
**Materials & Methods**

Human P450c17 Inhibition – IC50 values (IC50) for hydroxylase and lyase were determined using LC/MS/MS to measure the inhibition of conversion of pregnenolone to 17-OH pregnenolone and 17-OH lyase (lyase) (Figure 1). Reduction of extra-gonadal androgen production through CYP17 inhibition is a validated castration-refractory prostate cancer (CRPC) treatment paradigm. With the recently-approved CYP17 inhibitor, abiraterone acetate, increased overall survival in post-docetaxel CRPC patients (de Bono et al, N Engl J Med 2011; 364:1995-2005), although it is also suppressed cortisol and increased steroid concentrations up-stream of CYP17 hydroxylase, VT-464, which is currently in a Phase 1/2 clinical study for the treatment of CRPC, is an oral, non-steroidal, lyase-selective CYP17 inhibitor. The objectives of the study reported here were to compare the in vitro selectivity and in vivo primate endocrine response of VT-464 and abiraterone acetate (AA).

**Results**

In Vivo Results - Human P450c17 IC50 data are presented in Table 1. The authors would like to thank Amber Edwards and the animal care staff at the Wisconsin National Primate Research Center for their assistance with the primate studies.


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**Table 1 – P450c17 Lyase and Hydroxylase Enzyme Inhibition**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Human CYP17 Lyase IC50 (nM)</th>
<th>Human CYP17 Hydroxylase IC50 (nM)</th>
<th>Human CYP17 Lyase Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>VT-464</td>
<td>69</td>
<td>670</td>
<td>9.7</td>
</tr>
<tr>
<td>Abiraterone</td>
<td>15</td>
<td>2.5</td>
<td>6.17</td>
</tr>
</tbody>
</table>

**Summary**

VT-464 preferentially inhibited human CYP17 lyase relative to hydroxylase by approximately 10-fold whereas abiraterone preferentially inhibited human CYP17 hydroxylase relative to lyase by approximately 6-fold. Administration of the CYP17 inhibitors VT-464 and abiraterone acetate produced significant reductions of testosterone in this castrate monkey model. Cortisol was not significantly affected by VT-464 treatment, but was significantly suppressed in response to abiraterone acetate treatment. Progesterone, one of several steroids up-stream of CYP17 hydroxylase, was not significantly affected by VT-464 treatment, but was significantly elevated in response to abiraterone acetate treatment.

**Conclusions**

This study in a castrate monkey model is consistent with clinical findings of abiraterone acetate; namely androgen reduction in combination with cortisol suppression and an increase in steroids upstream of CYP17. The lyase-selective CYP17 inhibitor VT-464 also reduced androgens but did not significantly alter cortisol or up-stream steroid levels at the doses tested. The lyase-selective CYP17 inhibitor VT-464 should confer an advantage over abiraterone acetate since it should not require co-dosing with supplemental steroids (e.g., prednisone).

**Acknowledgements**

The authors would like to thank Amber Edwards and the animal care staff at the Wisconsin National Primate Research Center for their assistance with the primate studies.