) and those patients that had a definitive diagnosis versus patients that had either a probable or definitive diagnosis (all diagnoses). Approximately one-third of patients in the delafloxacin (83/240; ME1-TOC) and moxifloxacin (76/248; ME-1TOC) treatment groups had atypical pathogens and high rates of response were also observed for these pathogens.

**Efficacy by Monomicrobial or Polymicrobial Infection**

Microbiological responses (ME1-TOC) by baseline monomicrobial and polymicrobial infection for patients with a definitive diagnosis was similar between delafloxacin and moxifloxacin treated subjects (Table 5). Among monomicrobial infections, response rates were high for pathogens in the delafloxacin treatment group: > 90% for *S. pneumoniae*, *E. coli*, *P. aeruginosa*, *K. oxytoca*, *M. catarrhalis* and the atypical pathogens *M. pneumoniae*, *L. pneumophila*, *C. pneumoniae*. Per-pathogen response rates were similarly high for polymicrobial infections including > 90% for *S. pneumoniae*, *S. aureus* (MSSA and MRSA), *H. influenzae*, *E. coli*, *K.*
oxytoca, M. catarrhalis, E. cloacae complex and the atypical pathogens M. pneumoniae, L. pneumophila, C. pneumoniae.

**Outcomes by MIC**

The analysis of the per-pathogen microbiological response by baseline MIC values observed for delafloxacin treated patients with the definitive pathogen diagnoses in the ME-2TOC population is shown in Table 6. By analyzing the microbiological outcome data using definitive diagnoses only, the most conservative analysis of the microbiological outcome data is presented for each species. Given the high overall rates of success observed, there was little correlation observed between MIC and outcome with a high proportion of favorable outcomes observed across all delafloxacin MIC values at baseline. Favorable eradication rates were also observed for S. pneumoniae isolates with resistant phenotypes including PRSP 87.5% (7/8), MDRSP 100.0% (4/4) and MRSP 87.5% (14/16) with no apparent correlation between outcome and MIC value.

No fluoroquinolone non-susceptible S. pneumoniae were recovered. Most of the S. aureus isolated were MSSA (23/25) and only 2 isolates were MRSA. Both MRSA isolates had an outcome of eradication/presumed eradication with delafloxacin MIC values of 0.002 µg/mL and 0.004 µg/mL. One of the MSSA isolates was fluoroquinolone resistant (delafloxacin MIC=0.12 µg/mL; moxifloxacin MIC=2 µg/mL; levofloxacin MIC=4 µg/mL). This isolate was found to have QRDR mutations in grlA (S80F), grlB (D422E) and gyrA (S84L) by whole genome sequencing (WGS). Despite these QRDR mutations, the microbiologic outcome was eradicated/presumed eradicated for this isolate. This finding corroborates previously observed data for S. aureus isolates in the delafloxacin ABSSSI trial (6). For H. influenzae, favorable outcomes were prevalent across all MIC values except for a single isolate with an MIC value of 0.5 µg/mL. This isolate was moxifloxacin and levofloxacin non-susceptible, was found to have
QRDR mutations in gyrA (S84L, D88G), parC (S84I) and parE (D420N) by WGS. For *H. parainfluenzae*, favorable outcomes were prevalent across most MIC values except for isolates with delafloxacin MIC values of 0.015 µg/mL and 0.25 µg/mL. By WGS, the 0.015 µg/mL isolate was found to be wild type, while the 0.25 µg/mL isolate had a QRDR mutation in gyrA (S84F). In the delafloxacin treatment group, one isolate developed resistance upon therapy (> 4-fold increase in MIC). The isolate recovered during the EOT visit had a delafloxacin MIC 64-fold higher than the baseline isolate (baseline delafloxacin MIC = 0.015 µg/mL; EOT delafloxacin MIC = 1 µg/mL). Both isolates were screened for fluoroquinolone resistance mechanisms by WGS analysis. While the baseline isolate was confirmed to be wild type, the isolate recovered at EOT had mutations in genes gyrA (S84F and D88Y) and parC (S84Y). Both the baseline and the persistent isolate were subjected to pulsed field gel electrophoresis (PFGE) and the isolates found to be genetically related. A greater than 4-fold increase in fluoroquinolone MIC values were observed in 4 *H. parainfluenzae* isolates from moxifloxacin treated patients, however, the paired isolates were found to be unrelated by PFGE. No other organisms showed a greater than 4-fold increase in MIC value in this study.

