

A Phase 3 Study to Compare Delafloxacin With Moxifloxacin for the Treatment of Adults With Community-Acquired Bacterial Pneumonia (DEFINE-CABP)

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Background. The clinical and economic burden of community-acquired bacterial pneumonia (CABP) is significant and is anticipated to increase as the population ages and pathogens become more resistant. Delafloxacin is a fluoroquinolone antibiotic approved in the United States for the treatment of adults with acute bacterial skin and skin structure infections. Delafloxacin's shape and charge profile uniquely impact its spectrum of activity and side effect profile. This phase 3 study compared the efficacy and safety of delafloxacin with moxifloxacin for the treatment of CABP.

Methods. A randomized, double-blind, comparator-controlled, multicenter, global phase 3 study compared the efficacy and safety of delafloxacin 300 mg twice daily or moxifloxacin 400 mg once daily in adults with CABP. The primary end point was early clinical response (ECR), defined as improvement at 96 (± 24) hours after the first dose of study drug. Clinical response at test of cure (TOC) and microbiologic response were also assessed.

Results. In the intent-to-treat analysis population (ITT), ECR rates were 88.9% in the delafloxacin group and 89.0% in the moxifloxacin group. Noninferiority of delafloxacin compared with moxifloxacin was demonstrated. At TOC in the ITT population, the success rates were similar between groups. Treatment-emergent adverse events that were considered at least possibly related to the study drug occurred in 65 subjects (15.2%) in the delafloxacin group and 54 (12.6%) in the moxifloxacin group.

Conclusions. Intravenous/oral delafloxacin monotherapy is effective and well tolerated in the treatment of adults with CABP, providing coverage for Gram-positive, Gram-negative, and atypical pathogens.

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Keywords. CABP; delafloxacin; fluoroquinolone; moxifloxacin; pneumonia.

The most common cause for hospital admission in adults, community-acquired bacterial pneumonia (CABP), carries with it a significant clinical and economic burden. As the population ages and pathogens become more resistant, this burden is anticipated to increase [1–5].

The microbiological diagnosis of CABP decreases steadily with age, making empiric treatment necessary, as early appropriate antibiotic therapy is associated with improved clinical

outcomes [6]. At the same time, antimicrobial resistance continues to evolve as a serious problem in the United States and Europe, with only a few new antibiotics developed in recent years [7–11].

Delafloxacin, approved by the US Food and Drug Administration in 2017 for the treatment of acute bacterial skin and skin structure infection (ABSSSI), is an anionic fluoroquinolone with intravenous (IV) and oral formulations that differs from other quinolones in shape and charge profile, resulting in a beneficial spectrum of activity and side effect profile [12].

Unlike most other fluoroquinolones, delafloxacin inhibits DNA gyrase and topoisomerase IV in both Gram-positive and Gram-negative bacteria to a similar extent. With a broad spectrum of activity targeting Gram-positives, including methicillin-resistant *Staphylococcus aureus* (MRSA), Gram-negative organisms, and atypical and anaerobic organisms, this dual targeting also decreases the likelihood of resistance, particularly in Gram-positive organisms, by requiring the accumulation of multiple mutations affecting both enzymes [13, 14].

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Delafloxacin has the fluoroquinolone class safety warnings, but the unique attributes of delafloxacin may also offer a differentiated adverse event (AE) profile compared with other fluoroquinolones, primarily lack of corrected QT interval (QTc) prolongation, phototoxicity, and major central nervous system (CNS) events [15, 16].

Delafloxacin's susceptibility profile against respiratory pathogens, bioequivalent IV and oral formulations, and favorable safety profile support its use for the treatment of CABP [15]. This phase 3 study compared the efficacy and safety of delafloxacin with moxifloxacin for the treatment of CABP.

METHODS

Study Design and Conduct

ML-3341-306 (Compare Delafloxacin to Moxifloxacin for the Treatment of Adults with Community-Acquired Bacterial Pneumonia [DEFINE-CABP]) was a phase 3, randomized, double-blind, comparator-controlled, multicenter, global study comparing the efficacy and safety of IV/oral delafloxacin with that of IV/oral moxifloxacin in adults with CABP.

Eighty-eight study centers in 18 countries screened subjects, and 86 centers enrolled subjects into the study.

All study sites were granted approval by their independent ethics committee (IEC) or institutional review board (IRB). The study was conducted according to the principles of the International Conference on Harmonisation (ICH) E6(R2), World Medical Association Declaration of Helsinki, Good Clinical Practice Guidelines, and local laws and regulations. Documentation of all IEC and IRB approvals and compliance with (ICH) E6(R2) was maintained by each study site and available for review by the sponsor. All subjects provided written informed consent.

Randomization and Treatment

Subjects were randomly assigned in a 1:1 ratio to receive delafloxacin 300 mg as a 1-hour infusion every 12 (\pm 2) hours or moxifloxacin 400 mg as a 1-hour infusion every 24 (\pm 2) hours with blinding placebo to maintain a 12-hour schedule. Subjects who met clinical criteria could switch to oral treatment after a minimum of 6 IV doses. The total duration of treatment (IV and oral) was from 5 to 10 days, as clinically indicated.

To enable sensitivity analysis of the primary Food and Drug Administration (FDA) end points, randomization was stratified by Pneumonia Patient Outcomes Research Team (PORT) risk class, medical history of chronic obstructive pulmonary disease (COPD) or asthma, and prior single-dose/regimen systemic antimicrobial use.

If MRSA was confirmed, the investigator could elect to switch subjects from moxifloxacin to linezolid (600 mg IV every 12 hours) in a blinded fashion. Subjects randomized to delafloxacin continued to receive delafloxacin every 12 hours,

discontinued moxifloxacin placebo once daily, and started linezolid placebo every 12 hours.

Study Population

Subjects \geq 18 years of age with clinical and radiographic evidence consistent with CABP and PORT risk class of II, III, IV, or V comprised the ITT population. Enrollment included no more than 25% of subjects who were PORT Risk Class II. No more than 25% of subjects received 1 dose of a single, potentially effective, short-acting antimicrobial or drug regimen for treatment of CABP within 24 hours of enrollment. The complete inclusion/exclusion criteria are detailed in [Supplementary Table 1](#).

Study Visits

Key visits included early clinical response (ECR), 96 (\pm 24) hours after the start of the first dose of study drug; end of treatment (EOT), last dose + 1 calendar day; and test of cure (TOC), 5 to 10 days after last dose. A follow-up (FU) visit or phone contact was conducted at day 28 (\pm 2 days).

