**The Effect of Food on the Pharmacokinetics of Tivozanib**

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**Introduction**

This Phase I study was conducted to prospectively evaluate the effect of food on the PK of a single 1.5 mg dose of tivozanib in healthy subjects. This was a single-center, open-label, randomized, two-period, crossover Phase I study conducted at a clinical research unit (CRU). Subjects were screened for eligibility up to 28 days prior to study entry and were randomly assigned to treatment with a single oral dose of 1.5 mg tivozanib in the fasted state or the fed state. The PK parameters evaluated were maximal serum concentration (Cmax), Tmax, t½, area under the concentration–time curve extrapolated to infinity (AUC0–∞), apparent total clearance (CL/F), and volume of distribution (Vz/F). The primary objectives were to assess the tolerability of a single dose of 1.5 mg tivozanib in healthy subjects and to determine if the effect of food on the PK of tivozanib at a single 1.5 mg dose is a threshold effect or not.

**Results**

Subjects

- Thirty subjects (97%) completed the study (Table 1).
- Subjects had a mean age of 29 years.
- The Cmax and AUC0–∞ were lower with food, indicating decreased exposure to tivozanib with food. However, the decrease in serum concentration, while significant, is unlikely to have an impact on steady-state serum concentrations.

**Pharmacokinetics and Statistical Analysis**

- The geometric mean ratio (90% CI) of fed relative to fasted states for Cmax was 77.5% (102.8–112.3%); the 90% CI was within the 80–125% bioequivalence range (Table 4).
- The mean AUC0–∞ was similar between the fed and fasted states (geometric means, 2377 ng·hr/mL and 2198 ng·hr/mL, respectively) (Table 3 and Figure 2).

**Conclusions**

- Administration of a single oral dose of 1.5 mg tivozanib was well tolerated in this group of healthy male subjects.
- Despite the decrease in serum concentration, there was no significant difference in AUC0–∞ of tivozanib exposure was not equivalent between fed and fasted states.

**Table 1. Study Design**

<table>
<thead>
<tr>
<th>Period</th>
<th>Fasting Condition</th>
<th>Dosing</th>
<th>Outpatient Visit</th>
<th>Outpatient Visit</th>
<th>Outpatient Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period 1</td>
<td>Fasted</td>
<td>8 h post-dose</td>
<td>6-week washout</td>
<td>Fasted</td>
<td>8 h post-dose</td>
</tr>
<tr>
<td>Period 2</td>
<td>Fed</td>
<td>8 h post-dose</td>
<td>6-week washout</td>
<td>Fed</td>
<td>8 h post-dose</td>
</tr>
</tbody>
</table>

**Table 2. Pharmacokinetic Parameters for Tivozanib in the Fed and Fasted States**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fed</th>
<th>Fasted</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>12.6</td>
<td>15.0</td>
<td>0.84</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>3.0</td>
<td>9.0</td>
<td>0.33</td>
</tr>
<tr>
<td>AUC0–∞ (ng·hr/mL)</td>
<td>2377</td>
<td>2198</td>
<td>1.07</td>
</tr>
</tbody>
</table>

**Figure 1. Individual and ensemble mean Cmax (Serum tivozanib mean concentration profiles for individuals in the fed and fasted states).**

- Fed
- Fasted

**Figure 2. Individual and ensemble mean AUC0–∞ (Serum tivozanib mean area under curve extrapolated to infinity profiles for individuals in the fed and fasted states).**

- Fed
- Fasted