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A Phase 2 Study of the Safety and Efficacy of Oral Delafloxacin (DLX) in Community Acquired Pneumonia (CAP)

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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). The objective of this study was to determine the optimal dose of DLX for the treatment of CAP. 309 outpatients were enrolled in a double-blinded, randomized study receiving 100, 200, or 400 mg DLX capsules once daily (1:1:1 ratio) for 7 days. Patients (PTs) ≥18 yo had ≥2 clinical signs/symptoms, purulent sputum (gram strain qualified), and positive chest x-ray. Clinical and bacteriological cure rates were analyzed by the Cochran–Armitage test to determine a dose response. Safety was evaluated by history, physical examination, vital signs, ECGs, labs, monitoring of adverse events (AE) and concomitant medications. Enrolled subjects were 51% male, mean age and weight were 45.3 years and 75.4 kg. Clinical and bacteriological cure rates were similar in the 200 and 400 mg groups, and slightly lower for the 100 mg group (no statistical difference). Pathogen eradication rates for *S. pneumoniae* (46 PTs) were 88%, 86% and 100%, for *H. influenzae* and *parainfluenzae* (94 PTs) were 91%, 96%, and 97%, for atypicals (33 PTs) were 83%, 100% and 91% for 100, 200, and 400 mg, respectively; and for *S. aureus* (17 PTs) were 100% for all three dose groups.

Efficacy Endpoint at Test of Cure	DLX, 100 mg QD	DLX, 200 mg QD	DLX, 400 mg QD
Clinical Cure (ITT)	80% (83/104)	87% (79/91)	87% (90/104)
Clinical Cure (ME)	90% (54/60)	96% (48/50)	94% (47/50)
Bacteriologic Cure (ITT)	79% (54/68)	88% (49/56)	88% (53/60)
Bacteriologic Cure (ME)	88% (53/60)	96% (48/50)	96% (48/50)

DLX was generally well tolerated with an incidence of drug-related AEs of 23, 37, and 28% in the 100, 200, and 400 mg dose groups. The most common AEs were diarrhea, headache, and nausea. Although no subjects discontinued treatment due to diarrhea, the incidence was higher in the 200 (22%) and 400 (22%) mg groups compared to the 100 (7%) mg group. Most diarrhea cases were mild to moderate in severity. No clinically meaningful patterns of changes in laboratory values, ECGs, and vital signs were seen.
Although not statistically different, the 200 and 400 mg doses had higher rates of clinical and bacteriologic cure. DLX appears to be an effective treatment for CAP.

Introduction

According to one estimate, 915,900 episodes of CAP occur in adults ≥65 years of age each year in the United States[1]. Despite advances in antimicrobial therapy, mortality rates due to pneumonia have not decreased significantly since penicillin became routinely available[2]. Community-acquired pneumonia is etiologically diverse, being caused by viruses, bacteria and fungi. Bacteria most commonly responsible are *S. pneumoniae, H. influenzae, M catarrhalis* and less commonly *S. aureus*[3]. Atypical organisms may account for up to 28% of pneumonia cases[4]. Radezolid has good *in vitro* antibacterial activity against all of these organisms, including MRSA, and is available as an oral agent with good pharmacokinetics. The rising rate of resistance to first-line agents used to treat CAP increases the importance of testing potential new therapies such as delafloxacin (DLX, DLX).

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[5-7].

Methods

This was a Phase 2, double-blind, randomized, multicenter study in ambulatory subjects with CAP. Approximately 150 investigators were to enroll approximately 300 subjects diagnosed with CAP. Subjects who presented with clinical signs and symptoms and met all inclusion/exclusion criteria were randomly assigned (1:1:1) to receive a 7-day course of 100, 200, or 400 mg DLX once daily. Clinical, bacteriological, and radiographic assessments were performed within 48 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. Each subject received a total of 4 capsules per day for 7 days and returned to the clinic for various assessments 48 – 72 hours after study drug initiation, 48 – 72 hours after last dose of drug, and 9-14 days after last dose of study drug. A final contact was made by telephone to assess subject status at 37 – 39 days after therapy 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. Subjects could have been hospitalized during the course of the study for purpose of study procedure compliance.

Inclusion criteria:

1. Male or female subjects 18 years of age or older
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. Had a chest x-ray consistent with pneumonia as interpreted by the radiologist.
4. Was a suitable candidate for oral antibiotic therapy and able to swallow capsules intact.
5. Presented with recent respiratory illness consistent with diagnosis of CAP. Subjects requiring immediate therapy prior to culture results could have been entered with a presumptive diagnosis.
6. A pretreatment purulent sputum obtained within 24 hours before therapy for Gram stain and susceptibility testing.
7. Subject or legal guardian voluntarily signed the informed consent prior to initiation of study-related procedures.