**Discussion**

These data demonstrated the overall efficacy of IV/oral delafloxacin monotherapy in the treatment of patients with CABP. Delafloxacin was non-inferior to moxifloxacin in the primary endpoint, early clinical response. Based on MIC\textsubscript{90} values at baseline, delafloxacin exhibited at least 16-fold greater activity than moxifloxacin for all Gram-positive and fastidious Gram-negative pathogens in the culture-based MITT-2 population (supplementary index). Delafloxacin and moxifloxacin had similar activity against *M. pneumoniae* isolates (including 2 macrolide-resistant isolates), and delafloxacin had greater activity than moxifloxacin against *L. pneumophila* isolates (supplementary index). Delafloxacin retained activity against resistant...
phenotypes found in *S. pneumoniae* (penicillin-resistant, macrolide-resistant, multiple-drug resistant), *Haemophilus* species (β-lactamase producing and macrolide-non-susceptible) and *S. aureus* (MRSA and fluoroquinolone-non-susceptible MSSA). As noted, no fluoroquinolone non-susceptible *S. pneumoniae* isolates were recovered from this CABP clinical trial. This finding is not unusual as fluoroquinolone non-susceptible *S. pneumoniae* were also not recovered from patients in the LEAP 1 (22) or the OPTIC (23) CABP clinical trials. Overall, among 142 baseline *S. pneumoniae* isolates with susceptibility test results available, resistance rates were 24.6% for macrolide-resistance, 13.4% for penicillin-resistance, and 8.5% for multi-drug resistance. The findings from the ABSSSI clinical trial where delafloxacin demonstrated high rates of microbiological response against levofloxacin-non-susceptible isolates as well as isolates with documented mutations in the quinolone resistance-determining region (QRDR). Most of Enterobacteriaceae and *P. aeruginosa* isolates were fluoroquinolone susceptible. Delafloxacin demonstrated reduced activity to some isolates with fluoroquinolone-non-susceptible and ESBL phenotypes (Table 3).

By pathogen, the rates of microbiological success (documented or presumed eradicated) at TOC were similar between the delafloxacin group and the moxifloxacin group for the most common pathogens in the MITT-1, MITT-2, ME-1TOC, and ME-2TOC populations. For the ME-1TOC population, the microbiological success rates were: 92.7% for *S. pneumoniae* (87.5% for PRSP), 92.6% for *S. aureus* (100% for MRSA), 100% for *E. coli*, 82.4% for *K. pneumoniae*, 100% for *K. oxytoca*, 100% for *M. catarrhalis*, 91.7% for *H. influenzae* and 88.6% for *H. parainfluenzae*. For the atypical pathogens, the microbiologic success rates were: 96.7% for *M. pneumoniae*, 93.1% for *L. pneumophila*, and 100% for *C. pneumoniae*. There was little correlation observed...
between MIC and outcome with a high proportion of favorable outcomes observed across all delafloxacin MIC values at baseline.

For the *H. parainfluenzae* isolate in the delafloxacin arm where emergence of resistance was observed, it is noteworthy that the patient was successfully treated and the clinical response at both EOT and TOC was success. Interestingly, for the isolates with a >4-fold increase in fluoroquinolone MIC value from both arms, 3 out of the 4 isolates were genetically unrelated. Previous studies from Spain and South Africa reported fluoroquinolone resistance arising from mutations in the QRDR as well as plasmid mediated resistance (24, 25). The mutations observed in *H. parainfluenzae* in this study were also observed in isolates reported in the Spanish and South African studies. Since the pneumonia was community-acquired, this could explain the nonclonal nature of the isolates from the moxifloxacin arm.

In conclusion, these data suggest that delafloxacin may be considered a treatment option as monotherapy for CAP in adults, where broad spectrum coverage is desirable.