Efficacy Assessments and End Points

Efficacy was evaluated through assessment of clinical signs and symptoms of pneumonia, pathogen identification, and susceptibility testing of bacterial isolates. Key efficacy end points included the following:

The FDA primary end point of ECR was defined as improvement in at least 2 of the following symptoms: chest pain, frequency or severity of cough, amount and quality of productive sputum, dyspnea, and no worsening of the other symptoms in the ITT population. Subjects evaluated for ECR were classified as responders or nonresponders. Early clinical response with the addition of improvement in vital signs required as a response was a predefined FDA secondary efficacy end point of the study. In addition to meeting the criteria for the primary end point of ECR, subjects were required at ECR to show improvement and no worsening in all vital sign assessments. In addition, subgroups were predefined for analysis of efficacy outcomes.

The investigator defined the clinical outcome based on assessment of the subject's signs and symptoms of infection at TOC. Assessment of the clinical response was categorized as success, failure, or indeterminate/missing.

All-cause mortality was assessed at FU and compared between the treatment groups.

Microbiological Response

Causative pathogens were identified by isolation from a baseline culture specimen (respiratory specimen and/or blood), by urinary antigen, serology, and/or quantitative polymerase chain reaction analysis. In vitro susceptibility of pathogens to delafloxacin and other comparator antibiotics was determined at the central microbiology laboratory according to Clinical

and Laboratory Standards Institute and European Committee on Antimicrobial Susceptibility Testing guidelines for broth microdilution and disk diffusion [17–19]. Multidrug resistance (MDR) was defined as resistance to 3 or more antibiotic classes [20].

By-subject microbiological responses at TOC were determined by results of baseline and FU cultures (if available), and the investigator's clinical response if not, defined as eradication, presumed eradication, documented persistence, presumed persistence, or indeterminate/missing. By-pathogen microbiological responses were based on follow-up cultures performed at TOC. Clinical outcome at TOC by baseline pathogen was assessed and compared between the 2 treatment groups.

Safety Assessments/Safety End Points and Evaluation

Safety assessments included physical examination, AEs, vital signs, clinical laboratory tests, and 12-lead electrocardiograms (ECGs) at screening and if clinically indicated after screening by the investigator.

Treatment-emergent AEs (TEAE) were defined as events newly occurring or worsening from the time of the first dose of study drug through FU. Related TEAE was defined as a TEAE that was at least possibly related to the study drug, per the investigator. Subgroup analysis of safety outcomes was predefined.

Adverse events of special interest (AESIs) were selected based on medical issues of interest for the fluoroquinolone class of antibiotics. This assessment focused on AESIs of potential myopathy, *Clostridium difficile* diarrhea, convulsions, potential peripheral neuropathy, tendon disorder, potential QT prolongation, phototoxicity, allergic reactions, dysglycemias (hyperglycemia, hypoglycemia), and hepatic-related events.

Statistical Analysis/Methods

Assuming a rate of ECR for moxifloxacin therapy and delafloxacin of 77% and 74%, respectively, it was determined that 860 subjects in the ITT population would provide a 90% power to assess an FDA-directed noninferiority margin of 12.5% of delafloxacin vs moxifloxacin. The differences in proportions for the responders from the 2 treatment groups (delafloxacin minus moxifloxacin) were tested for noninferiority using confidence intervals (CIs) generated by the Miettinen-Nurminen method without stratification. Continuous secondary efficacy measures were analyzed using an analysis of covariance (ANCOVA) model with treatment as the main effect, adjusted for PORT risk class, medical history of COPD or asthma, and prior antimicrobial therapy, and the baseline measure was the covariate. All statistical analyses, unless otherwise specified, were based upon 2-sided 95% CIs around the difference in treatment outcomes.

All analyses and summaries were produced using SAS software (SAS Institute, Inc, Cary, NC, USA), version 9.4

(or higher). Medical Dictionary for Regulatory Activities (MedDRA), version 19.1, was used for coding AEs and medical history. The prior and concomitant medications were coded using the World Health Organization (WHO) Drug Dictionary (WHODrug), version March 2016 [21].

RESULTS

This study enrolled 859 subjects; 431 subjects were randomized to the delafloxacin group, and 428 subjects were randomized to the moxifloxacin group. For the ITT population, 783 subjects (91.2%) completed the study with participation through TOC (394 [91.4%] in the delafloxacin group and 389 [90.9%] in the moxifloxacin group). Of the 76 subjects (8.8%) who did not complete the study through TOC, the most common reasons for premature withdrawal were lack of efficacy (3.1%), AE (2.2%), and withdrawal of consent (1.3%) (Figure 1). The median duration of total IV and oral treatment was 9 days in each group (median, 6 days IV and 2 days oral).

Subject Baseline Characteristics/Demographics

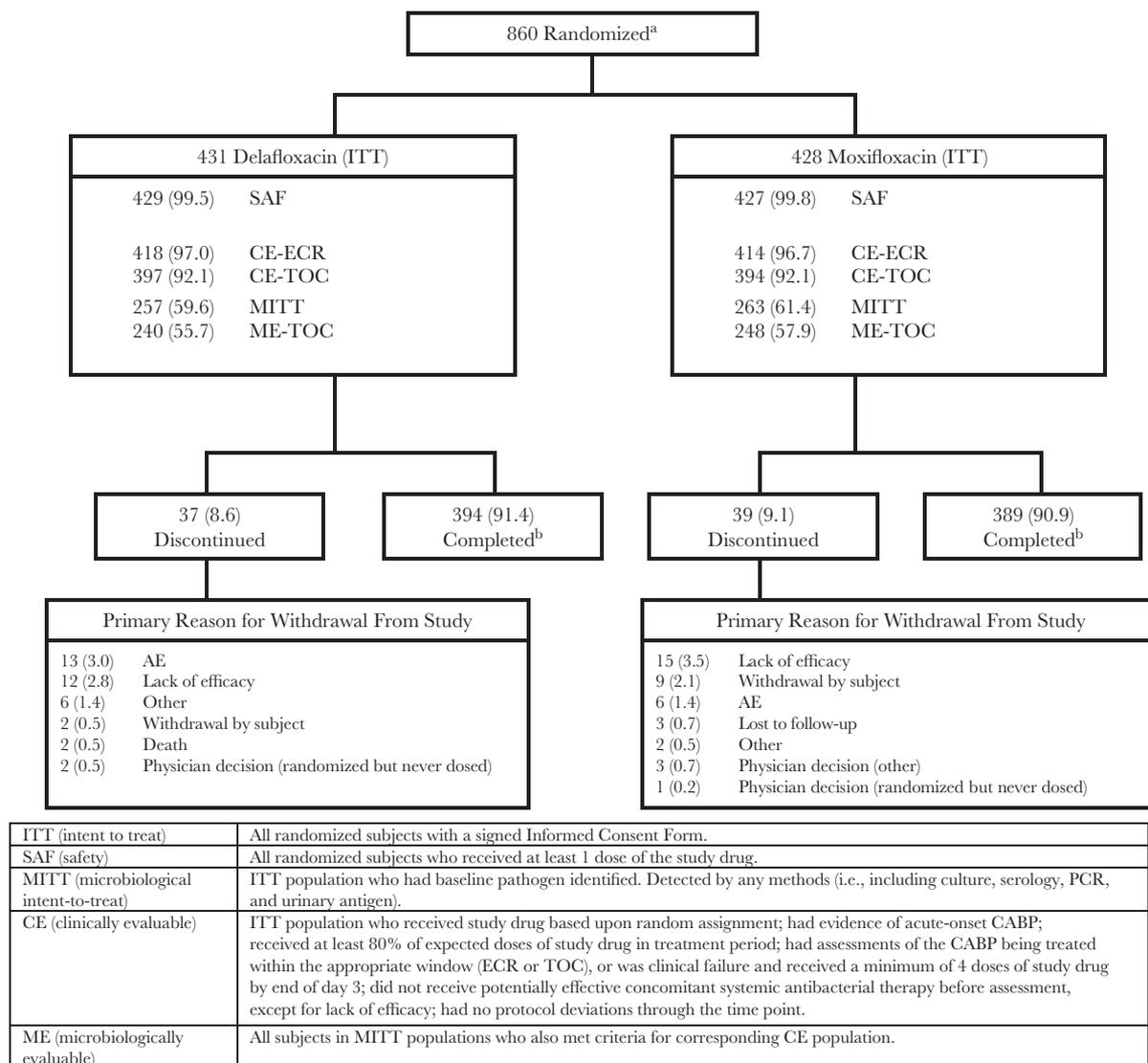
Demographic and baseline characteristics were similar between the 2 treatment groups. Subjects in the ITT population were predominantly men (58.7%), white (91.5%), and European (85.7%); 6.4% were Hispanic or Latino. A higher percentage of subjects in the delafloxacin group were aged ≥ 65 years (47.1%) compared with the moxifloxacin group (41.8%), whereas about one-fifth of subjects in both treatment groups were aged ≥ 75 years. Of subjects in the ITT population, 60.5% had a baseline pathogen identified (Table 1).