Major Exclusion criteria:

1. Prior hospitalization within 4 weeks or residence in chronic care facility
2. Evidence of active tuberculosis, empyema, lung abscess, pulmonary embolism, edema, cystic fibrosis, lung tumor, bronchial obstruction, a history of post-obstructive pneumonia or known or suspected *Pneumocystis carinii* pneumonia.
3. Treatment with a long-acting injectable within 4 weeks or other systemic antibiotics within 2 weeks prior to study drug.
4. Evidence of uncontrolled, clinically significant cardiovascular, pulmonary, metabolic, gastrointestinal, neurological, psychiatric or endocrine disease, malignancy, or other abnormality.
5. Required parenteral antimicrobial therapy for treatment.
6. Any underlying condition or disease that would interfere with study drug absorption.
7. Was immunocompromised, receiving immunosuppressive agents, or with known HIV infection.
8. Subjects >50 yo with either respiratory rate ≥30/minute, systolic blood pressure <90 mm Hg, temperature <35 or ≥ 40ºC, or pulse >125 bpm.
9. 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.
10. Known or suspected CNS disorder that might predispose the subject to seizures or lower the seizure threshold.

Results

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

Clinical Cure (Visit 4 only): Improvement or lack of progression in all pulmonary infiltrates consistent with pneumonia on chest radiograph AND either resolution of all signs and symptoms of CAP present at enrollment, OR resolution of tachypnea, dyspnea, pleuritic chest pain, rigors/chills and fever, plus a decrease in severity of cough by at least one category, normalization of WBCs or bands and no worsening of auscultatory findings as assessed at Visit 4 (Test-of-Cure).

Clinical Failure (all visits): The subject was considered to be a therapy failure under the following conditions:

1. Persistence or worsening in signs or symptoms of the acute process after 3 to 5 days of therapy or requirement of additional antibiotic for initial pneumonia;
2. Failure to show improvement in at least 3 of the clinical findings after 3 days of therapy;
3. Initial improvement in at least 3 of the clinical signs and symptoms followed by clinically significant worsening in one or more of these clinical findings after 3 to 5 days of therapy;
4. Development of new pulmonary infection or extrapulmonary infection requiring antimicrobial therapy other than, or in addition to, the study drug;
5. Progression of chest radiographic abnormalities;
6. Death due to pneumonia.

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).

Radiographic success rate was defined as the percentage of subjects who demonstrated resolution or improvement in chest x-ray evidence of pneumonia. Radiographic response was based on the radiologist's interpretation of the chest radiograph and was rated by the investigator as complete clearing of the chest x-ray evidence of pneumonia (resolution) or reduction in the chest x-ray evidence of pneumonia in comparison to the pretreatment x-ray (improvement).

Figure 1. Structure of DLX

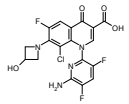

Table 1. Subject Disposition for Phase 2 CAP Study

Subject Disposition	DLX Treatment Group, n (%)		
	100 mg	200 mg	400 mg
Number of Subjects Planned	100	100	100
All Randomized and Treated Subjects	110	93	106
Completed Study Drug Treatment	97 (88%)	85 (91%)	102 (96%)
Prematurely Discontinued from Study Drug	13 (12%)	8 (9%)	4 (4%)
Prematurely Discontinued from Study Drug due to Adverse Event	5 (5%)	2 (2%)	2 (2%)
Completed Study	93 (85%)	82 (88%)	100 (94%)
Prematurely Discontinued from Study	17 (15%)	11 (12%)	6 (6%)

Table 2. Clinical Efficacy Rates at Visit 4 (Test of Cure) by Dose

Efficacy Endpoints	DLX 100 mg	DLX 200 mg	DLX 400 mg	Cochran-Armitage Trent Test p-value
Subject Clinical Cure Rate				
CE	90% (83/92)	95% (79/83)	93% (90/97)	0.509
ITT	80% (83/104)	87% (79/91)	87% (90/104)	0.182
ME	90% (54/60)	96% (48/50)	94% (47/50)	0.382
Radiographic Success				
CE	89% (81/91)	93% (75/81)	92% (89/97)	0.516
ITT	80% (83/104)	85% (77/91)	88% (92/104)	0.086
ME	88% (52/59)	92% (46/50)	92% (46/50)	0.480
Subject Bacteriological Cure Rate				
ITT	88% (53/60)	96% (48/50)	96% (48/50)	0.103
ME	79% (54/68)	88% (49/56)	88% (53/60)	0.154

CE = clinically evaluable; ITT = Intent to treat; ME = microbiologically evaluable

