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# A Phase 2 Study of the Safety and Efficacy of Oral Delafloxacin (DLX) in Subjects with Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB)

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## Abstract

DLX is an investigational fluoroquinolone active against Gram-positive and -negative bacteria, including methicillin- and quinolone-resistant strains of *Staphylococcus aureus* (MRSA, QRSA). This study compared the safety and efficacy of DLX to levofloxacin (LVX) for the treatment of ABECB. 280 outpatients were enrolled in a double-blinded, randomized study receiving 100, 200, or 400 mg DLX capsules once daily for 5 days, or LVX 500 mg tablets for 7 days (1:1:1:1 ratio). Patients (Pts) ≥40 yo had clinical signs/symptoms, purulent sputum (gram strain qualified), and clinical documentation of ABECB. Clinical and bacteriological cure rates were analyzed by the Cochran-Armitage test to examine a dose response. Safety was evaluated by history, physical examination, vital signs, ECGs, labs, monitoring of adverse events (AE) and concomitant medications.

| Efficacy Endpoint at Test of Cure | DLX, 100 mg QD | DLX, 200 mg QD | DLX, 400 mg QD | LVX, 500 mg QD |
|---|---|---|---|---|
| Clinical Cure (ITT) | 72% (49/68) | 69% (47/68) | 79% (54/68) | 75% (52/69) |
| Clinical Cure (ME) | 77% (20/26) | 88% (22/25) | 94% (31/33) | 94% (33/35) |
| Bacteriologic Cure (ITT) | 71% (24/34) | 85% (28/33) | 87% (34/39) | 74% (35/47) |
| Bacteriologic Cure (ME) | 81% (21/26) | 96% (24/25) | 97% (32/33) | 94% (33/35) |

Subjects were 56% female, mean age 60.8 yo, mean weight 81.1 kg. Pathogen eradication rates for *S. pneumoniae* (22 PTs) and *H. influenzae* (39 PTs) were 100% for all groups, for *M. catarrhalis* (31 PTs) were 67%, 80%, 100%, and 100%, and for *H. parainfluenzae* (38 PTs) were 90%, 100%, 90%, and 83% for 100, 200, 400 mg DLX, and 500 mg LVX, respectively. The incidence of all treatment-emergent adverse events was similar across all arms (53%, 57%, 55%, and 49% for 100, 200, 400 mg DLX, and 500 mg LVX, respectively). The most common AEs were diarrhea, headache, and nausea. There was an increase in the incidence of diarrhea as the dose of DLX increased (11%, 16%, 26% for 100, 200, 400 mg DLX, respectively). The diarrhea was mostly mild to moderate in nature. No clinically meaningful patterns of changes in laboratory values, ECGs, and vital signs were seen. Clinical response was similar in the four treatment groups, and a statistically significant dose-response trend was observed with DLX groups for bacteriologic response in the ME population. Both the 200mg and 400mg DLX doses were equivalent to the 500 mg dose of LVX in terms of efficacy.

## Introduction

Chronic bronchitis is a condition in which cough and excessive secretion of mucus occur that are not attributable to other diseases such as asthma, bronchiectasis or tuberculosis. The most common bacterial isolates associated with ABECB include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Infection can cause acute respiratory decompensation and is the most common identifiable cause of death in these subjects. Typical choices for therapy against ABECB include many agents that may not be active against certain species including resistant organisms. This suggests the need for a broad-spectrum antimicrobial agent alternative for ABECB treatment.

DLX is an investigational fluoroquinolone active against Gram-positive and -negative bacteria, including methicillin- and quinolone-resistant strains of *Staphylococcus aureus* (MRSA, QRSA). In general, the in vitro antibacterial activity of DLX is more potent than that of levofloxacin (LVX) against most quinolone-susceptible pathogens. DLX is more active than LVX against most gram-positive pathogens, and notably is 64-fold more active than LVX against MRSA isolates, including LVX-nonsusceptible isolates. In addition, DLX has good activity against gram-negative organisms that are susceptible to LVX, atypical, and anaerobic organisms (1-3).