Of the 26% of subjects who received systemic antibiotic therapy in the 7 days before enrollment, 21.5% received a single dose of a short-acting antimicrobial within 24 hours of enrollment, and 4.5% had a prior documented treatment failure.

Clinical Outcomes

In the ITT population, similar percentages of subjects in each arm were responders at ECR. Response rates were 88.9% in the delafloxacin group and 89.0% in the moxifloxacin group (−0.2%; 95% CI, −4.4% to 4.1%). As the lower bound of the 95% CI was greater than −12.5%, using the Miettinen-Nurminen method without stratification, noninferiority of delafloxacin compared with moxifloxacin was demonstrated. Regardless of the analysis population, responder rates were comparable between treatment groups. (Figure 2). In the ITT population, at ECR, responder rates, when combined with improvement in vital signs, significantly favored delafloxacin (52.7%) over moxifloxacin (43.0%), with a difference of 9.7% (95% CI, 3.0% to 16.3%).

Responder rates were similar between the delafloxacin and moxifloxacin groups for all subgroups analyzed, except for subjects with COPD or asthma, where delafloxacin was significantly better than moxifloxacin (93.4% vs 76.8%; difference, 16.7%; 95% CI, 4.1% to 30.2%) (Figure 2).



Abbreviations: AE, adverse event; ECR, Early Clinical Response; EOT, End of Treatment; PK, pharmacokinetics; TOC, Test of Cure.

^a One subject mistakenly was randomized into the interactive voice and web response system but did not provide informed consent; therefore, this subject was not included in the ITT population.

^b Completed the study through TOC.

Figure 1. Subject disposition and analysis populations. ^aOne subject was mistakenly randomized into the interactive voice and web response system but did not provide informed consent; therefore, this subject was not included in the intent-to-treat population. ^bCompleted the study through TOC. Abbreviations: AE, adverse event; ECR, early clinical response; EOT, end of treatment; PK, pharmacokinetics; TOC, test of cure.

At TOC in the ITT population, the success rates were 90.5% in the delafloxacin treatment group and 89.7% in the moxifloxacin group, with a difference of 0.8% (95% CI, -3.3% to 4.8%). Clinical outcomes were comparable between treatment groups in the other analysis sets (Figure 3).

Among subjects with bacteremia at baseline, 1 delafloxacin-treated subject with *Klebsiella pneumoniae* and 1 moxifloxacin-treated subject with *Streptococcus pneumoniae* were nonresponders at the early time point. The delafloxacin subject went on to have presumed eradication of the pathogen and a

clinical outcome of success at TOC, whereas the moxifloxacin subject was a failure at EOT.

Similar percentages of subjects in the delafloxacin (1.9%) and moxifloxacin groups (1.4%) died during the study (up to day 28). All events were considered unrelated to the study drug.

Microbiological Outcomes

Five hundred twenty subjects (60.5%) had at least 1 pathogen detected at baseline by any method (Table 2). Overall, *S. pneumoniae* was the most commonly identified pathogen, in 43.5% of subjects in the MITT population, followed by *Haemophilus parainfluenzae*

Table 1. Subject Demographics and Baseline Characteristics (ITT Population)