**Acknowledgements.** The authors would like to acknowledge the laboratorians of Covance Central Laboratories, JMI Laboratories, Emory University, University of Alabama, Birmingham, and Special Pathogens Laboratory for their roles in generating the microbiology data and Firma Clinical Research for data and statistical analyses for this clinical study.
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### Table 1: Pathogen Identification and Level of Microbiological Evidence of CABP by Detection Method

| Pathogen   | Specimen Type | Method of Detection | Definitive Diagnosis | Probable Diagnosis |
|------------|---------------|---------------------|----------------------|--------------------|
### Table 2: Comparison of Diagnostic Method Yields by Baseline Pathogen by Analysis

| Population (MITT-1) | Delafloxacin | Moxifloxacin |
|---------------------|--------------|--------------|
|                     | MITT-1 (All Diagnoses) | MITT-1 (Definitive) | MITT-1 (All Diagnoses) | MITT-1 (Definitive) |
| S. pneumoniae | | | | |
| Sputum, ETA Culture and Gram-stain | Positive culture with Gram-stain of <10 SECs and/or >25 PMN/lpf | Positive culture without Gram-stain of <10 SECs and/or >25 PMN/lpf | | |
| Lavage fluid (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 without Gram-stain of <10 SECs and/or >25 PMN/lpf | | |
| Lavage fluid (BAL, mini BAL), PSB, pleural fluid and blood | Culture | Positive Culture | | |
| Mycoplasma pneumoniae | Oropharyngeal swab | Culture | Positive culture | |
| Serum | Serology<sup>a</sup> | | 4-fold increase in titer reaching ≥ 160 | |
| Legionella pneumophila | Sputum, lavage fluid (BAL, mini-BAL), PSB, pleural fluid | Culture | Positive culture | |
| Urine | Urinary antigen | Positive urinary antigen | | |
| Serum | Serology<sup>a</sup> | 4-fold increase in titer reaching ≥ 128 | | |
| Chlamydia pneumoniae | Serum | Serology<sup>a</sup> | 4-fold increase to ≥ 64 | |

**Abbreviations:** BAL = bronchoalveolar lavage; CABP = community-acquired bacterial pneumonia; ETA = endotracheal or transtracheal aspirate; lpf = low-power field; NP = nasopharyngeal; PCR = polymerase chain reaction; PMN = polymorphonuclear neutrophil; PSB = protected specimen brush; SEC = squamous epithelial cell.

<sup>a</sup> Organisms recovered by culture were reviewed on a case-by-case basis by the Sponsor prior to database lock to determine eligibility as a CABP pathogen.

<sup>b</sup> For subjects that were NP culture positive with corresponding lytA PCR < 1000 copies per mL, these subjects were considered carriers of *S. pneumoniae*, unless *S. pneumoniae* was detected by another method.

<sup>c</sup> For serology testing, any 4-fold increase between subsequent visits was considered as having a positive baseline pathogen, even if the 4-fold increase was between 2 post-baseline visits.
| Pathogen                                           | N=All MITT-1 patients and all methods | N=257 n (%) | N=263 n (%) |
|---------------------------------------------------|---------------------------------------|--------------|--------------|
| *S. pneumoniae*                                   | 120 (46.7)                            | 98 (38.1)    | 106 (40.3)   |
| Sputum culture                                    | 30 (11.7)                             | 25 (9.7)     | 37 (14.1)    |
| Blood Culture                                     | 4 (1.6)                               | 4 (1.6)      | 6 (2.3)      |
| Bronchoulveolar Lavage Culture                    | 3 (1.2)                               | 3 (1.2)      | 0            |
| NP swab culture with *lytA* PCR (>1000 gene copies/mL) | 56 (21.8)                            | 56 (21.8)    | 47 (17.9)    |
| Urinary Antigen                                   | 44 (17.1)                             | 44 (17.1)    | 31 (11.8)    |
| *Legionella pneumophila*                          | 29 (11.3)                             | 29 (11.3)    | 33 (12.5)    |
| Sputum culture                                    | 4 (1.6)                               | 4 (1.6)      | 1 (0.4)      |
| Urinary Antigen                                   | 8 (3.1)                               | 8 (3.1)      | 6 (2.3)      |
| Serology                                          | 26 (10.1)                             | 26 (10.1)    | 31 (11.8)    |
| *Mycoplasma pneumoniae*                           | 35 (13.6)                             | 35 (13.6)    | 30 (11.4)    |
| Oropharyngeal swab culture                        | 11 (4.3)                              | 11 (4.3)     | 12 (4.6)     |
| Serology                                          | 32 (12.5)                             | 32 (12.5)    | 27 (10.3)    |
| *Chlamydia pneumoniae*                            | 25 (9.7)                              | 25 (9.7)     | 16 (6.1)     |
| Serology                                          | 25 (9.7)                              | 25 (9.7)     | 16 (6.1)     |

