**Molecular Characterization of Fluoroquinolone Resistance Mechanisms in Gram-Negative Isolates from the Delafloxacin Acute Bacterial Skin and Skin Structure Infections Clinical Trials**

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**Introduction**

Delafloxacin is a novel anionic fluoroquinolone antibiotic with broad-spectrum activity, including activity against Gram-negative organisms, Gram-positive organisms, and anaerobic oral pathogenic bacteria (e.g., *Prevotella*, *Chryseobacterium*, and *Porphyromonas*). This study characterized the fluoroquinolone resistance mechanisms among Gram-negative isolates from the Delafloxacin Acute Bacterial Skin and Skin Structure Infections Clinical Trials. The microbiologic responses of patients in the ME and MITT analysis data sets were based on the results of baseline and postbaseline cultures (follow-up [FU]) screens for fluoroquinolone resistance present in a curated database. The enrollment period spanned from April 2013 to January 2016. All patients included in this study had favorable microbiologic response (eradication) at FU, except for 1 subject with a persistent erlotinib-resistant AKT mutant for the delafloxacin study arm, were included. All patients included in this study had favorable microbiologic response (eradication) at FU, except for 1 subject with a persistent *P. aeruginosa* isolate that overexpressed efflux-pump genes when at least a 5-fold greater difference of transcripts was detected as compared with a wild-type reference control strain. The presence of polymicrobial infection and/or isolates with fluoroquinolone-resistance determinants do not appear to affect fluoroquinolone microbiologic response when treating ABSSSI.

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**Materials and Methods**

Subjects and clinical isolates

A total of 1,510 subjects were enrolled in the delafloxacin phase 3 trials for ABSSSI – P. aeruginosa were hospitalized in medical sites located in 23 countries, including the United States (20.2%), and countries in Europe (30.2%), South America (6.0%), and Asia (7.0%).

- The enrollment period spanned from April 2013 to January 2016.
- The microbiological isolates recovered from the microbiologically evaluable (ME) and microbiologically evaluable at follow-up (MEFU) consisted of 806 subjects (n = 516 subjects in the delafloxacin arm; n = 254 subjects in the vancomycin-plus-etli+ arm).
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Growth of fluoroquinolone resistance mechanisms

- All isolates were eradicated at follow-up visit or late follow-up visit, except for isolate #1109 (persistence) causing a monomicrobial infection.

**Results**

- All subjects infected with Gram-negative isolates tested with delafloxacin MIC results of 0.12µg/mL had polymicrobial infections, except for 4 patients (Table 3).
- Clinical samples from these isolates were tested with the Fluoroquinolone Minimum Inhibitory Concentration (MIC) assay, and the samples were inoculated into Fluka Petri dishes.
- Growth of fluoroquinolone resistance mechanisms

**Conclusions**

- Fluoroquinolone resistance mechanisms present in these selected Gram-negative isolates were associated with delafloxacin MIC values of ≥1.25µg/mL.
- All patients included in this study had favorable microbiologic response (eradication) at FU, except for 1 subject with a persistent erlotinib-resistant AKT mutant for the delafloxacin study arm, were included. All patients included in this study had favorable microbiologic response (eradication) at FU, except for 1 subject with a persistent *P. aeruginosa* isolate that overexpressed efflux-pump genes when at least a 5-fold greater difference of transcripts was detected as compared with a wild-type reference control strain. The presence of polymicrobial infection and/or isolates with fluoroquinolone-resistance determinants do not appear to affect fluoroquinolone microbiologic response when treating ABSSSI.

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**References**


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**Acknowledgements**

This research and poster were supported by Melinta Therapeutics, New Haven, Connecticut.

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**Table 1**

*List of bacteria and polymicrobial infections in the MEFU populations at baseline by ABSSSI study arm*

<table>
<thead>
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<th>Organism</th>
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<td>Species</td>
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<tr>
<td><em>Escherichia coli</em></td>
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<td><em>Staphylococcus hominis</em></td>
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<td>1</td>
</tr>
<tr>
<td><em>Staphylococcus haemolyticus</em></td>
<td>5</td>
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</tbody>
</table>

**Table 2**

*Fluoroquinolone-resistance mechanism and virulence factor profiles of the study population by baseline in vitro susceptibility*.

- GyrA and ParC (encoding for DnaG) genes and ParD and ParE (encoding for topoisomerase IV) sequences were extracted from assembled genomes and screened for mutations in the quinolone-resistance-determinant regions (QRDRs) and deoxyribonucleic acid (DNA).

**Table 3**

*Fluoroquinolone-resistance mechanism and virulence factor profiles of the study population by baseline*.

- The transcription levels of efflux-pump (MexAB, MexCD, MexEF, and MexXY) genes were determined using quantitative real-time PCR analysis (qPCR).

**Table 4**

*Transcription levels of constitutive efflux-pump genes in polyclonal strains*.

- All isolates were eradicated at follow-up visit or late follow-up visit, except for isolate #1109 (persistence) causing a monomicrobial infection.

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