| Characteristic | Delafloxacin (n = 431) | Moxifloxacin (n = 428) | Total (n = 859) |
|----------------------------------------|------------------------|------------------------|-----------------|
| Age, y | | | |
| Mean (SD) | 60.7 (16.06) | 59.3 (16.58) | 60.0 (16.33) |
| Median | 63.0 | 61.0 | 62.0 |
| Min, max | 18, 89 | 18, 93 | 18, 93 |
| Age category, No. (%) | | | |
| <65 y | 228 (52.9) | 249 (58.2) | 477 (55.5) |
| ≥65 y | 203 (47.1) | 179 (41.8) | 382 (44.5) |
| ≥75 y | 85 (19.7) | 97 (22.7) | 182 (21.2) |
| Sex, No. (%) | | | |
| Male | 251 (58.2) | 253 (59.1) | 504 (58.7) |
| Female | 180 (41.8) | 175 (40.9) | 355 (41.3) |
| Race, No. (%) | | | |
| White | 398 (92.3) | 388 (90.7) | 786 (91.5) |
| Black or African American | 22 (5.1) | 33 (7.7) | 55 (6.4) |
| Asian | 5 (1.2) | 5 (1.2) | 10 (1.2) |
| American Indian or Alaska Native | 4 (0.9) | 0 | 4 (0.5) |
| Other | 2 (0.5) | 2 (0.5) | 4 (0.5) |
| Region, No. (%)^a | | | |
| Europe | 371 (86.1) | 365 (85.3) | 736 (85.7) |
| South Africa | 30 (7.0) | 41 (9.6) | 71 (8.3) |
| Latin America | 29 (6.7) | 17 (4.0) | 46 (5.4) |
| North America | 1 (0.2) | 5 (1.2) | 6 (0.7) |
| Weight, kg | | | |
| Mean (SD) | 76.40 (17.389) | 77.23 (16.765) | 76.82 (17.076) |
| Median | 75.00 | 75.65 | 75.00 |
| Min, max | 39.2, 160.0 | 33.5, 136.0 | 33.5, 160.0 |
| BMI category, No. (%) | | | |
| <30 kg/m ² | 328 (76.1) | 316 (73.8) | 644 (75.0) |
| ≥30 kg/m ² | 103 (23.9) | 112 (26.2) | 215 (25.0) |
| Diabetes, No. (%) | | | |
| Yes | 70 (16.2) | 61 (14.3) | 131 (15.3) |
| COPD/asthma, No. (%) | | | |
| Yes | 61 (14.2) | 56 (13.1) | 117 (13.6) |
| Multilobar pneumonia, No. (%) | | | |
| Yes | 125 (29.0) | 120 (28.0) | 245 (28.5) |
| CrCl group, No. (%)^b | | | |
| Severe (<30 mL/min) | 5 (1.2) | 7 (1.6) | 12 (1.4) |
| Moderate (30–<60 mL/min) | 80 (18.6) | 79 (18.5) | 159 (18.5) |
| Mild (60–<90 mL/min) | 142 (32.9) | 134 (31.3) | 276 (32.1) |
| Normal (≥90 mL/min) | 194 (45.0) | 199 (46.5) | 393 (45.8) |
| Missing | 10 (2.3) | 9 (2.1) | 19 (2.2) |
| PORT risk class, No. (%) | | | |
| 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) |
| PORT risk score | | | |
| Mean (SD) | 84.5 (15.75) | 84.7 (17.43) | 84.6 (16.60) |
| Median | 83.0 | 81.0 | 82.0 |
| Min, max | 50, 146 | 48, 161 | 48, 161 |
| Bacteremia, No. (%) | | | |
| Yes | 5 (1.2) | 8 (1.9) | 13 (1.5) |
| Pathogen identified at baseline | | | |
| | 257 (59.6) | 263 (61.4) | 520 (60.5) |

Abbreviations: BMI, body mass index; BSA, body surface area; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; CRF, case report form; CURB-65, confusion, urea, respiratory rate, blood pressure, age 65 or older; ITT, intent-to-treat; Max, maximum; Min, minimum; NIH, National Institutes of Health; PMN, polymorphonuclear neutrophil; PORT, Patient Outcomes Research Team; SEC, squamous epithelial cell.

^aEurope comprises Bulgaria, Georgia, Germany, Hungary, Latvia, Poland, Romania, Russia, Serbia, Spain, Slovenia, and Ukraine. North America comprises the United States. Latin America comprises Argentina, Columbia, Peru, and Dominican Republic.

^bCrCl was based on the Cockcroft-Gault formula without correction for BSA.

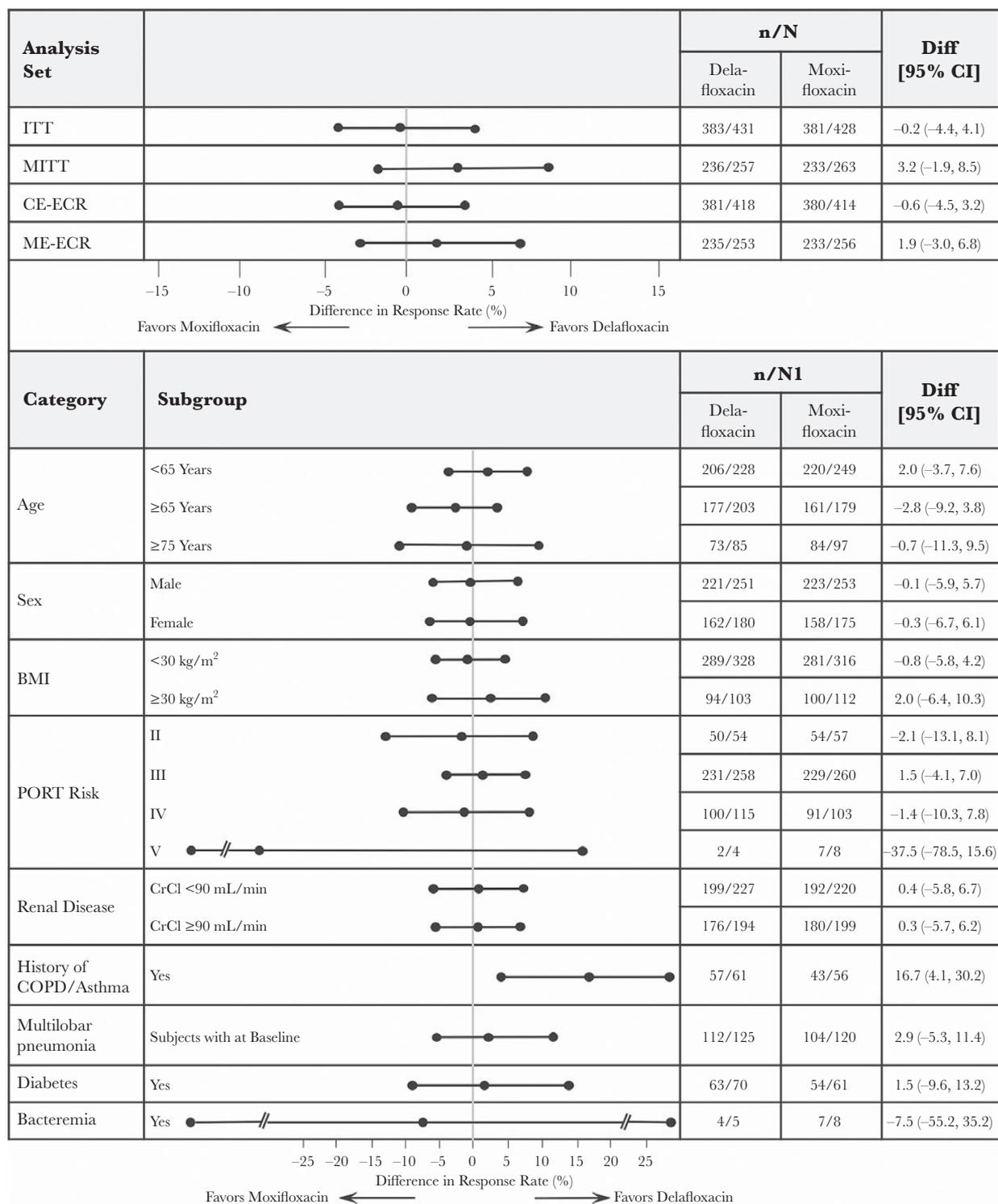


Figure 2. Early clinical response by analysis set and subgroup (ITT population). Difference was the difference in ECR response rates (delafloxacin treatment group minus moxifloxacin treatment group). The CIs were calculated using the Miettinen-Nurminen method without stratification. Abbreviations: CE, clinically evaluable; CI, confidence interval; ECR, early clinical response; ITT, intent-to-treat; LCL, 95% lower confidence limit; ME, microbiologically evaluable; MITT, microbiological intent-to-treat; UCL, 95% upper confidence limit.

