A Drug-Drug Interaction Study To Study the Effects of Multiple Doses of the CYP3A4 Modulators Itraconazole and Rifampin on the Single Dose Pharmacokinetics of Vatiquinone

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RESULTS – SUBJECTS/PHARMACOKINETICS

Part I: 25 subjects enrolled and 23 subjects (13 females, 10 males) completed the study. Two subjects withdrew from the study. Mean age was 33.7 years (range: 22-44 years).

Part II: 24 subjects enrolled and all 24 subjects (12 females, 12 males) completed the study. Mean age was 35.4 years (range: 18-45 years).

The effects of CYP3A4 inhibition and induction on the single dose pharmacokinetics of vatiquinone are presented in Table 1.

- The shapes of the mean vatiquinone plasma concentrations were not affected by itraconazole with a Cmax reached at a median Tmax of 6.00 hours. However, vatiquinone C0–t, AUC0–t, and AUC0–∞ values were affected by itraconazole: the geometric mean values of C0–t, AUC0–t, and AUC0–∞ increased by 245%, 244%, and 188%, respectively.
- The ratios of geometric means plus 90% confidence intervals for C0–t, AUC0–t, and AUC0–∞ were respectively 64% [46%, 88%], 59% [47%, 74%], and 54% [45%, 65%]. Median T1/2 for vatiquinone was 10.6 hours without itraconazole and 12.3 hours with itraconazole.
- The shapes of the mean vatiquinone plasma concentrations were not substantially affected by rifampin with a Cmax reached at a median Tmax of 5.00 hours. However, vatiquinone C0–t, AUC0–t, and AUC0–∞ values were affected by rifampin: the geometric mean values of C0–t, AUC0–t, and AUC0–∞ decreased by 36%, 41%, and 46% respectively.
- The ratios of geometric means plus 90% confidence intervals for C0–t, AUC0–t, and AUC0–∞ were respectively 64% [46%, 88%], 59% [47%, 74%], and 54% [45%, 65%]. Median T1/2 for vatiquinone was 10.3 hours without rifampin and 10.7 hours with rifampin.

Table 1. The effect of Itraconazole and Rifampin on the Single Dose Pharmacokinetics of Vatiquinone

<table>
<thead>
<tr>
<th></th>
<th>Vatiquinone</th>
<th>Vatiquinone + Itraconazole</th>
<th>Vatiquinone + Itraconazole (Test)/ Vatiquinone (Reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>23</td>
<td>992</td>
<td>343.46 [244.71, 487.67]</td>
</tr>
<tr>
<td>AUC0–t (ng*h/ml)</td>
<td>23</td>
<td>3130</td>
<td>344.04 [234.85, 464.48]</td>
</tr>
<tr>
<td>AUC0–∞ (ng*h/ml)</td>
<td>22</td>
<td>3850</td>
<td>288.78 [231.15, 332.05]</td>
</tr>
</tbody>
</table>

CONCLUSIONS

CYP3A4 inhibition
- Co-administration with itraconazole increased the peak concentration (Cmax) and systemic exposure (AUC0–∞) of vatiquinone by approximately 3.5 and 2.9 fold respectively.

CYP3A4 induction
- Co-administration with rifampin decreased the peak concentration (Cmax) and systemic exposure (AUC0–∞) of vatiquinone by approximately 0.64 and 0.54 fold respectively.

RESULTS – SAFETY/TOLERABILITY

In both parts of the study, vatiquinone was shown to be safe and well tolerated. This was indicated by a very small number of subjects with TEAEs, all of which were mild, temporary, and judged to be unrelated to the administration of vatiquinone.

METHODS

Study Design: A two parts study and each part had an open label, fixed sequence, 2-period, single and multiple dose design.

Subjects: In each part, 24 healthy male and female subjects, aged between 18 and 45 years of age, were enrolled.

Treatments Part I and 2: a single oral dose of 400 mg vatiquinone was given on Day 1, followed by a washout of 7 days, followed by

Part I: multiple oral doses of 200 mg itraconazole once daily from Day 8 to Day 13 with co-administration of a single oral dose of 400 mg vatiquinone on Day 12.

Part 2: multiple oral doses of 600 mg rifampin (QD) from Day 8 to Day 23 with co-administration of a single oral dose of 400 mg vatiquinone on Day 22.

Frequent blood samples for the bioanalyses of vatiquinone were collected on Day 1 and Day 12 (Part I) and Day 22 (Part 2).

Evaluation For each part, a mixed effects model with treatment as a fixed effect and subject as a random effect was performed for each PK parameter, for the test treatment (vatiquinone + itraconazole or rifampin) relative to the reference treatment (vatiquinone alone) and expressed as a percentage.

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