Abbreviations: NP = nasopharyngeal; PCR = polymerase chain reaction

1 Patients with the same pathogen detected by multiple methods are counted once in the overall and once for each diagnostic method with a positive result. A pathogen is considered "Definitive" if at least one microbiologic diagnosis is "Definitive"; a pathogen is considered "Probable" if all microbiologic diagnoses are "Probable". Small numbers of patients (<10%) had probable diagnoses and thus are not included in the table.

Table 3  Summary of Delafloxacin by MIC Against Baseline Pathogens (MITT-2; Moxifloxacin and Delafloxacin Treatment Groups Combined)
| Baseline Target Pathogen                          | n  | MIC Range (µg/mL) | MIC<sub>50</sub> (µg/mL) | MIC<sub>90</sub> (µg/mL) |
|-------------------------------------------------|----|------------------|-----------------|------------------|
| **Gram-positive organisms**                     |    |                  |                  |                  |
| *Streptococcus pneumoniae*                      | 142| 0.004–0.03       | 0.015            | 0.015            |
| PSSP                                            | 102| 0.004–0.03       | 0.015            | 0.015            |
| PISP                                            | 25 | 0.008–0.03       | 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-susceptible                          | 108| 0.004–0.03       | 0.015            | 0.015            |
| Macrolide-non-susceptible                      | 34 | 0.004–0.015      | 0.015            | 0.015            |
| *Staphylococcus 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      | —                | —                |
| Fluoroquinolone-susceptible                    | 54 | 0.001–0.008      | 0.002            | 0.004            |
| Fluoroquinolone-non-susceptible                | 3  | 0.12–0.12        | —                | —                |
| **Gram-negative fastidious organisms**          |    |                  |                  |                  |
| *Haemophilus parainfluenzae*                    | 75 | 0.0005–4         | 0.008            | 0.5              |
| Macrolide-susceptible                          | 67 | 0.0005–4         | 0.008            | 0.5              |
| Macrolide-non-susceptible                      | 8  | 0.002–2         | —                | —                |
| β-lactamase-negative                           | 71 | 0.0005–4         | 0.008            | 0.5              |
| β-lactamase-positive                           | 4  | 0.001–0.008      | —                | —                |
| *Haemophilus influenzae*                       | 61 | 0.00025–0.5      | 0.001            | 0.002            |
| Macrolide-susceptible                          | 59 | 0.00025–0.5      | 0.0005           | 0.002            |
| Macrolide-non-susceptible                      | 2  | 0.001–0.002      | —                | —                |
| β-lactamase-negative                           | 58 | 0.00025–0.5      | 0.0005           | 0.002            |
| β-lactamase-positive                           | 3  | 0.0005–0.002     | —                | —                |
| *Moraxella catarrhalis*                        | 12 | 0.002–0.015      | 0.004            | 0.004            |
| **Gram-negative organisms**                    |    |                  |                  |                  |
| *Klebsiella pneumoniae*                        | 33 | 0.03–>256        | 0.12             | 0.25             |
| Fluoroquinolone-susceptible                    | 31 | 0.03–2          | 0.12             | 0.25             |
| Fluoroquinolone-non-susceptible                | 2  | >256–>256       | —                | —                |
| ESBL-negative                                  | 29 | 0.03–2          | 0.12             | 0.25             |
| ESBL-positive                                  | 4  | 0.12–256        | —                | —                |
| *Escherichia coli*                             | 27 | 0.015–4         | 0.06             | 4                |
| Fluoroquinolone-susceptible                    | 24 | 0.015–4         | 0.03             | 0.06             |
| Fluoroquinolone-non-susceptible                | 3  | 4–4             | —                | —                |
| ESBL-negative                                  | 23 | 0.03–4          | 0.06             | 0.06             |
| ESBL-positive                                  | 4  | 0.015–4         | —                | —                |
| *Enterobacter cloacae complex*                 | 14 | 0.06–256        | 0.12             | 0.25             |
| Fluoroquinolone-susceptible                    | 13 | 0.06–0.25       | 0.12             | 0.25             |
| Fluoroquinolone-non-susceptible                | 1  | 256             | —                | —                |
| *Klebsiella oxytocca*                          | 10 | 0.06–4          | 0.12             | 2                |
## Table 4  Summary of Per-Pathogen Microbiological Response at Test of Cure by Most Common Baseline Pathogens (ME-1TOC; Delafloxacin and Moxifloxacin Treatment Groups)