(14.6%), *Mycoplasma pneumoniae* (12.5%), *Legionella pneumophila* (11.9%), *Haemophilus influenzae* (11.9%), *S. aureus* (11.0%), and *Chlamydia pneumoniae* (7.9%). Of the 142 baseline

S. pneumoniae isolates identified, 13.4% were penicillin-resistant (PRSP), 24.6% macrolide-resistant (MRSP), and 8.5% multiple drug-resistant (MDRSP). *S. aureus* was encountered frequently,

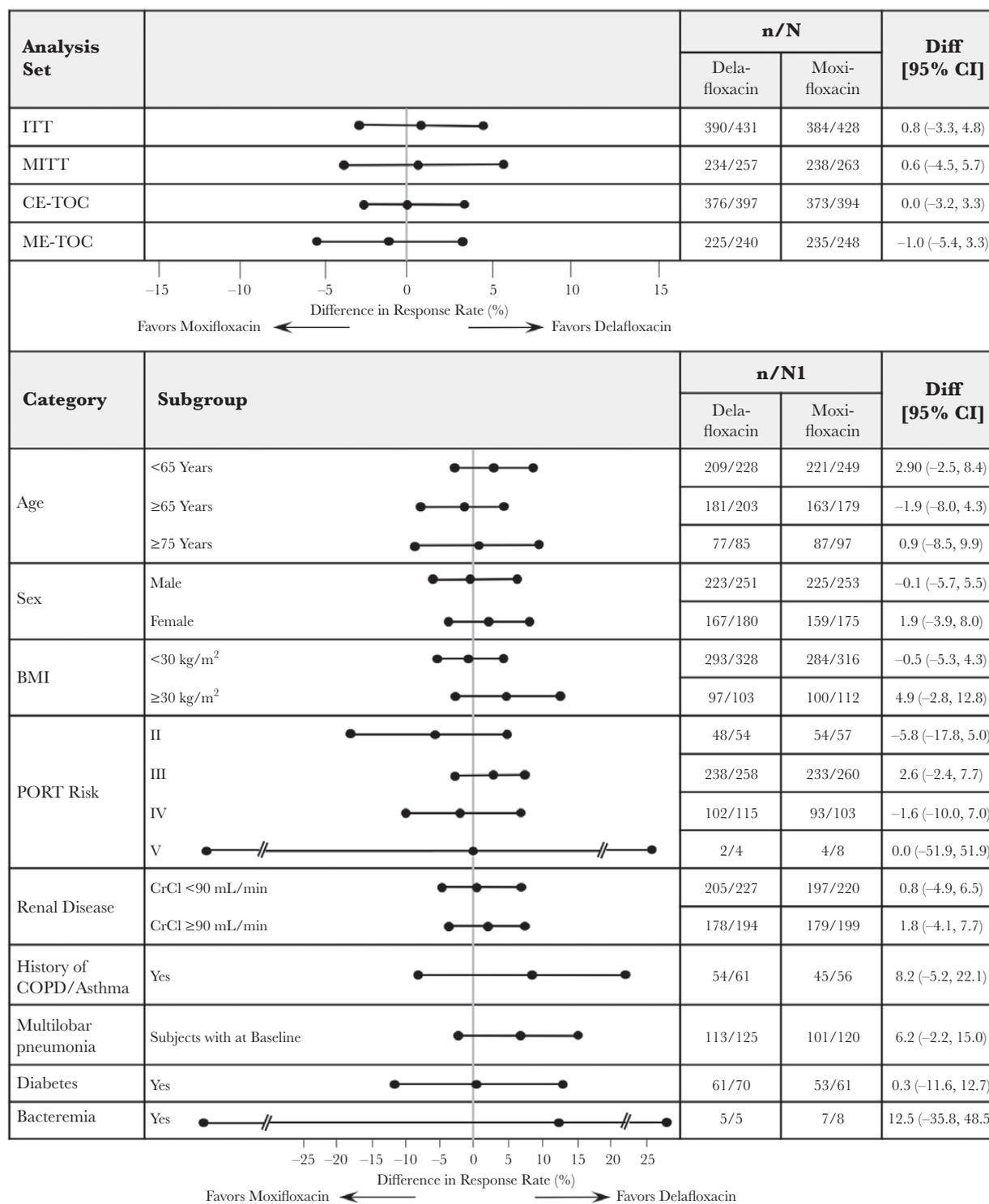


Figure 3. Clinical outcome at test of cure by analysis set and subgroup (ITT population). Difference was the difference in ECR response rates (delafloxacin treatment group minus moxifloxacin treatment group). The CIs were calculated using the Miettinen-Nurminen method without stratification. Abbreviations: CE, clinically evaluable; CI, confidence interval; ECR, early clinical response; ITT, intent-to-treat; LCL, 95% lower confidence limit; ME, microbiologically evaluable; MITT, microbiological intent-to-treat; UCL, 95% upper confidence limit.

with only 2 MRSA isolates identified, both in the delafloxacin treatment group and both deemed a clinical/microbiological success at TOC. Gram-negative pathogens ≥4% included

K. pneumoniae, *Escherichia coli*, and *Pseudomonas aeruginosa* (6.3%, 5.2%, and 4.6%, respectively). Based on MIC₉₀ (Minimum Inhibitory Concentration [MIC]) values at baseline, delafloxacin

Table 2. Pathogens Identified at Baseline in >1% of Subjects (MITT Population)

| Baseline Pathogens | No. (%) of Subjects |
|-----------------------------------|---------------------|
| | Total (n = 520) |
| <i>Streptococcus pneumoniae</i> | 226 (43.5) |
| PSSP | 102 (19.6) |
| PISP | 25 (4.8) |
| PRSP | 19 (3.7) |
| MDRSP | 12 (2.3) |
| MRSP | 35 (6.7) |
| <i>Haemophilus parainfluenzae</i> | 76 (14.6) |
| <i>Mycoplasma pneumoniae</i> | 65 (12.5) |
| <i>Legionella pneumophila</i> | 62 (11.9) |
| <i>Haemophilus influenzae</i> | 62 (11.9) |
| <i>Staphylococcus aureus</i> | 57 (11.0) |
| MRSA | 2 (0.4) |
| MSSA | 55 (10.6) |
| <i>Chlamydia pneumoniae</i> | 41 (7.9) |
| <i>Klebsiella pneumoniae</i> | 33 (6.3) |
| <i>Escherichia coli</i> | 27 (5.2) |
| <i>Pseudomonas aeruginosa</i> | 24 (4.6) |
| <i>Klebsiella oxytoca</i> | 10 (1.9) |
| <i>Moraxella catarrhalis</i> | 12 (2.3) |

Pathogens were identified by culture and/or nonculture methods. Organisms isolated by culture were reviewed on a case-by-case basis by the sponsor to determine eligibility as a causative CABP pathogen. Pathogens identified by nonculture methods were determined programmatically. For each subject, if a pathogen was identified by more than 1 method, the subject was counted only once. Subjects with both MRSA and MSSA, or any combination of PSSP, PISP, or PRSP, were counted once in the overall category for that organism.

