Effect of CYP3A5 Genotype on the Pharmacokinetics of Maraviroc and Metabolites in Healthy Subjects

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Introduction

Maraviroc (MVC) is a member of the C3S class of small molecules that is primarily metabolized by CYP3A4 and CYP3A5. Both CYP3A4 and CYP3A5 are polymorphic, with CYP3A5*1B (40% frequency) and CYP3A5*2 allele (1% frequency) being the most common null alleles observed. Significantly different exposure and metabolite concentrations have been observed in individuals with CYP3A5 null alleles compared to those with CYP3A5 wild-type alleles [1, 2].

Methods

Study design: An open-label, parallel-group, multi-center study recruiting 120 healthy Caucasian men aged 18–55 years. Participants were randomly assigned to receive 1 of 4 treatments: MVC 150 mg QD (24 subjects), MVC 300 mg BID (24 subjects), MVC 150 mg QD + DRV/c 800/150 mg QD (24 subjects), or MVC 300 mg BID + DRV/c 800/150 mg QD (24 subjects). MVC samples were analyzed by Pfizer Clinical Pharmacogenomics (Groton, CT, USA) using custom TaqMan assays.

Results

In screening, the majority of CAU subjects were CYP3A5 PM while the majority of AA PM subjects were CYP3A5 IM. The primary CYP3A5 genotype (IM vs. PM) was analyzed by Pfizer Clinical Pharmacogenomics (Groton, CT, USA) using custom TaqMan assays (Table 4). At screening, the majority of AA PM subjects were CYP3A5 IM (23/30) while the majority of CAU PM subjects were CYP3A5 PM (30/30) (Table 4).

Discussion

The Pharmacogenomics sample was analyzed by Pfizer Clinical Pharmacogenomics (Groton, CT, USA) using custom TaqMan assays. The primary CYP3A5 genotype (IM vs. PM) was analyzed by Pfizer Clinical Pharmacogenomics (Groton, CT, USA) using custom TaqMan assays (Table 4).

Table 4. Statistical Summary of Cohort Comparison for MVC Plasma PK Parameters—Part 1 and Part 2

<table>
<thead>
<tr>
<th>Parameter (unit)</th>
<th>Metabolite</th>
<th>Reference</th>
<th>Test</th>
<th>Ratio (Test/Reference)</th>
<th>90% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVC Cavg Exposure (ng/mL)</td>
<td>Cohort 1 - AA PM vs Cohort 2 - AA IM</td>
<td>MVC only</td>
<td>MVC + DRV/c</td>
<td>0.63 (0.54, 0.75)</td>
<td>0.02048</td>
<td>0.01585</td>
</tr>
<tr>
<td>Part 1 PK – MVC 300 mg BID</td>
<td>MVC only</td>
<td>MVC only</td>
<td>MVC + DRV/c</td>
<td>0.63 (0.54, 0.75)</td>
<td>0.02048</td>
<td>0.01585</td>
</tr>
<tr>
<td>Part 2 PK – MVC 150 mg QD + DRV/c 800/150 mg QD</td>
<td>MVC only</td>
<td>MVC only</td>
<td>MVC + DRV/c</td>
<td>0.63 (0.54, 0.75)</td>
<td>0.02048</td>
<td>0.01585</td>
</tr>
</tbody>
</table>

Conclusion

CYP3A5 genotype, race, and CYP3A5 genotype/race interaction did not impact MVC efficacy or MVC Cavg (based on population PK methods). MVC Cavg was not lower among CYP3A5 IM subjects compared to PM subjects. CYP3A5 IM was not associated with a reduction in MVC efficacy or MVC Cavg.