| Pathogens               | Delafloxacin (N = 240) | Moxifloxacin (N = 248) | Delafloxacin (N = 240) | Moxifloxacin (N = 248) |
|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| **Gram-positive organisms** |                         |                         |                         |                         |
| *Streptococcus pneumonia* | 102/110 (92.7)          | 93/99 (93.9)            | 85/91 (93.4)            | 72/77 (93.5)            |
| PSSP                    | 46/49 (93.9)            | 44/47 (93.6)            | 45/47 (95.7)            | 41/44 (93.2)            |
| PISP                    | 16/17 (94.1)            | 6/7 (85.7)              | 13/14 (92.9)            | 5/6 (83.3)              |
| PRSP                    | 7/8 (87.5)              | 11/11 (100.0)           | 7/8 (87.5)              | 11/11 (100.0)           |
| MDRSP                   | 4/4 (100.0)             | 8/8 (100.0)             | 4/4 (100.0)             | 8/8 (100.0)             |
| Macrolide resistant     | 15/17 (88.2)            | 17/18 (94.4)            | 15/16 (93.8)            | 17/18 (94.4)            |
| Culture Diagnosis (ME-2TOC) | 66/71 (93.0)          | 60/64 (93.8)            | 66/71 (93.0)            | 60/64 (93.8)            |
| *Staphylococcus 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)            |
| MRSA                    | 2/2 (100.0)             | 0                       | 2/2 (100.0)             | 0                       |

Abbreviations: — = not applicable; MDR = multiple drug-resistant; MIC₅₀ = 50th percentile of MIC values from all pathogens; MIC₉₀ = 90th percentile of MIC values from all pathogens; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; n = number of pathogens; PISP = penicillin-intermediate *S. pneumoniae*; PRSP = penicillin-resistant *S. pneumoniae*; PSSP = penicillin-susceptible *S. pneumoniae*.  

a MIC₅₀ and MIC₉₀ values were calculated only when 10 or more isolates were available.
Table 5  Microbiologic Response at Test of Cure by Baseline Monomicrobial versus Polymicrobial Infections (ME1-TOC; Definitive Diagnosis; Delafloxacin and Moxifloxacin Treatment Groups)

| Pathogens                     | Delafloxacin (N = 240) | Moxifloxacin (N = 248) | Delafloxacin (N = 240) | Moxifloxacin (N = 248) |
|--------------------------------|------------------------|------------------------|------------------------|------------------------|
| Haemophilus parainfluenzae     | 31/35 (88.6)           | 32/37 (86.5)           | 27/31 (87.1)           | 30/34 (88.2)           |
| Haemophilus influenzae         | 22/24 (91.7)           | 31/35 (88.6)           | 17/19 (89.5)           | 27/30 (90.0)           |
| Moraxella catarrhalis         | 6/6 (100.0)            | 6/6 (100.0)            | 4/4 (100.0)            | 5/5 (100.0)            |
| **Gram-negative organisms**   |                        |                        |                        |                        |
| Klebsiella pneumoniae         | 14/17 (82.4)           | 16/16 (100.0)          | 13/15 (86.7)           | 16/16 (100.0)          |
| Escherichia coli              | 13/13 (100.0)          | 9/9 (100.0)            | 13/13 (100.0)          | 6/6 (100.0)            |
| Pseudomonas aeruginosa        | 11/12 (91.7)           | 11/11 (100.0)          | 9/10 (90.0)            | 11/11 (100.0)          |
| Klebsiella oxytoca            | 6/6 (100.0)            | 3/4 (75.0)             | 6/6 (100.0)            | 3/4 (75.0)             |
| Enterobacter cloacae complex  | 3/4 (75.0)             | 8/8 (100.0)            | 2/3 (66.7)             | 7/7 (100.0)            |
| **Atypical organisms**        |                        |                        |                        |                        |
| Mycoplasma pneumoniae         | 29/30 (96.7)           | 29/29 (100.0)          | 29/30 (96.7)           | 29/29 (100.0)          |
| Culture Diagnosis (ME-2TOC)   | 11/11 (100.0)          | 11/11 (100.0)          | 11/11 (100.0)          | 11/11 (100.0)          |
| Legionella pneumophila        | 27/29 (93.1)           | 32/32 (100.0)          | 27/29 (93.1)           | 32/32 (100.0)          |
| Chlamydia pneumoniae          | 24/24 (100.0)          | 15/15 (100.0)          | 24/24 (100.0)          | 15/15 (100.0)          |