## Methods

This was a Phase 2, double-blind, parallel-group, randomized, multicenter study in ambulatory male and female subjects with ABECB. Approximately 60 investigators were to enroll approximately 320 subjects (80 subjects per treatment group) ≥ 40 years of age with a diagnosis of ABECB. Subjects who presented with clinical signs and symptoms of ABECB and met all inclusion/exclusion criteria were randomly assigned (1:1:1:1) to receive either a 5-day course of 100, 200, or 400 mg DLX once daily or a 7-day course of LVX 500 mg once daily. Subjects could have had chronic obstructive pulmonary disease (COPD) but were not to have bronchiectasis as an underlying pulmonary condition. Clinical, bacteriological, and radiographic assessments were performed within 72 hours before Evaluation 1, and a lower respiratory tract specimen was obtained for microbial testing (required to be >25 WBC and <10 squamous epithelial cells per field in 10-20 fields at 100x magnification prior to study entry. Each subject received a total of 4 capsules per day for 7 days and returned to the clinic for various assessments on Day 3, Days 7-8, and Days 16-19 after study drug initiation. Clinical signs and symptoms were assessed and chest x-ray (if clinically indicated) was obtained at each visit. Safety was determined through periodic laboratory tests, medical history, ECGs, physical examination, measurement of vital signs, recording of other medications and supplements, and monitoring of adverse events.

**Inclusion criteria:**

1. Male or female subjects ≥ 40 years of age
2. A female was to be non-lactating and be postmenopausal for 1 year, surgically sterile, or if of childbearing potential utilize highly effective method of birth control.
3. Ambulatory subject who did not require IV therapy.
4. Had a medical history of chronic bronchitis defined as cough and sputum production on most days during ≥3 consecutive months/year for >2 successive years AND presumptive clinical diagnosis of ABECB supported by at least 2 of the following signs and symptoms: increased dyspnea, increased sputum volume, or increased sputum purulence.
5. Had evidence of at least 1 of the following:
   - Chest x-ray findings consistent with COPD
   - Pulmonary function test abnormalities ($FEV_1/FVC \leq 70\%$ of predicted)
   - History of regular medication use to treat pulmonary disease or its consequences validated by medical record documentation.
   - Chronic supplemental oxygen use validated by medical record documentation.
6. Onset of signs and symptoms of the current ABECB exacerbation occurred within 14 days before Visit 1
7. A pretreatment purulent sputum obtained within 24 hours before therapy
8. Suitable candidate for oral antibiotic therapy and able to swallow capsules intact
9. Subject or legal guardian voluntarily signed the informed consent prior to initiation of study-related procedures.

**Major Exclusion criteria:**

1. History of hypersensitivity, allergic, or adverse reactions to quinolone antibiotics.
2. Evidence of bronchiectasis, active tuberculosis, empyema, lung abscess, pulmonary embolism, edema, cystic fibrosis or lung tumor.
3. Active sinusitis or suspected or known pneumonia.
4. Evidence of uncontrolled, clinically significant cardiovascular, pulmonary, metabolic, gastrointestinal, neurological, psychiatric or endocrine disease, malignancy, or other abnormality.
5. Required parenteral antimicrobial therapy, use of a concomitant systemic antibiotic, or hospitalization for treatment.
6. Had known significant renal or hepatic impairment indicated by recent chemistries.
7. Was immunocompromised, receiving immunosuppressive agents, or with known HIV infection.
8. Receiving antacids containing aluminum or magnesium, sucralfate, iron, or zinc supplements, and multivitamin preparations containing iron or zinc within 2 hours before or after dosing with study drug.
9. Known or suspected CNS disorder that might predispose the subject to seizures or lower the seizure threshold.
10. Was receiving or likely to require oral or parenteral steroids 10 mg/day during the period between Visit 1 and 4.
11. Received previous treatment with DLX or other investigational agents within 4 weeks before study drug administration.

## Results

**Clinical response definitions**
The investigator compared the clinical findings at Visit 4 to those obtained prior to study treatment and to pre-acute clinical findings for each subject and assigned a clinical response. Bacteriological results were not considered when assigning clinical response.

**Clinical Cure (Visit 4 only)**: Resolution of acute signs and symptoms of ABECB (dyspnea, sputum volume and purulence) to pre-acute levels or the resolution of at least 2 of those signs and symptoms to pre-acute levels with improvement in at least half of the remaining signs and symptoms from Visit 1.

**Clinical Failure (Visit 4 or time of premature discontinuation)**: Continuation or worsening of the signs and symptoms of ABECB at Visit 4 compared to Screening/Visit 1, or at the time of premature discontinuation from the study, or further additional antibiotic therapy was warranted.

**Indeterminate (Visit 4 or at time of premature discontinuation)**: Evaluation was not possible (e.g. lost to follow-up, disallowed medication, adverse event or protocol violation).

The bacteriologic response was assigned by the Sponsor before breaking the blind for each valid pretreatment pathogen by comparing the culture results at Visit 1 and 4.