Abbreviations: CABP, community-acquired bacterial pneumonia; MDRSP, multiple drug-resistant *Streptococcus pneumoniae*; MITT, microbiological intent-to-treat; MRSA, methicillin-resistant *Staphylococcus aureus*; MRSP, macrolide-resistant *Streptococcus pneumoniae*; MSSA, methicillin-susceptible *Staphylococcus aureus*; PISP, penicillin-intermediate *Streptococcus pneumoniae*; PRSP, penicillin-resistant *Streptococcus pneumoniae*; PSSP, penicillin-susceptible *Streptococcus pneumoniae*.

exhibited at least 16-fold greater activity than moxifloxacin for all Gram-positive and fastidious Gram-negative pathogens in the MITT population.

In the ME-TOC population, the clinical success rates by pathogen were similar between the delafloxacin group and the moxifloxacin group (Table 3). Three subjects in the delafloxacin group and 4 in the moxifloxacin group had documented persistence of a baseline pathogen. All 3 subjects in the delafloxacin arm had a clinical outcome of success at TOC. In the moxifloxacin arm, 1 of 3 subjects had a clinical outcome of failure at EOT and TOC; the others had an outcome of success at TOC.

Safety and Tolerability

Overall, 131 subjects (30.5%) in the delafloxacin group and 112 (26.2%) in the moxifloxacin group experienced TEAEs. Of these, 65 (15.2%) in the delafloxacin group and 54 (12.6%) in the moxifloxacin group were considered at least possibly related to the study drug. Most were mild in severity. Nineteen subjects (4.4%) in the delafloxacin group and 14 (3.3%) in the moxifloxacin group experienced

TEAEs assessed as severe. Two (0.5%) in the delafloxacin group (hypersensitivity and *C. difficile* colitis) and none in the moxifloxacin group had SAEs that were considered potentially related to the study drug. Fifteen subjects (3.5%) in the delafloxacin group and 7 (1.6%) in the moxifloxacin group discontinued the study drug because of TEAEs (Tables 4 and 5). Nine subjects (2.1%) in the delafloxacin group and 7 (1.6%) in the moxifloxacin group had TEAEs leading to death. Of these, 2 deaths, 1 in each treatment group, occurred after day 28. All events were considered unrelated to the study drug.

There were no TEAEs reported in $\geq 5\%$ of subjects in either treatment group. Diarrhea, increased transaminases, and headache were the only TEAEs reported in $\geq 2\%$ of subjects. A subgroup analysis of adverse events based upon medical history and demographic subgroups was completed. With small numbers of subjects among subgroups, there were no differences observed in related events.

In the safety analysis set, TEAEs of special interest (AESI) were chosen based upon medical issues of interest for the fluoroquinolone class. Because of recent fluoroquinolone class labeling updates, a search for events related to potential aortic dissection/rupture was included (Table 6). No subject in either group experienced a potential peripheral neuropathy, tendon disorder, phototoxicity, or potential aortic rupture/dissection. No subjects in the delafloxacin group had a potential myopathy or QT prolongation, whereas 5 subjects (1.2%) and 2 subjects (0.5%) in the moxifloxacin group experienced a potential myopathy or QT prolongation, respectively. Two subjects (0.5%) in the delafloxacin group and 1 subject (0.2%) in the moxifloxacin group had a TEAE of *C. difficile* colitis. One subject in each treatment group discontinued treatment because of the AE. In all 3 subjects, the TEAE resolved within 10 to 17 days.

A higher percentage of subjects in the delafloxacin group (5.1%) compared with the moxifloxacin group (2.8%) had hepatic TEAEs, with transaminase increase reported most frequently. The hepatic TEAEs were all mild or moderate in severity except for 1 subject in the moxifloxacin group. There were 2 and 1 treatment discontinuations, respectively, for delafloxacin and moxifloxacin due to liver enzyme elevations. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values $>5\times$ the upper limit of normal (ULN) at any time during the trial were observed in a similar percentage of subjects in the delafloxacin (1.4% and 0.9%) and moxifloxacin groups (1.6% and 0.5%) (Supplementary Table 2). No subject in either treatment group met Hy's Law criteria.

Mean values and changes from baseline in hematology and serum chemistry levels were similar across treatment groups at all time points. There were no unexpected changes in either treatment group.

Table 3. Clinical Outcome at Test of Cure by Baseline Pathogen (ME-TOC Population)

| All Pathogens | Clinical Success, n/N (%) ^a | |
|----------------------------------------------|----------------------------------------|------------------------|
| | Delafloxacin (n = 240) | Moxifloxacin (n = 248) |
| <i>Streptococcus pneumoniae</i> ^b | 103/110 (93.6) | 94/99 (94.9) |
| PSSP | 47/49 (95.5) | 44/47 (93.6) |
| PISP | 16/17 (94.1) | 6/7 (85.7) |
| PRSP | 7/8 (87.5) | 11/11 (100) |
| MDRSP | 4/4 (100) | 8/8 (100) |
| MRSP | 16/17 (94.1) | 17/18 (94.4) |
| <i>Haemophilus parainfluenzae</i> | 32/35 (91.4) | 34/37 (91.9) |
| <i>Mycoplasma pneumoniae</i> | 29/30 (96.7) | 29/29 (100) |
| <i>Legionella pneumophila</i> | 27/29 (93.1) | 32/32 (100) |
| <i>Staphylococcus aureus</i> ^b | 25/27 (92.6) | 28/30 (93.3) |
| MSSA | 23/25 (92.0) | 28/30 (93.3) |
| MRSA | 2/2 (100) | 0/0 (NA) |
| <i>Chlamydia pneumoniae</i> | 24/24 (100) | 15/15 (100) |
| <i>Haemophilus influenzae</i> | 23/24 (95.8) | 31/35 (88.6) |
| <i>Klebsiella pneumoniae</i> | 14/17 (82.4) | 16/16 (100) |
| <i>Escherichia coli</i> | 13/13 (100) | 9/9 (100) |
| <i>Pseudomonas aeruginosa</i> | 11/12 (91.7) | 11/11 (100) |
| <i>Klebsiella oxytoca</i> | 6/6 (100) | 3/4 (75.0) |
| <i>Moraxella catarrhalis</i> | 6/6 (100) | 6/6 (100) |
| <i>Enterobacter cloacae</i> complex | 3/4 (75.0) | 8/8 (100) |

Abbreviations: MDRSP, multiple drug-resistant *Streptococcus pneumoniae*; ME, microbiologically evaluable; MRSA, macrolide-resistant *Staphylococcus aureus*; MRSP, macrolide-resistant *Streptococcus pneumoniae*; MSSA, methicillin-susceptible *Staphylococcus aureus*; PISP, penicillin-intermediate *Streptococcus pneumoniae*; PSSP, penicillin-susceptible *Streptococcus pneumoniae*; PRSP, penicillin-resistant *Streptococcus pneumoniae*; TOC, test of cure.

