Introduction

Doravirine (MK-1439) is a novel, potent, once-daily, non-nucleoside reverse transcriptase inhibitor in development for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in combination with other antiretroviral therapies.

Following oral administration, doravirine is largely excreted unchanged in feces, while approximately 13% of the administered drug dose is excreted in urine.

Doravirine is primarily metabolized by cytochrome P450 3A4 (CYP3A4) and, subsequently, the oxidized component is predominantly excreted in urine.

Reduced renal function is becoming an increasingly prevalent and may own stock and/or stock options.

The influence of severe RI on drug disposition via altered gene expression and inhibition of CYP450 and transporters has been previously documented for treatments that, like doravirine, are primarily hepatically metabolized.

The effect of severe renal impairment (RI) on exposure to doravirine was evaluated in HIV-negative subjects due to the potential for severe renal insufficiency to alter hepatic drug metabolism and transport.

Although renal excretion represents a minor route of elimination, the effect of severe renal impairment (RI) on exposure to doravirine was evaluated in HIV-negative subjects due to the potential for severe renal insufficiency to alter hepatic drug metabolism and transport.

Despite this, the effect of severe RI on drug disposition via altered gene expression and inhibition of CYP450 and transporters has been previously documented for treatments that, like doravirine, are primarily hepatically metabolized.

The effect of severe renal impairment (RI) on exposure to doravirine was evaluated in HIV-negative subjects due to the potential for severe renal insufficiency to alter hepatic drug metabolism and transport.

Methods

Study design

Open-label, single-treatment, RI study in subjects aged 18–75 years with severe RI (GFR<60 mL/min/1.73 m²) based on the Modification of Diet in Renal Disease Study equation (1900–2500 mL/min/1.73 m² and not on dialysis) and healthy matched controls (PLASMA: n=42; A2000: n=23).

- Control group was matched to the mean age (±10 years) and weight (±10 kg) of severe RI group.

- Medication for RI and associated conditions was permitted at the discretion of the investigator and sponsor only if the treatment was not a strong inhibitor or inducer of CYP3A or P-gp/Polysorbate 80.

Safety was assessed by adverse event (AE) monitoring, laboratory evaluations, vital signs, physical examination, and electrocardiogram.

The study was performed in accordance with Institutional Review Board/Independent Ethics Committee and International Conference on Harmonisation Good Clinical Practice Guidelines and all subjects provided written informed consent prior to any study procedures.

Treatment

- A single dose of doravirine 100 mg was administered following an overnight fast of at least 8 hours; water was restricted 1 hour prior to and following study drug administration.

Pharmacokinetic assessments

- Doravirine plasma pharmacokinetic samples were collected up to 72 hours (controls) or 96 hours (severe RI) postdose.

- The values of pharmacokinetic parameters were fitted to the curve from peak to infinity (AUC infinity, maximum measured concentration ([C max]), and concentration 24 hours postdose ([C 24]) were naturally-log transformed and then analyzed using an analysis of covariance (ANCOVA) model. The ANCOVA model included a categorical factor for population (severe RI; healthy matched control) and continuous covariates for age and body mass index.

- The 95% confidence interval of the geometric means/standard errors (SE) were calculated from the ANCOVA model.

- Additionally, time to C max ([T max]) apparent terminal half-life ([t 1/2]), apparent area under the curve (AUC), and apparent volume of distribution (Vz/F) were calculated.

Safety

- Administration of doravirine 100 mg was generally well tolerated by both the subjects with severe RI and the control subjects.

- The most frequently occurring adverse event was diarrhea, which was reported by 17% of severe RI and 13% of control subjects.

- No significant differences were reported between the severe RI and control groups in terms of the incidence of mild nausea, which was deemed to be treatment related.

- These were no clinically meaningful changes in the other safety parameters.

Results

Study population

- Eight subjects were enrolled to each of the study groups (severe RI and control) – subject demographics are summarized in Table 1.

- All enrolled subjects completed the study.

Table 1. Subject baseline characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Severe renal impairment</th>
<th>Healthy matched control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled, N</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>5 (62.5)</td>
<td>7 (87.5)</td>
</tr>
<tr>
<td>Age, years (range)</td>
<td>61 (52–69)</td>
<td>60 (52–69)</td>
</tr>
<tr>
<td>Weight, mean kg (range)</td>
<td>90.93 (81.6–98.3)</td>
<td>90.86 (71.1–128.1)</td>
</tr>
<tr>
<td>Height, mean cm (range)</td>
<td>172.50 (160.4–181.2)</td>
<td>172.70 (160.3–181.2)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>5 (62.5)</td>
<td>7 (87.5)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td>Non-Hispanic and Hispanic</td>
<td>3 (37.5)</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>5 (62.5)</td>
<td>7 (87.5)</td>
</tr>
</tbody>
</table>

Discussion

- The influence of severe RI on drug disposition via altered gene expression and inhibition of CYP3A and transporters (WAC) has been previously documented for treatments that, like doravirine, are primarily hepatically metabolized.

- Severe RI resulted in a modest, but not clinically meaningful, impact on doravirine pharmacokinetics relative to the controls. AUC 0–24•h was decreased by 17% in subjects with severe RI versus the controls. AUC 0–∞ was decreased by 15% in subjects with severe RI versus the controls. As the C24 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

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Disclosures

Funding for this research was provided by Merck & Co., Inc., Kenilworth, NJ, USA, Merck, Co & Co., Inc., Kenilworth, NJ, USA, WA, MRC, HSC, AK, AL, LE, SG, and Bill are currently or former employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. and may own stock and/or stock options.

FASI guidelines for disclosure.