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

Microbiological Endpoints	DLX 100 mg	DLX 200 mg	DLX 400 mg	Cochran-Armitage Trent Test p-value
Overall pathogen eradication rate (ME)	91% (70/77)	95% (60/63)	97% (58/60)	0.150
S. pneumoniae	88% (14/16)	86% (12/14)	100% (16/16)	0.362
M. catarrhalis	100% (6/6)	100% (4/4)	0/0	ND
H. influenzae	93% (14/15)	100% (13/13)	94% (15/16)	>0.999
H. parainfluenzae	90% (18/20)	93% (14/15)	100% (15/15)	0.307
S. aureus	100% (8/8)	100% (7/7)	100% (2/2)	ND
L. pneumophila	0/0	100% (1/1)	100% (1/1)	ND
M. pneumoniae	88% (7/8)	100% (6/6)	100% (8/8)	0.727
C. pneumoniae	75% (3/4)	100% (3/3)	50% (1/2)	>0.999
Overall pathogen eradication rate (ITT)	84% (72/86)	87% (61/70)	89% (64/72)	0.340
S. pneumoniae	78% (14/18)	71% (12/17)	100% (17/17)	0.121
M. catarrhalis	100% (7/7)	80% (4/5)	0/0	0.417
H. influenzae	83% (15/18)	100% (13/13)	80% (16/20)	0.820
H. parainfluenzae	82% (18/22)	88% (15/17)	95% (18/19)	0.244
S. aureus	100% (8/8)	88% (7/8)	100% (3/3)	>0.999
L. pneumophila	0/0	100% (1/1)	100% (1/1)	ND
M. pneumoniae	78% (7/9)	100% (6/6)	89% (8/9)	0.750
C. pneumoniae	75% (3/4)	100% (3/3)	33% (1/3)	0.442

ND = not done

Table 4. Patient Demographics for Phase 2 CAP Study

Demographic Characteristic	DLX Treatment Group			
	100 mg	200 mg	400 mg	P-value[a]
Total Treated	110	93	106	
Sex				0.742
Female	55 (50%)	48 (52%)	49 (46%)	
Male	55 (50%)	45 (48%)	57 (54%)	
Race				0.863
White	86 (78%)	74 (80%)	86 (81%)	
Black	16 (15%)	18 (19%)	13 (12%)	
Asian	3 (3%)	0 (0%)	5 (5%)	
Other	5 (5%)	1 (1%)	2 (2%)	
Age (years)				0.581
Mean (SD)	46.3 (14.6)	44.0 (14.6)	45.5 (17.3)	
Range	20 – 76	18 – 80	18 – 82	
Weight (kg)				0.568
Mean (SD)	74.6 (20.7)	77.4 (20.6)	74.7 (20.9)	
Range	40 – 152	41 – 144	44 – 165	

[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. Adverse Events Grouped by Body System (excluding events judged not related or probably not related to study drug) for Patients in the Phase 2 CAP Study

Body System	Number (% of Subjects)[a]		
	DLX 100 mg (n=110)	DLX 200 mg (n=98)	DLX 400 mg (n=106)
Overall[b]	25 (23%)	34 (37%)	30 (28%)
Body as a whole	4 (4%)	7 (8%)	3 (3%)
Cardiovascular	1 (1%)	3 (3%)	1 (1%)
Digestive	18 (16%)	25 (27%)	25 (24%)
Gastrointestinal	15 (14%)	24 (26%)	23 (22%)
Other	3 (3%)	5 (5%)	5 (5%)
Hemic and Lymphatic System	0 (0%)	0 (0%)	1 (1%)
Metabolic and Nutritional Disorders	0 (0%)	1 (1%)	0 (0%)
Musculoskeletal	2 (2%)	0 (0%)	0 (0%)
Nervous	2 (2%)	0 (0%)	1 (1%)
Respiratory	0 (0%)	0 (0%)	1 (1%)
Skin and Appendages	1(1%)	0 (0%)	1 (1%)
Special Senses	1 (1%)	1 (1%)	1 (1%)
Urogenital	2 (2%)	1 (1%)	4 (4%)

[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

- No statistically significant dose-response trends and no statistically significant pair-wise differences were observed among the three oral doses of DLX.
- All three doses of DLX eradicated established CAP pathogens at a high rate of 86 – 100%.
- The incidence of all treatment-emergent adverse events was 42% in the 100 mg group, 49% in the 200 mg group, and 47% in the 400 mg group.
- Mild diarrhea was the most commonly reported study drug-related adverse event in all treatment groups, but no patients were prematurely discontinued due to diarrhea.
- 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 well tolerated and were effective in resolving or improving clinical signs and symptoms of CAP, eradicating the target pathogens, and resolving or improving radiographic evidence of pneumonia.

References

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