Effect of Severe Renal Impairment on Doravirine Pharmacokinetics

Introduction

- Doravirine (MK-1439) is a novel, potent, non-nucleoside reverse transcriptase inhibitor in development for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in combination with other antiretroviral therapies1.
- Following oral administration, doravirine is largely excreted unchanged in urine, while approximately 10% of the administered dose is excreted in urine.
- Doravirine is primarily metabolized by hepatic cytochrome P450 3A (CYP3A) and, subsequently, the oxidized product is predominantly excreted in urine.
- Reduced renal function becomes an increasingly prevalent comorbidity as modern therapies extend the life expectancy of individuals infected with HIV2.
- Though renal excretion represents a minor route of elimination, the effect of severe renal impairment (RI) on exposure to doravirine is evaluated in HIV-negative subjects due to the potential for severe renal insufficiency to alter hepatic drug metabolism and transport3.

Objectives

- This study was undertaken to evaluate the effect of severe RI compared with normal renal function on the plasma pharmacokinetics of the Phase 3 dose of doravirine.
- The secondary objective of the study was to assess the safety and tolerability of doravirine in subjects with severe RI.

Methods

- Study design:
  - Open-label, single-dose, RI study in subjects aged 18–75 years with severe RI (GFR<30 mL/min/1.73 m² based on the Modification of Diet in Renal Disease Study equation4) or non-Renal Impairment (RI) and matched controls (Protocol no: MK-430-016).
  - Control group was matched to the mean age (±10 years) and weight population (severe RI, healthy matched control) and continuous variables were compared using the Modification of Diet in Renal Disease equation.
  - The 95% confidence interval of the geometric least-squares means ratio (GMR; severe RI/healthy matched controls) were obtained from the ANCOVA model.
- Outcome measures:
  - Doravirine pharmacokinetics:
    - Doravirine plasma concentration–time profiles were shown in Figure 1.
    - Cmax, and trough concentration 24 hours postdose (C24) were analyzed using a non-compartmental approach.
    - Cmax and C24 were increased by 43% and 28%, respectively, while Cmin was decreased by 17% in subjects with severe RI versus the controls (Table 2 and Figure 2).
- Study population:
  - Eight subjects were enrolled to each of the study groups (severe RI and the control) – subject demographics are summarized in Table 1.
  - All enrolled subjects completed the study.

Results

Table 1. Subject baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Severe renal impairment</th>
<th>Healthy matched control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean years)</td>
<td>57.6 (±7.9)</td>
<td>58.8 (±7.9)</td>
</tr>
<tr>
<td>Gender (n, %)</td>
<td>5 (62.5)</td>
<td>3 (37.5)</td>
</tr>
<tr>
<td>White</td>
<td>3 (37.5)</td>
<td>2 (25.0)</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>3 (37.5)</td>
<td>3 (37.5)</td>
</tr>
<tr>
<td>Non-Latino</td>
<td>2 (25.0)</td>
<td>4 (50.0)</td>
</tr>
<tr>
<td>Weight, mean kg (range)</td>
<td>170.94 (155.2–184.0)</td>
<td>196.0 (170–214)</td>
</tr>
<tr>
<td>Height, mean cm (range)</td>
<td>60.0 (51–69)</td>
<td>60.8 (51–69)</td>
</tr>
<tr>
<td>Body mass index, mean kg/m²</td>
<td>26.8 (21.8–34.7)</td>
<td>26.5 (21.3–34.5)</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>1.38 (0.99, 1.92)</td>
<td>1.38 (0.99, 1.92)</td>
</tr>
</tbody>
</table>

Doravirine pharmacokinetics

- Doravirine plasma concentration–time profiles are shown in Figure 1.
- AUC0–24h, and Cmax were increased by 43% and 28%, respectively, while Cmin was decreased by 17% in subjects with severe RI versus the controls (Table 2 and Figure 2).
- In addition, subjects with severe RI demonstrated increased t1/2 and decreased CL/F compared with the controls (Table 2). Doravirine t1/2 was not altered by severe RI versus the controls.

Table 2. Doravirine plasma pharmacokinetics — summary statistics in subjects with severe renal impairment and healthy matched controls administered single-dose doravirine 100 mg

<table>
<thead>
<tr>
<th>Character</th>
<th>Severe renal impairment</th>
<th>Healthy matched control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doravirine Cmax (nM)</td>
<td>104.8 (84–126)</td>
<td>71.0 (51–92)</td>
</tr>
<tr>
<td>Doravirine C24 (nM)</td>
<td>129 (28.3)</td>
<td>1580 (1210, 2080)</td>
</tr>
<tr>
<td>Doravirine CL/F (L/h)</td>
<td>1.43 (0.99, 1.92)</td>
<td>1.43 (0.99, 1.92)</td>
</tr>
<tr>
<td>Doravirine Vz/F (L)</td>
<td>95% confidence interval</td>
<td></td>
</tr>
</tbody>
</table>

Safety

- Administration of doravirine 100 mg was generally well tolerated by both the subjects with severe RI and healthy matched controls previously documented for treatments that, like doravirine, are primarily metabolized by renal excretion.
- Severe RI resulted in a modest, but not clinically meaningful, impact on doravirine pharmacokinetics relative to the controls. AUC0–24h, and Cmax increased by 43% and 38%, respectively, while Cmin decreased by 17%.
- In the severe RI group, one subject experienced mild conjunctivitis and another experienced mild phlebitis. This was not considered to be treatment-related.
- There were no clinically meaningful changes in the other safety parameters.

Discussion

- The influence of severe RI on drug disposition via hepatic excretion has been previously well documented.
- Phase 3 dose of doravirine 100 mg was demonstrated tolerability in a 48-week study.
- It is important to further evaluate the impact of severe RI on doravirine pharmacokinetics because the Phase 3 dose of doravirine 100 mg in Phase IV trials was not considered to be efficacious. As the Cmax values in subjects with severe RI were not decreased relative to the controls, severe RI is not anticipated to have an effect on the efficacy of doravirine.

Conclusions

- Severe RI had a modest, but not clinically meaningful effect, on the pharmacokinetics of a 100 mg dose of doravirine.
- Doravirine 100 mg was generally well tolerated by both healthy subjects and subjects with severe RI.

References


Acknowledgments

The authors wish to thank all of the investigators and clinical staff who participated in the study. Medical writing assistance was provided by Edward Rochford, PhD of Complete Medical Communications, Inc., Hanover, Maryland. This assistance was funded by Merck & Co., Inc., Kenilworth, NJ, USA.

Disclosures

Funding for this research was provided by Merck & Co., Inc., Kenilworth, NJ, USA; AstraZeneca, Cambridge, MA, USA; Merck & Co., Inc., Kenilworth, NJ, USA; and the University of Miami, Miami, FL, USA.