Determination of the Effect of Age and Gender on the Pharmacokinetics (PK) and Tolerability of a Single Dose of Finafloxacin HCl (FIN) in Healthy Volunteers

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Abstract

Background

• Finafloxacin is a novel pH activated, broad spectrum fluoroquinolone in development for infection indications in the hospital and critical care setting.[1, 2]
• Finafloxacin exhibits enhanced activity at low pH and under other environmental conditions associated with infection.[1, 2]
• Finafloxacin exhibits bactericidal activity against forms of quiescent growth, thought to be relevant in vivo e.g. non-growing cells, biofilms and persisters.[3]
• Other fluoroquinolones lose activity under such conditions. Consequently, finafloxacin exhibited superior activity in a series of infection models.[4, 5]

The activity of finafloxacin under infection relevant conditions and against infection relevant growth forms in combination with the high dosing potential predicted from its safety profile [6, 7], suggest finafloxacin will offer improved properties over currently marketed fluoroquinolones.

Previous clinical studies have indicated that finafloxacin is well tolerated with few adverse events (AEs). As a part of the clinical development of finafloxacin, other PK studies are required to determine the effect of other variables on the PK profile of finafloxacin.

The primary objective of the study was as follows:
• To assess the PK profile of finafloxacin in healthy young and elderly volunteers.

The secondary objective of the study was as follows:
• To determine the safety and tolerability of finafloxacin in healthy young and elderly volunteers.

Methods

All pertinent study documents were reviewed by the independently functioning Celerion Institutional Review Board (IRB) prior to study initiation. The IRB operations are in compliance with the U.S. Code of Federal Regulations (21 CFR Part 56) and International Conference on Harmonization (ICH) guidelines. This study was conducted under the FDA investigational new drug number IND 106,076.

This was a single-center, open-label, single-dose study in 40 healthy subjects. The subjects were assigned to 1 of 8 groups comprised of the following: 10 healthy young adult males, 10 healthy young adult females, 10 healthy elderly adult males, and 10 healthy elderly adult females.

The subjects fasted for 10 hours and were administrated 400 mg finafloxacin (as 2 x 200 mg tablets) administrated with 240 ml of water.

Blood samples were withdrawn at the following times: predose, and at 30, 45, 60, 75, 90, 120, 180, 240, 360 minutes (6 hours) post dose.

Urine samples were collected from subjects over a 24-hour period postdose at the following intervals: baseline (predose) sample, 0 – 4 hours, 4 – 8 hours, 8 – 12 hours, and 12 – 24 hours.

Finafloxacin PK parameters were summarized using descriptive statistics. The comparisons between the four age-gender groups administrated 400 mg finafloxacin were assessed using an analysis of variance (ANOVA).

The safety assessments included laboratory evaluations, physical examinations, AEs, standard 12-lead ECG parameters, and vital sign assessments.

Results

Summary of the Mean Pharmacokinetic Parameters for Plasma Finafloxacin in all Treatment Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Young Males</th>
<th>Young Females</th>
<th>Elderly Males</th>
<th>Elderly Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>200 (57)</td>
<td>150 (43)</td>
<td>300 (86)</td>
<td>250 (73)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.5 ± 0.2</td>
<td>1.5 ± 0.2</td>
<td>1.5 ± 0.2</td>
<td>1.5 ± 0.2</td>
</tr>
<tr>
<td>CL/F (L/hr/kg)</td>
<td>0.2 ± 0.1</td>
<td>0.2 ± 0.1</td>
<td>0.2 ± 0.1</td>
<td>0.2 ± 0.1</td>
</tr>
<tr>
<td>Vz/F (L)</td>
<td>6000 ± 2000</td>
<td>6000 ± 2000</td>
<td>6000 ± 2000</td>
<td>6000 ± 2000</td>
</tr>
</tbody>
</table>

Summary of the Mean Pharmacokinetic Parameters for Urine Finafloxacin in all Treatment Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Young Males</th>
<th>Young Females</th>
<th>Elderly Males</th>
<th>Elderly Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (mg)</td>
<td>80 (20)</td>
<td>80 (20)</td>
<td>100 (25)</td>
<td>100 (25)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>Mean (Median – Minimum)</td>
<td>6 (4 – 8)</td>
<td>5 (4 – 7)</td>
<td>6 (5 – 8)</td>
</tr>
<tr>
<td>Vz/F (L)</td>
<td>6000 ± 2000</td>
<td>6000 ± 2000</td>
<td>6000 ± 2000</td>
<td>6000 ± 2000</td>
</tr>
</tbody>
</table>

Conclusions

• The average systemic availability (AUC0-24/F) of finafloxacin was approximately 12% greater in elderly versus young subjects (not statistically significant). Mean systemic exposure was similar in males and females (<16% difference).
• The mean peak exposure (Cmax) of FIN was similar in elderly (630 – 630 ng/mL) and young (630 – 630 ng/mL) subjects. The mean exposure (Cmax) was slightly higher in females versus males.
• The activity of finafloxacin under infection relevant conditions and in environmental conditions associated with infection [1, 2] will offer improved properties over currently marketed fluoroquinolones.
• The activity of finafloxacin under infection relevant conditions and against infection relevant growth forms in combination with the high dosing potential predicted from its safety profile [6, 7], suggest finafloxacin will offer improved properties over currently marketed fluoroquinolones.

References