Background: Doravirine is a novel, non-nucleoside reverse transcriptase inhibitor (NNRTI) for the treatment of HIV-1 infection and is primarily metabolized via oxidation via CYP3A4.

Aims:

- To evaluate the effect of coadministration of a single dose of rifampin on the pharmacokinetics of doravirine.
- To evaluate the effect of coadministration of multiple doses of rifampin on the pharmacokinetics of doravirine.

Methods:

- Study Design: Open-label, parallel, 2-bolus, fixed-sequence, study to assess the effects of coadministration of single and multiple doses of the rifampin on the pharmacokinetics of doravirine.
- Subjects: A total of 33 healthy, white adult male volunteers (age range, 18–55 years; body mass index, 18.5–32.0 kg/m²; n=11 for each treatment group) were enrolled.
- Doravirine Alone: Single oral dose of 100 mg doravirine (1 x 100 mg tablet) on Day 1 of Period 1.
- Doravirine + SD rifampin: Single oral dose of 100 mg doravirine (1 x 100 mg tablet) coadministered with a single oral dose of 600 mg rifampin (2 x 300 mg capsules) on Day 1.
- Doravirine Alone: Single oral dose of 100 mg doravirine (1 x 100 mg tablet) on Day 1 of Period 2.
- Doravirine + SD rifampin: Single oral dose of 100 mg doravirine (1 x 100 mg tablet) coadministered with a single oral dose of 600 mg rifampin (2 x 300 mg capsules) on Day 1.

Safety and tolerability:

- Doravirine was generally well tolerated when administered alone or coadministered with single or multiple oral doses of rifampin in healthy adult male subjects.
- No severe adverse experiences or interactions were reported and no subject discontinued because of an adverse experience.

Results and Discussion:

- CYP3A4 is the predominant enzyme involved in the metabolism of doravirine and the induction of CYP3A4 by rifampin on the plasma pharmacokinetic profile of doravirine.
- The small increase in Cₚ₀ was observed when doravirine was administered alone.
- The geometric least-squares mean ratio (GMR) was 1.00 for both the single- and multiple-dose comparisons of doravirine compared to doravirine administered alone.
- The geometric mean (GM) for the single- and multiple-dose comparisons of doravirine were 1.00 ± 20% for both the single- and multiple-dose comparisons of Cₚ₀.

Conclusion:

- CYP3A4 is the predominant enzyme involved in the metabolism of doravirine.
- The small increase in Cₚ₀ was observed when doravirine was administered alone.
- The geometric least-squares mean ratio (GMR) was 1.00 for both the single- and multiple-dose comparisons of doravirine compared to doravirine administered alone.
- The geometric mean (GM) for the single- and multiple-dose comparisons of doravirine were 1.00 ± 20% for both the single- and multiple-dose comparisons of Cₚ₀.

The Effect of Single and Multiple Dose Rifampin on the Pharmacokinetics of Doravirine

Ka Lai Yee1, Helen Manthous2, Sauzanne Khalillieh1, Rachael Liu1, Rosa I. Sanchez1, Matt S. Anderson1, Candice Smith-Bradley2, Timothy Judge2, John Brojda1, Peter Sklar1, Joan R. Butterton1

1Merck & Co., Inc., Kenilworth, NJ, USA; 2Celerion, Lincoln, NE, USA

Study Design: Open-label, parallel, fixed-sequence, study to assess the effects of coadministration of single and multiple doses of rifampin on the pharmacokinetics of doravirine.

Subjects: A total of 33 healthy, white, adult male volunteers (age range, 18–55 years; body mass index, 18.5–32.0 kg/m²; n=11 for each treatment group) were enrolled.

Treatment:

- Doravirine Alone: Single oral dose of 100 mg doravirine (1 x 100 mg tablet) on Day 1.
- Doravirine + SD rifampin: Single oral dose of 100 mg doravirine (1 x 100 mg tablet) coadministered with a single oral dose of 600 mg rifampin (2 x 300 mg capsules) on Day 1.
- Doravirine Alone: Single oral dose of 100 mg doravirine (1 x 100 mg tablet) on Day 17 of Period 2.
- Doravirine + SD rifampin: Single oral dose of 100 mg doravirine (1 x 100 mg tablet) coadministered with a single oral dose of 600 mg rifampin (2 x 300 mg capsules) on Day 17 of Period 2.

