An iterative approach was taken in which the PK data from the IV studies was fit first. The determination of DFX in human plasma was performed by means of liquid PK Data Collection and Assay.

The objectives of these analyses were to develop a structural population model for DFX. Core PPK parameter estimates were estimated with excellent precision (%SEM values of 2 to 6%); %CV in clearance parameters was moderate (30 to 40%).

INTRODUCTION

Methods

A PK simulation was conducted in which all subjects received a hypothetical dose-normalized AUC0-24,ss. The final dataset contained 258 subjects and 9,716 plasma concentrations.

RESULTS

Data

A two-compartment PPK model with a mix of linear and non-linear elimination provided an excellent fit to the pooled data from IV and PO studies. Overall, the modeling approach enabled estimation of body weight, BSA, and sex.

Conclusions

The availability of DFX exposure data and the development of a two-compartment PPK model will be critical for the effective design of future clinical trials. This model is expected to provide reliable estimates of DFX exposure in future clinical trials.

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ABSTRACT

Delafloxacin (DFX) is a broad spectrum fluoroquinolone with activity against methicillin-susceptible and –resistant Staphylococcus aureus. Several Phase 1 and 2 studies have been conducted as part of the IND and NDA development program. Core PK parameters were estimated with excellent precision (%SEM values of 2 to 6%); %CV in clearance parameters was moderate (30 to 40%).

A multivariable linear regression model was constructed to assess the statistical significance of any differences apparent in the exploratory plots.

Table 1. Final PPK model – final parameter estimates and standard errors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Population mean</th>
<th>Standard error</th>
<th>Nominal</th>
<th>Standard error</th>
<th>SEM</th>
<th>CV</th>
<th>Pred. Error</th>
<th>SEM</th>
<th>CV</th>
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<tr>
<td>V</td>
<td>4.85 [0.20]</td>
<td>0.06</td>
<td>123.7</td>
<td>9.1</td>
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<tr>
<td>CL</td>
<td>3.16 [0.15]</td>
<td>0.08</td>
<td>96.5</td>
<td>5.6</td>
<td>1.1</td>
<td>1.1</td>
<td>0.6</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>CL/F</td>
<td>1.39 [0.07]</td>
<td>0.04</td>
<td>34.5</td>
<td>2.0</td>
<td>0.4</td>
<td>0.4</td>
<td>0.2</td>
<td>0.0</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Figure 1. Goodness-of-fit plots for the final PPK model

Figure 2. Unavailable scatters plots illustrating potential PK covariate relationships