**Effect of Ketoconazole on the Pharmacokinetics of Doravirine (MK-1439), a Novel Non-Nucleoside Reverse Transcriptase Inhibitor for the Treatment of HIV-1 Infection**

**Introduction**

- Doravirine (MK-1439) is a novel, well-tolerated, once-daily, non-nucleoside reverse transcriptase inhibitor in development for the treatment of human immunodeficiency virus-1 (HIV-1) infection in combination with other antiretroviral therapy (ART).
- Pseudokinase, doravirine is a potent inhibitor of HIV-1 wild-type virus and the K103N, Y181C, and K103N/Y181C mutant viruses.
- In a 48-week study in combination with TRUVADA™ (emtricitabine/tenofovir), doravirine has been shown to be efficacious in treating ART-naïve HIV-1-infected patients over the investigated 25-200 mg dose range.
- The anticipated clinical dose of doravirine is 100 mg administered once daily.

- Doravirine is primarily metabolized by oxidation via CYP3A4, shows no inhibitory or inductive potential on CYP3A4-mediated metabolism in vivo, and is not an inducer or inhibitor of major CYP enzymes or transporters.
- Doravirine was also shown to be a substrate, but not an inhibitor of, human P-glycoprotein (P-gp).
- Modest increases in doravirine maximum plasma concentration (Cmax) and time to reach Cmax (Tmax), as well as significant elevations in plasma concentration (AUC0-∞) and total area under the plasma concentration-time curve (AUC0-24h) were observed when doravirine was co-administered with ritonavir, a clinical inhibitor and inducer of CYP3A4 and an inducer of glucuronidation.
- The antifungal ketoconazole is a potent inhibitor of CYP3A4 and the P-gp transporter and was, therefore, used in this study to probe the interaction of doravirine with these pathways.

**Objective**

- To assess the effect of multiple doses of ketoconazole on the single-dose plasma pharmacokinetic (PK) profile of doravirine.

**Methods**

**Study Design**

- This was an open-label, 2-period, fixed-sequence study. - In Period 1, subjects received a single oral dose of 100 mg doravirine on Day 1. Following a washout of at least 7 days, subjects received oral doses of 400 mg ketoconazole once daily for 10 days (beginning Day 1 of Period 2), with co-administration of a single oral dose of 100 mg doravirine on Day 2 of Period 2.
- Blood samples for determination of doravirine concentrations were collected at predose and at 0.5, 1, 2, 3, 6, 12, 24, 48, 72, 96, 120, 144, 168, 192, and 216 hours following the single dose of doravirine in Period 1, and at predose and at 1, 1.5, 2, 3, 6, 12, 24 hours after dosing in Period 2.
- Safety evaluations, including vital signs, electrocardiogram (ECG), laboratory assessments (hematology, biochemistry, and urinalysis) and adverse event (AE) monitoring, were conducted throughout the study.

**Study Population**

- Healthy subjects, aged 19-50 years inclusive, were enrolled. Subjects using drugs or substances known to interact with CYP3A4 were not enrolled. Subjects using drugs or substances known to interact with CYP3A4 were not enrolled.

**Statistical Analysis**

- PK parameters (AUC0-∞, Cmax, and C24h) were natural-log-transformed prior to analysis and evaluated using a linear mixed-effects model with a fixed-effect term for treatment and an unstructured covariance matrix allowed for unequal variances of the within-subject residuals.
- Back-transformed LSM and CI from linear mixed-effects model performed on natural-log–transformed prior to analysis and evaluated using a linear mixed-effects model with a fixed-effect term for treatment and an unstructured covariance matrix allowed for unequal variances of the within-subject residuals.