Safety and tolerability:

- Doravirine was generally well tolerated when administered alone or coadministered with single or multiple oral doses of rifampin in healthy adult male subjects.
- No severe adverse experiences or interactions were reported and no subject discontinued because of an adverse experience.

Results and Discussion:

- CYP3A4 is the predominant enzyme involved in the metabolism of doravirine and the induction of CYP3A4 by rifampin on the plasma pharmacokinetic profile of doravirine.
- The small increase in Cₚ₀ was observed when doravirine was administered alone.
- The geometric least-squares mean ratio (GMR) was 1.00 for both the single- and multiple-dose comparisons of doravirine compared to doravirine administered alone.
- The geometric mean (GM) for the single- and multiple-dose comparisons of doravirine were 1.00 ± 20% for both the single- and multiple-dose comparisons of Cₚ₀.

Conclusion:

- CYP3A4 is the predominant enzyme involved in the metabolism of doravirine.
- The small increase in Cₚ₀ was observed when doravirine was administered alone.
- The geometric least-squares mean ratio (GMR) was 1.00 for both the single- and multiple-dose comparisons of doravirine compared to doravirine administered alone.
- The geometric mean (GM) for the single- and multiple-dose comparisons of doravirine were 1.00 ± 20% for both the single- and multiple-dose comparisons of Cₚ₀.

Figure 1. Arithmetic Mean (± SD) Plasma Concentration-Time Profiles of Doravirine Following the Administration of a Single Dose of Doravirine With or Without the Coadministration of a Single Dose of 500 mg Rifampin in Healthy Adult Subjects

Figure 2. Arithmetic Mean (± SD) Plasma Concentration-Time Profiles of Doravirine Following the Administration of a Single Dose of Doravirine With or Without the Coadministration of Multiple Oral Doses of 600 mg Rifampin in Healthy Adult Subjects

Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th>Subject Characteristics</th>
<th>n=11</th>
<th>n=11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Male N (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Female N (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Race (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Hispanic (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>White (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>24.3</td>
<td>24.3</td>
</tr>
<tr>
<td>Measurements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.7</td>
<td>68.7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>179</td>
<td>179</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>24.3</td>
<td>24.3</td>
</tr>
</tbody>
</table>

Table 2. Statistical Comparisons of Plasma Pharmacokinetics of Doravirine Following the Administration of a Single Dose of 500 mg Rifampin With or Without the Coadministration of Multiple Oral Doses of 600 mg Rifampin in Healthy Adult Subjects

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Single Dose</th>
<th>Multiple Dose</th>
<th>GM (90% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cₚ₀ (μM)</td>
<td>0.14 ± 0.12</td>
<td>0.31 ± 0.23</td>
<td>2.19 (1.03, 4.66)</td>
<td>0.041</td>
</tr>
<tr>
<td>AUC (μM·h)</td>
<td>140 ± 107</td>
<td>340 ± 322</td>
<td>2.47 (1.42, 4.23)</td>
<td>0.001</td>
</tr>
<tr>
<td>t₁/2 (hr)</td>
<td>2.4 ± 0.2</td>
<td>2.6 ± 0.3</td>
<td>1.00 (0.55, 1.85)</td>
<td>0.989</td>
</tr>
</tbody>
</table>

Table 3. Statistical Comparisons of Plasma Pharmacokinetics of Doravirine Following the Administration of a Single Dose of 500 mg Rifampin With or Without the Coadministration of Multiple Oral Doses of 600 mg Rifampin in Healthy Adult Subjects

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Single Dose</th>
<th>Multiple Dose</th>
<th>GM (90% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cₚ₀ (μM)</td>
<td>0.14 ± 0.12</td>
<td>0.31 ± 0.23</td>
<td>2.19 (1.03, 4.66)</td>
<td>0.041</td>
</tr>
<tr>
<td>AUC (μM·h)</td>
<td>140 ± 107</td>
<td>340 ± 322</td>
<td>2.47 (1.42, 4.23)</td>
<td>0.001</td>
</tr>
<tr>
<td>t₁/2 (hr)</td>
<td>2.4 ± 0.2</td>
<td>2.6 ± 0.3</td>
<td>1.00 (0.55, 1.85)</td>
<td>0.989</td>
</tr>
</tbody>
</table>

References: