INTRODUCTION

Delafloxacin, a new fluorquinolone under development by Melinta Therapeutics, has good activity against Escherichia coli and Pseudomonas aeruginosa, both in vitro and in vivo model infections. Delafloxacin was demonstrated to be efficacious against E. coli and P. aeruginosa in a mouse peripheral infection model with similar ED90 values to trovafloxacin and ciprofloxacin against E. coli. Unlike other fluorquinolones, the delafloxacin free-drug AUC0-24/MIC ratio (AUC0-24/MIC) combines with optimal clinical and microbiological outcome data in the mouse thigh infection model (MTIM) (Melinta, 2016) to define a PK/PD target for net stasis and P. aeruginosa isolates. The Hill slope for bacterial reduction was -3.78 for delafloxacin, whereas bacterial reduction with DLX (MIC of 7.8) was -6.01. This study presents a PK/PD analysis of data obtained using a neupatic edema mouse thigh infection model for delafloxacin versus three strains of E. coli, and three strains of P. aeruginosa.

MATERIALS AND METHODS

**Microorganisms**

The strains of *E. coli* and *P. aeruginosa* used in this study were: 
- *E. coli* (EC): PAO1, KE413, V517, M003, EM152 and M001.
- *P. aeruginosa* (PA): ATCC 27853, PA-203, PA0448, PAO1, PA 27853.

**Drug Formulations**

- Delafloxacin: Hemibiot 1 mg/mL, oral microdilution (OD), 200 mg/mL, and 500 mg/mL, in phosphate buffer.
- ciprofloxacin: 500 mg/mL, oral microdilution (OD).

**Microbiology Methods**

- **Susceptibility Testing:** The minimal inhibitory concentration (MIC) for the strains were determined using CLSI guidelines for broth microdilution method using microtiter plates (Clontech Laboratories). The broth microdilution MICs were determined using the broth microdilution method with CLSI guidelines (2007). The broth microdilution MICs were determined using the broth microdilution method with CLSI guidelines (2007).
- **Animal Infections:** Three mL of bacterial suspensions in saline were used to infect each mouse. The bacterial suspensions were prepare at a concentration of 1 x 10^8 CFU/mL. The inocula were administered IP. A PK model was developed for each strain to estimate the AUC0-24 values for each concentration level.

**Pharmacokinetic and Pharmacodynamic Studies**

- **PK/PD Indices:** AUC0-24/MIC was used to assess the PK/PD index, as recommended by the FDA (2005).
- **PK/PD Methods:** PK/PD analyses were done using Bayes MIX Model (GraphPad). Simulations were conducted using NONMEM software package (Greneau et al., 2005).

**PK Model**

- A 3-Compartment model was used to describe the PK profile of delafloxacin. The model was used to estimate the AUC for each concentration level and to predict the AUC values for different dose levels.

**PD Model**

- A single-hit biological process model was used to describe the bacterial reductions. The model was used to estimate the bacterial reduction for each dose level and to predict the bacterial reduction for different dose levels.

**Statistical Analysis**

- For statistical analysis, the mean bacterial reduction was used to determine its significance using the Dunnett's test.

RESULTS

**Pharmacokinetic and Pharmacodynamic Studies**

- **PK/PD Indices:** AUC0-24/MIC was used to assess the PK/PD index, as recommended by the FDA (2005).
- **PK/PD Methods:** PK/PD analyses were done using Bayes MIX Model (GraphPad). Simulations were conducted using NONMEM software package (Greneau et al., 2005).

**PK Model**

- A 3-Compartment model was used to describe the PK profile of delafloxacin. The model was used to estimate the AUC for each concentration level and to predict the AUC values for different dose levels.

**PD Model**

- A single-hit biological process model was used to describe the bacterial reductions. The model was used to estimate the bacterial reduction for each dose level and to predict the bacterial reduction for different dose levels.

**Statistical Analysis**

- For statistical analysis, the mean bacterial reduction was used to determine its significance using the Dunnett's test.

**Conclusions**

- The activity of delafloxacin against *Escherichia coli* and *Pseudomonas aeruginosa* was tested in vivo in a neupatic edema mouse thigh infection model. For *E. coli*, using strains with high, intermediate, and low susceptibility to delafloxacin, the results from analysis of the pooled data suggested that bacterial stasis would be achieved at an AUC0-24/MIC ratio of 14.5, and a 1-log10 bacterial reduction would be achieved at an AUC0-24/MIC ratio of 20. For *P. aeruginosa*, using strains with varying susceptibility to delafloxacin, the results from analysis of the pooled data suggested that bacterial stasis would be achieved at an AUC0-24/MIC ratio of 3.81, and a 1-log10 bacterial reduction would be achieved at an AUC0-24/MIC ratio of 5.20.