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**RESULTS**

**Table 1. Subject Disposition**

<table>
<thead>
<tr>
<th>Enrolled, N (%)</th>
<th>10 (100)</th>
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<tbody>
<tr>
<td>Male, n (age range, years)</td>
<td>8 (22–50)</td>
</tr>
<tr>
<td>Female, n (age range, years)</td>
<td>2 (48–49)</td>
</tr>
<tr>
<td>Completed, n (%)</td>
<td>10 (100)</td>
</tr>
</tbody>
</table>

**Table 2. PK Parameters for Doravirine**

| PK parameter | Doravirine alone | Doravirine + ketoconazole | GMR | 90% CI | 90% CI
<table>
<thead>
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</thead>
<tbody>
<tr>
<td>AUC0-∞ (nM•h)</td>
<td>1404.80 (1160.00, 1760.20)</td>
<td>1758.56 (1404.32, 2110.80)</td>
<td>1.25 (1.05, 1.45)</td>
<td>0.85 (0.70, 1.02)</td>
<td></td>
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<tr>
<td>Cmax (nM)</td>
<td>109.56</td>
<td>1402.12 (1160.00, 1760.20)</td>
<td>2.75 (2.54, 2.98)</td>
<td>1.25 (1.05, 1.45)</td>
<td></td>
</tr>
<tr>
<td>T½ (h)</td>
<td>15.23</td>
<td>28.09</td>
<td>1.82 (1.63, 2.04)</td>
<td>0.67 (0.54, 0.82)</td>
<td></td>
</tr>
</tbody>
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**Figure 1. Arithmetic Mean Doravirine Plasma Concentration Profiles With and Without Co-administration of Ketoconazole:**

A) Linear Scale (±SD) and B) Semi-log Scale

**Figure 2. Plasma PK for Doravirine**

- The mean Cmax for doravirine (1402.12 nM) increased after co-administration with ketoconazole (to 1759.92 nM) (Figure 1 and Table 2).
- Doravirine AUC0-∞, Cmax, and C24h were increased by co-administration with ketoconazole (Table 2).

**Figure 3. 90% Confidence Intervals (CIs) for doravirine in Period 2.**

- The 90% confidence intervals (CIs) were generated for doravirine in Period 2.

**Table 3. 90% Confidence Intervals (CIs) for doravirine in Period 2.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-∞ (nM•h)</td>
<td>1160.00</td>
<td>1760.20</td>
</tr>
<tr>
<td>Cmax (nM)</td>
<td>1404.32</td>
<td>2110.80</td>
</tr>
<tr>
<td>T½ (h)</td>
<td>14.49</td>
<td>15.49</td>
</tr>
</tbody>
</table>

**Safety**

- No serious clinical or laboratory AEs were reported during the study.
- Six subjects reported a total of 18 AEs, 13 of which were considered drug-related (6 related to doravirine only, 5 related to ketoconazole only, and 2 related to both doravirine and ketoconazole); all were judged by the investigator as mild in intensity and transient, none led to discontinuation.
- All drug-related AEs occurred during Period 2. The drug-related AEs (occurrence, drug): were:
  - nausea (1, ketoconazole; 1, doravirine; 2, both)
  - headache (1, ketoconazole; 1, doravirine)
  - palpary rash (2, doravirine)
  - insomnia (1, ketoconazole)
  - restless leg syndrome (1, ketoconazole)
  - hirnorea (1, ketoconazole)
  - papule (1, doravirine)
  - pruritus (1, doravine).
- No clinically significant changes were observed in laboratory values, vital signs, or ECG safety parameters.

**Conclusions**

- Doravirine single-dose plasma exposure was increased by co-administration with ketoconazole. Doravirine plasma AUC0-∞, and Cmax increased by approximately 3-fold and 2-fold, respectively, primarily by reducing the rate of CYP3A-mediated clearance.
- The minimal increase in Cmax suggests that P-gp inhibition does not impact the absorption of doravirine.
- The increase in doravirine exposure observed in this study is similar to the effect of ritonavir on doravirine, suggesting that a significant proportion of doravirine metabolism in humans proceeds through CYP3A4.
- Alignment of doravirine plasma PK changes with those observed upon co-administration of doravirine with ritonavir suggests that pathways other than CYP3A4 metabolism are not a clinically significant route of doravirine elimination in humans.
- Single oral doses of doravirine were generally well tolerated when administered alone or in combination with multiple oral doses of ketoconazole in the healthy subjects.
- These changes in doravirine exposure are likely not clinically meaningful based on available safety data to date and the lack of an exposure-response relationship for efficacy or safety up to a dose of 200 mg in a Phase 2 study.
- These findings do not warrant restrictions on the use of potent CYP3A4 inhibitors in Phase 3 trials of doravirine.

**References**


**Acknowledgments**

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**Disclosures**

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