**Figure 1. Structure of DLX**

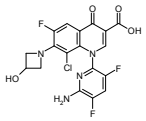

**Table 1. Subject Disposition for Phase 2 ABECB Study**

| Subject Disposition | DLX Treatment Group n (%) | | | LVX |
|---|---|---|---|---|
| | 100 mg | 200 mg | 400 mg | |
| Number of Subjects Planned | 80 | 80 | 80 | 80 |
| All Randomized and Treated Subjects | 70 | 68 | 69 | 73 |
| Completed Study Drug Treatment | 63 (90%) | 62 (91%) | 68 (99%) | 66 (90%) |
| Prematurely Discontinued from Study Drug | 7 (10%) | 6 (9%) | 1 (1%) | 7 (10%) |
| Prematurely Discontinued from Study Drug due to Adverse Event | 3 (4%) | 4 (6%) | 1 (1%) | 1 (1%) |
| Completed Study | 58 (83%) | 57 (84%) | 63 (91%) | 61 (84%) |
| Prematurely Discontinued from Study | 12 (17%) | 11 (16%) | 6 (9%) | 12 (16%) |

**Table 2. Clinical Efficacy Rates at Visit 4 (Test of Cure) by Treatment Group**

| Efficacy Endpoints at Visit 4 | DLX 100 mg | DLX 200 mg | DLX 400 mg | LVX | Cochran-Armitage Trent Test p-value |
|---|---|---|---|---|---|
| Subject Clinical Cure Rate | | | | | |
| CE | 83% (43/52) | 84% (41/49) | 88% (51/58) | 91% (50/55) | 0.439 |
| ITT | 72% (49/68) | 69% (47/68) | 79% (54/68) | 75% (52/69) | 0.331 |
| ME | 77% (20/26) | 88% (22/25) | 94% (31/33) | 94% (33/35) | 0.057 |
| Subject Bacteriological Cure Rate | | | | | |
| ME | 81% (21/26) | 96% (24/25) | 97% (32/33) | 94% (33/35) | 0.030* |
| ITT | 71% (24/34) | 85% (28/33) | 87% (34/39) | 74% (35/47) | 0.075 |
| *Statistically significant dose-response trend based on Cochran-Armitage trend test for DLX dosage groups. | | | | | |

**Table 3. Microbiological Efficacy Rates at Visit 4 (Test of Cure) by Dose**

| Microbiological Endpoints | DLX 100 mg | DLX 200 mg | DLX 400 mg | LVX | Cochran-Armitage Trent Test p-value |
|---|---|---|---|---|---|
| Overall pathogen eradication rate (ME) | 85% (28/33) | 97% (29/30) | 98% (43/44) | 93% (43/46) | 0.028* |
| *S. pneumoniae* | 100% (3/3) | 100% (4/4) | 100% (8/8) | 100% (7/7) | ND |
| *M. catarrhalis* | 67% (4/6) | 80% (4/5) | 100% (9/9) | 100% (11/11) | 0.157 |
| *H. influenzae* | 100% (9/9) | 100% (9/9) | 100% (10/10) | 100% (11/11) | ND |
| *H. parainfluenzae* | 90% (9/10) | 100% (6/6) | 90% (9/10) | 83% (10/12) | >0.999 |
| *S. aureus* | 67% (2/3) | 100% (1/1) | 100% (4/4) | 100% (1/1) | 0.375 |
| *K. pneumoniae* | 100% (1/1) | 100% (2/2) | 0/0 | 50% (1/2) | ND |
| *P. aeruginosa* | 0% (0/1) | 100% (3/3) | 100% (3/3) | 100% (2/2) | 0.143 |
| Overall pathogen eradication rate (ITT) | 72% (31/43) | 87% (34/39) | 90% (45/50) | 76% (47/62) | 0.023* |
| *S. pneumoniae* | 100% (3/3) | 100% (5/5) | 89% (8/9) | 88% (7/8) | 0.706 |
| *M. catarrhalis* | 50% (4/8) | 57% (4/7) | 100%(9/9) | 73% (11/15) | 0.033* |
| *H. influenzae* | 90% (9/10) | 100% (10/10) | 91% (10/11) | 80% (12/15) | >0.999 |
| *H. parainfluenzae* | 69% (11/16) | 89% (8/9) | 79% (11/14) | 65% (11/17) | 0.532 |
| *S. aureus* | 67% (2/3) | 100% (2/2) | 100% (4/4) | 100% (3/3) | 0.333 |
| *K. pneumoniae* | 100% (2/2) | 67% (2/3) | 0/0 | 50% (1/2) | >0.999 |
| *P. aeruginosa* | 0% (0/1) | 100% (3/3) | 100% (3/3) | 100% (2/2) | 0.143 |