^aMicrobiological success was defined as documented or presumed eradication.

^bSubjects with both MRSA and MSSA, or any combination of PSSP, PISP, or PRSP, were counted once in the overall category for that organism.

DISCUSSION

In this study, IV/oral delafloxacin was noninferior to IV/oral moxifloxacin at the FDA primary efficacy end point of ECR. ECR responder rates with improvement in vital signs favored delafloxacin over moxifloxacin. Clinical outcome success rates at TOC were comparable regardless of population, stratification, or subgroup, documenting a sustained clinical response. At TOC, microbiological eradication rates were comparable in both treatment groups.

The mean age of subjects was 60 years, with 44.5% of subjects aged ≥ 65 years and 21.2% aged ≥ 75 years. This study only enrolled 12.5% of PORT 2 subjects in the delafloxacin arm. The rest were PORT 3 and above, representing the serious nature of this infection type.

A predefined exploration of efficacy across subgroups that addressed underlying comorbidities seen in patients with CABP demonstrated that delafloxacin was comparable to moxifloxacin in all subgroups except subjects with a history of COPD or asthma, who at ECR, favored delafloxacin over moxifloxacin. However, the clinical outcome at TOC was not statistically better for delafloxacin. Because adults with COPD have a 6–8-times greater risk of developing CABP than healthy individuals and the risk of morbidity, mortality, and economic burden in these individuals is greater, further study is warranted [22].

For clinical outcome (success) at TOC, delafloxacin was comparable to moxifloxacin, regardless of subgroup.

Delafloxacin has a broad spectrum of activity and exhibits 2–4-fold lower MICs compared with other fluoroquinolones for common CABP pathogens [23]. In this study, based on baseline MIC₉₀ values, delafloxacin exhibited 16-fold greater activity than moxifloxacin for all Gram-positive and Gram-negative pathogens and was used to successfully treat subjects with the range of pathogens typically seen in CABP, including MRSP and atypical CABP pathogens plus MRSA. With macrolide resistance rates in *S. pneumoniae* near 40% and an increased trend of atypical pathogens seen over the last several years with a low testing frequency, coverage for these organisms is important [24–26].

Postinfluenza bacterial pneumonia continues to play a significant role in the morbidity and mortality associated with influenza and where MRSA is a significant pathogen inducing postinfluenza CABP [27]. That this population was not captured and that a low number of MRSA isolates was seen are limitations of this study.

Delafloxacin appeared to be safe and well tolerated in this study, with a discontinuation rate of 2.1% due to related TEAEs. These results were qualitatively consistent with, though numerically different from, an analysis of integrated safety data

Table 4. Overall Summary of Treatment-Emergent Adverse Events (Safety Population)

| TEAE Category | Delafloxacin (n = 429) | Moxifloxacin (n = 427) |
|----------------------------------------------------------------|------------------------|------------------------|
| Total No. of TEAEs | 215 | 204 |
| No. (%) of subjects with any ^a | | |
| TEAE | 131 (30.5) | 112 (26.2) |
| TEAE at least possibly related to study treatment ^b | 65 (15.2) | 54 (12.6) |
| TEAE by maximum severity ^a | | |
| Mild | 67 (15.6) | 56 (13.1) |
| Moderate | 45 (10.5) | 42 (9.8) |
| Severe | 19 (4.4) | 14 (3.3) |
| Serious TEAE | 23 (5.4) | 20 (4.7) |
| TEAE leading to study drug discontinuation | 15 (3.5) | 7 (1.6) |
| TEAE leading to death | 9 (2.1) | 7 (1.6) |
| TEAE of special interest | 34 (7.9) | 32 (7.5) |

TEAEs were coded using MedDRA, version 19.1.

Abbreviation: TEAE, treatment-emergent adverse event.

^aAt each level of subject summarization, a subject with 1 or more reported TEAEs was counted only once, and the most severe reported TEAE was used for the maximum severity.

^bRelated includes possibly, probably, and definitely related.

Table 5. TEAEs in >1% of Subjects in the Safety Population

| MedDRA System Organ Class and Adverse Event (Preferred Term) | No. (%) of Subjects With TEAE | | | |
|--------------------------------------------------------------|-------------------------------|----------------------|------------------------|----------------------|
| | Delafloxacin (n = 429) | | Moxifloxacin (n = 427) | |
| | Total | Related ^a | Total | Related ^a |
| Gastrointestinal disorders | | | | |
| Diarrhea | 20 (4.7) | 16 (3.7) | 14 (3.3) | 13 (3.0) |
| Nausea | 5 (1.2) | 3 (0.7) | 5 (1.2) | 4 (0.9) |
| Investigations | | | | |
| Transaminases increased | 13 (3.0) | 11 (2.6) | 6 (1.4) | 4 (0.9) |
| Nervous system disorders | | | | |
| Headache | 8 (1.9) | 2 (0.5) | 11 (2.6) | 10 (2.3) |
| Metabolism and nutrition disorders | | | | |
| Hypokalemia | 8 (1.9) | 1 (0.2) | 2 (0.5) | 0 |
| Hyperglycemia | 2 (0.5) | 0 | 6 (1.4) | 2 (0.5) |
| Respiratory, thoracic, and mediastinal disorders | | | | |
| Pulmonary embolism | 1 (0.2) | 0 | 6 (1.4) | 1 (0.2) |

TEAEs were coded using MedDRA, version 19.1.

Abbreviation: MedDRA, Medical Dictionary for Regulatory Activities.

^aRelated includes possibly, probably, and definitely related.

across the 4 active-controlled phase 2 and phase 3 ABSSSI clinical studies [28]. The mean age in this study was 60 years, and subjects had a higher incidence of comorbidities compared with those in the ABSSSI studies, with a mean age of 48 years.

A range of well-known risks associated with fluoroquinolones has been recognized, and regulatory agencies have expanded class safety labeling changes. The historical knowledge of the class safety profile informed a prospective assessment of AESIs in the development of delafloxacin. Preclinical and clinical studies have differentiated the safety profile of delafloxacin from other fluoroquinolones [15, 26].

