A Randomized, Crossover, Phase 1 Study to Evaluate the Effect of a Strong CYP3A4 Inhibitor on Tivantinib (ARQ 197) Pharmacokinetics in Healthy Subjects

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ABSTRACT

Tivantinib is a selective, oral, small-molecule inhibitor of c-MET. In vitro data suggest that CYP2C19 and CYP3A4 are the major metabolic enzymes that metabolize tivantinib. Therefore, the effect of tivantinib on CYP2C19 and CYP3A4 activity was assessed in vitro and in vivo. In vitro data using human liver microsome and recombinant human isozyme systems showed that CYP3A4 contributed ~79% to tivantinib metabolism, whereas CYP2C19 contributed ~7% and ~19% of tivantinib metabolism. In the human liver microsome system, contributions of CYP2C19 and CYP3A4 were similar. CYP2C19 EM and IM subjects who received ketoconazole concomitantly had substantially increased tivantinib exposure. Tivantinib was then co-administered with ketoconazole in a randomized, crossover, phase 1 study. Tivantinib total exposure and maximum concentration were increased ~2-fold and ~1.4-fold, respectively. Peak exposure in IM subjects was 2 times the exposure in EM subjects, and median half-life was 84% higher.

METHODS

• Phase I, random, single-center, open-label, crossover study in healthy subjects
• Subjects were fasted overnight (at least 10 hours) and received a standardized high-fat breakfast 1 hour before drug administration
• Four treatment periods were conducted in each subject

RESULTS—Baseline Characteristics

<table>
<thead>
<tr>
<th>Race</th>
<th>n (%)</th>
<th>BMI, kg/m2 (SD)</th>
<th>Age, y (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>5 (31.3)</td>
<td>23.7 (2.6)</td>
<td>31.9 (8)</td>
</tr>
<tr>
<td>Black</td>
<td>9 (56.3)</td>
<td>24.1 (2.4)</td>
<td>32.6 (7)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (6.3)</td>
<td>24.5 (2.7)</td>
<td>33.0 (9)</td>
</tr>
</tbody>
</table>

Table 1. Subject Baseline Characteristics and Demographics

Pharmacokinetics

Plasma Concentrations

In the 2 subject cohorts, concentrations were greater when ketoconazole was co-administered, as compared with tivantinib alone (Figure 2). Similar increases in tivantinib concentrations were observed in 1A2 and 1A2 subjects.

Adverse Events

• No drug-related serious AEs were reported
• 2 subjects discontinued because of AEs: 1 with mild creatinine level increase and 1 with mild white blood cell count increase

Table 3. Incidence of Treatment-Emergent Adverse Events

<table>
<thead>
<tr>
<th>Subjects, n (%)</th>
<th>Treatment</th>
<th>BMI, kg/m2 (SD)</th>
<th>Age, y (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
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CONCLUSIONS

• Because there was a ketoconazole-tivantinib interaction in CYP2C19 EM and IM subjects, stage 2 of the current study was not conducted
• Tivantinib total exposure and maximum concentration were increased ~2-fold and ~1.4-fold, respectively
• Peak exposure in IM subjects was 2 times the exposure in EM subjects, and median half-life was 84% higher
• This study was sponsored by Daiichi Sankyo, Inc. and ArQule, Inc.

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Reference