*Statistically significant dose-response trend based on Cochran-Armitage trend test for DLX dosage groups.
ND=not determined

**Table 4. Patient Demographics for Phase 2 ABECB Study**

| Demographic Characteristic | DLX Treatment Group | | | LVX | P-value[a] |
|---|---|---|---|---|---|
| | 100 mg | 200 mg | 400 mg | | |
| Total Treated | 70 | 68 | 69 | 73 | |
| Sex | | | | | 0.624 |
| Female | 35 (50%) | 39 (57%) | 42 (61%) | 42 (58%) | |
| Male | 35 (50%) | 29 (43%) | 27 (39%) | 31 (42%) | |
| Race | | | | | 0.471 |
| White | 62 (89%) | 65 (96%) | 63 (91%) | 98 (93%) | |
| Black | 5 (7%) | 3 (4%) | 5 (7%) | 4 (5%) | |
| Other | 3 (4%) | 0 (0%) | 1 (1%) | 1 (1%) | |
| Age (years) | | | | | 0.488 |
| Mean (SD) | 62.6 (12.0) | 60.7 (12.3) | 60.1 (10.6) | 59.9 (11.2) | |
| Range | 40 – 86 | 31 – 85 | 39 – 86 | 37 – 87 | |
| Weight (kg) | | | | | 0.512 |
| Mean (SD) | 81.8 (21.3) | 84.1 (22.1) | 79.5 (17.2) | 79.3 (23.3) | |
| Range | 43 – 146 | 36 – 143 | 48 – 118 | 39 – 175 | |

[a]P-values are from Fisher's exact test comparing treatment groups (sex, race, ethnicity), or one-way analysis of variance models comparing treatment groups (age, weight). Races other than white were pooled in the computation of the race p-value.
SD = standard deviation

## Results

**Table 5. All Adverse Events for Patients in the Phase 2 ABECB Study**

| Body System | Number (% of Subjects)[a] | | | |
|---|---|---|---|---|
| | DLX 100 mg (n=70) | DLX 200 mg (n=68) | DLX 400 mg (n=69) | LVX (n=73) |
| Overall[b] | 37 (53%) | 39 (57%) | 38 (55%) | 36 (49%) |
| Body as a whole | 15 (21%) | 15 (22%) | 7 (10%) | 11 (15%) |
| Cardiovascular | 4 (6%) | 1 (1%) | 5 (7%) | 4 (5%) |
| Digestive | 18 (26%) | 26 (38%) | 26 (38%) | 13 (18%) |
| Gastrointestinal | 14 (20%) | 17 (25%) | 24 (35%) | 4 (5%) |
| Other | 4 (6%) | 11 (16%) | 3 (4%) | 10 (14%) |
| Hemic and Lymphatic System | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Metabolic and Nutritional Disorders | 4 (6%) | 1 (1%) | 5 (7%) | 7 (10%) |
| Musculoskeletal | 0 (0%) | 2 (3%) | 2 (3%) | 1 (1%) |
| Nervous | 3 (4%) | 5 (7%) | 3 (4%) | 7 (10%) |
| Respiratory | 9 (13%) | 12 (18%) | 11 (16%) | 14 (19%) |
| Skin and Appendages | 4 (6%) | 4 (6%) | 2 (3%) | 4 (5%) |
| Special Senses | 4 (6%) | 0 (0%) | 1 (1%) | 4 (5%) |
| Urogenital | 2 (3%) | 2 (3%) | 7 (10%) | 1 (1%) |

[a]Subjects with more than 1 event within a body system are counted only once in the total for that body system.
[b]Number of subjects with 1 or more adverse events.

## Conclusions

- Clinical response was similar across treatment groups and no statistically significant dose-response trends were noted.
- Overall bacteriological responses were similar in the DLX 200, 400 mg and LVX groups, but lower in the 100 mg DLX group.
- Among DLX dose groups, there was a statistically significant dose-response trend in bacteriological cure rate in the ME population.
- There was a dose dependent increase in the incidence of gastrointestinal AEs with mild, self-limiting diarrhea being the most common.
- There were no patient deaths and no clinically meaningful patterns of laboratory values and vital sign changes during the study.
- All three doses of DLX were safe and effective in resolving or improving clinical signs and symptoms of ABECB and eradicating target pathogens.

## References

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