A higher percentage of subjects in the delafloxacin group (5.1%) than in the moxifloxacin group (2.8%) reported hepatic TEAEs, primarily transaminase increases, with all in the delafloxacin group characterized as mild to moderate. There were

no target criteria for investigators to report laboratory changes as AEs. More objective examination of laboratory results showed no difference in the overall worst postbaseline assessment between the groups at $>5\times$ ULN (Supplementary Table 2).

Animal studies with delafloxacin showed no microscopic findings of liver injury; in a pooled analysis of phase 1 studies (n = 814), hepatic events were seen in 0.9% of subjects and did not increase with increased dose. In a pooled analysis of the phase 3 ABSSSI studies with nonfluoroquinolone comparators vancomycin (VAN) and aztreonam (AZ), the rates of treatment-related hepatic events were 2.2% (n = 741) and 2.7% (n = 751) for delafloxacin and VAN/AZ, respectively [13].

A limitation of this study is that subjects with a history of QT prolongation or arrhythmias were excluded due to

Table 6. Treatment-Emergent Adverse Events of Special Interest by Type and Preferred Term (Safety Population)

| MedDRA System Organ Class and Adverse Event (Preferred Term) | No. (%) of Subjects | | | |
|--------------------------------------------------------------|------------------------|----------------------|------------------------|----------------------|
| | Delafloxacin (n = 429) | | Moxifloxacin (n = 427) | |
| | Total | Related ^a | Total | Related ^a |
| Total No. of AESIs ^b | 35 | 25 | 34 | 16 |
| Subjects with any AESI, No. (%) ^b | 34 (7.9) | 24 (5.6) | 32 (7.5) | 16 (3.7) |
| Hepatic-related events | 22 (5.1) | 16 (3.7) | 12 (2.8) | 8 (1.9) |
| Transaminases increased | 13 (3.0) | 11 (2.6) | 6 (1.4) | 4 (0.9) |
| ALT increased | 4 (0.9) | 2 (0.5) | 2 (0.5) | 1 (0.2) |
| Hepatic enzyme increased | 3 (0.7) | 3 (0.7) | 3 (0.7) | 3 (0.7) |
| Hepatic steatosis | 2 (0.5) | 0 | 0 | 0 |
| GGT increased | 1 (0.2) | 1 (0.2) | 0 | 0 |
| Hepatic lesion | 0 | 0 | 1 (0.2) | 0 |
| Potential allergic reactions | 8 (1.9) | 6 (1.4) | 4 (0.9) | 3 (0.7) |
| Rash | 2 (0.5) | 2 (0.5) | 0 | 0 |
| Urticaria | 2 (0.5) | 2 (0.5) | 0 | 0 |
| Bronchospasm | 1 (0.2) | 0 | 1 (0.2) | 0 |
| Dermatitis allergic | 1 (0.2) | 1 (0.2) | 2 (0.5) | 2 (0.5) |
| Gingival swelling | 1 (0.2) | 0 | 0 | 0 |
| Hypersensitivity | 1 (0.2) | 1 (0.2) | 0 | 0 |
| Rash pruritic | 0 | 0 | 1 (0.2) | 1 (0.2) |
| <i>Clostridium difficile</i> diarrhea | 2 (0.5) | 2 (0.5) | 1 (0.2) | 0 |
| <i>C. difficile</i> colitis | 2 (0.5) | 2 (0.5) | 1 (0.2) | 0 |
| Hyperglycemia | 2 (0.5) | 0 | 7 (1.6) | 2 (0.5) |
| Hyperglycemia | 2 (0.5) | 0 | 6 (1.4) | 2 (0.5) |
| Blood glucose increased | 0 | 0 | 1 (0.2) | 0 |
| Hypoglycemia | 0 | 0 | 3 (0.7) | 1 (0.2) |
| Hypoglycemia | 0 | 0 | 3 (0.7) | 1 (0.2) |
| Potential myopathy | 0 | 0 | 5 (1.2) | 2 (0.5) |
| Acute kidney injury | 0 | 0 | 1 (0.2) | 0 |
| Blood creatinine phosphokinase increased | 0 | 0 | 2 (0.5) | 1 (0.2) |
| Blood creatinine increased | 0 | 0 | 1 (0.2) | 1 (0.2) |
| Myalgia | 0 | 0 | 1 (0.2) | 0 |
| Potential QT prolongation | 0 | 0 | 2 (0.5) | 0 |
| ECG QT prolonged | 0 | 0 | 1 (0.2) | 0 |
| Sudden death | 0 | 0 | 1 (0.2) | 0 |

AESIs were coded using MedDRA, version 19.1. If an AESI did not occur, it was not presented in the table. There were no events of phototoxicity, tendon disorder, neuropathy, or convulsions. Abbreviations: AESI, adverse event of special interest; ALT, alanine aminotransferase; ECG, electrocardiogram; GGT, γ -glutamyl transferase; MedDRA, Medical Dictionary for Regulatory Activities; SOC, MedDRA System Organ Class.

^aAssessments of possibly or probably related.

^bThe total number of AESIs counts all AESIs for subjects. Within an SOC, a subject was counted once if they reported >1 type of AESI.

moxifloxacin being the comparator. However, although there were no events of QT prolongation reported for delafloxacin in this trial, 2 subjects in the moxifloxacin group experienced this TEAE. Because preclinical and animal studies document that delafloxacin does not cause QTc prolongation, there was no requirement to directly measure QTc intervals in the phase 3 trials. There were no QT prolongation–related events reported with delafloxacin in the phase 3 ABSSSI trials, and there is no warning for QTc prolongation on the current delafloxacin label.

Although the FDA Class Boxed warning regarding tendon rupture, peripheral neuropathy, CNS effects, myasthenia gravis, and aortic aneurysm and dissection is included on the delafloxacin label, QT/torsades, photosensitivity, hepatotoxicity/hepatitis, and multiple classes of drug interactions are not found in the Warnings/

Precautions sections of the delafloxacin labeling [16]. However, monitoring use in the clinic for potential adverse events observed with other fluoroquinolones is clinically prudent.

Additional study limitations include a low number of subjects enrolled from the United States. Similar to other recent CABP clinical trials, this enrollment imbalance was due to a combination of exclusion criteria and the requirement that no more than 25% of subjects could receive 1 dose of an antibiotic for treatment of the CABP within 24 hours of the study drug.

CONCLUSIONS

With properties unique from other fluoroquinolones, delafloxacin monotherapy is effective and well tolerated in the

treatment of adult patients with CABP, providing coverage for Gram-positive (including MRSA), Gram-negative, and atypical pathogens commonly associated with CABP. The results of this study were consistent across a wide array of comorbid conditions and ages. With both an IV and oral formulation, delafloxacin provides expanded treatment options for patients with CABP that offer continuity and simplicity of treatment as patients transition out of the hospital.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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