Abbreviations: ME = microbiologically evaluable; TOC = Test of Cure; PSSP = penicillin-susceptible *S. pneumoniae*; PISP = penicillin-intermediate *S. pneumoniae*; PRSP = penicillin-resistant *S. pneumoniae*; MDRSP = multiple drug-resistant *S. pneumoniae*; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*.  

* Success was defined as documented or presumed eradication.  

* Patients any combination of PSSP, PISP, or PRSP were counted once in the overall category for that organism.
Table 6: Summary of Correlation of Delafloxacin Baseline MIC to Microbiological Eradication Rate at TOC (ME-2TOC-541) - Definitive Diagnosis-Delafloxacin Treatment Group for Proposed CABP Indication Pathogens

| Organism | Microbiological Eradication Rate (n/N) by MIC (µg/mL) | 0.00025 | 0.0005 | 0.001 | 0.002 | 0.004 | 0.008 | 0.011 | 0.015 | 0.03 | 0.06 | 0.12 | 0.25 | 1 | 2 | 4 | > 4 |
|----------|-----------------------------------------------------|---------|---------|-------|-------|-------|-------|-------|-------|------|------|------|------|---|---|---|-----|
| **Gram-positive organisms** | | | | | | | | | | | | | | | | | | |
| S. pneumoniae | All | - | - | - | - | 2/2 (100) | 4/4 (100) | 16/17 (94.1) | 16/17 (94.1) | 2/2 (100) | - | - | - | | | | | |
| S. aureus | 2/25 | - | - | 1/1 (100) | - | - | - | - | - | - | - | - | - | - | - | - | - |
| MRSA | 2/2 | - | - | 0/0 (0) | - | - | - | - | - | - | - | - | - | - | - | - | - |
| MSSA | 2/23 | - | - | 0/0 (0) | - | - | - | - | - | - | - | - | - | - | - | - | - |
| **Gram-negative organisms** | | | | | | | | | | | | | | | | | | |
| K. pneumoniae | 6/15 (40.0) | - | - | - | - | - | - | - | - | - | - | - | - | | | | |
| K. oxytoca | 4/8 (50.0) | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| E. coli | 1/1 (100) | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| P. aeruginosa | 1/1 (100) | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| **Gram-negative organisms (fastidious)** | | | | | | | | | | | | | | | | | | |
| H. influenzae | 1/1 (100) | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| H. parainfluenzae | 2/2 (100) | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| M. catarrhalis | 1/1 (100) | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| **Atypical organisms** | | | | | | | | | | | | | | | | | | |

On May 6, 2020 by guest
| Organism         | Microbiological Eradication Rate (n/N) by MIC (µg/mL) |
|------------------|-------------------------------------------------------|
|                  | All 0.00025 0.0005 0.001 0.002 0.004 0.008 0.015 0.03 0.06 0.12 0.25 0.5 1 2 4 > 4 |
|                  | All 0.00025 0.0005 0.001 0.002 0.004 0.008 0.015 0.03 0.06 0.12 0.25 0.5 1 2 4 > 4 |
| M. pneumoniae    | 7/7 (100)  -  -  -  -  -  -  -  -  -  -  -  -  - 1/1 (100) 1/4 (100) 4/4 (100) 2/2 (100) -  -  -  - |
| L. pneumophila   | 3/4 (75.0) 1/1 (100) 1/2 (50) 1/1 (100) -  -  -  -  -  -  -  -  -  -  -  -  |

Abbreviations: MIC = minimum inhibitory concentration; n = total number of patients with the indicated MIC at baseline and microbiological eradication (presumed and documented) at test-of-cure; N = total number of patients with the indicated MIC at baseline. MRSA = methicillin-resistant S. aureus; MSSA = methicillin-susceptible S. aureus.
