Cabotegravir (CAB), an HIV integrase inhibitor primarily metabolized by UGT1A1, is in development as an oral tablet and long-acting (LA) injectable for the treatment and prevention of HIV infection. CAB LA has a prolonged absorption phase, typical of flip-flop pharmacokinetics (PK), which yields prolonged drug exposure compared with oral administration.

### Introduction

- **CAB** is an integrase inhibitor primarily metabolized by UGT1A1.
- CAB LA has a prolonged absorption phase, typical of flip-flop pharmacokinetics.
- DNA from 210 HIV-infected subjects with PGx confirmed to receive oral or LA CAB in the LATTE study.
- UGT1A1 variants (*1, *28, *36, *37) were used to classify subjects with genetically predicted UGT1A1 activity.
- LA CAB PK parameters were significantly associated with steady-state oral CAB PK parameters, with ~1.5-fold increases in mean CₚKₐₐₐₐmax and AUCₚ₀ₗ₀₀ₐmax.
- The present analysis assessed the impact of UGT1A1 genotypes on CAB LA PK parameters in HIV-infected subjects receiving oral and LA CAB in the LATTE-2 study.
- DNA from 210 HIV-infected subjects with PGx confirmed to receive oral or LA CAB was genotyped.
- Linear regression analysis, adjusting for significant nongenetic covariates, was used to determine 1.5-fold increases in CAB PK parameters with reduced UGT1A1 activity.

### Discussion

- Genetically predicted UGT1A1 activity was statistically associated with CAB CₚKₐₐₐₐmax and AUCₚ₀ₗ₀₀ₐmax.
- Nongenetic covariates of age, weight, dosing regimen, body mass index, and weight were significantly associated with CAB mean PK parameters.

### Conclusions

- UGT1A1 reduced-function polymorphisms modestly increased CAB PK parameters in HIV-infected patients who received CAB by oral or IM administration.
- The approximate 1.2-fold difference in mean PK parameter values between patients with low versus normal predicted UGT1A1 activity was lower than that observed with oral CAB and is not considered to have a clinically relevant impact.
- Based on the accumulated safety profile of CAB, individuals with UGT1A1 reduced-function polymorphisms do not require dose adjustment for either oral or LA CAB administration.

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**Table 1. Effects of Genetically Predicted UGT1A1 Activity on CAB LA PK Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study</th>
<th>Genotype</th>
<th>Mean Value</th>
<th>Fold Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>CₚKₐₐₐₐmax</td>
<td>LATTE-2</td>
<td>Reduced</td>
<td>1.20 (1.03, 10.5)</td>
<td>0.687 (0.460, 1.03)</td>
</tr>
<tr>
<td>AUCₚ₀ₗ₀₀ₐmax</td>
<td>LATTE-2</td>
<td>Reduced</td>
<td>3.68 (2.77, 6.65)</td>
<td>0.787 (0.484, 1.31)</td>
</tr>
</tbody>
</table>

**Figure 1. LATTE-2 (NCCT21923152) Study Design**

**Figure 2. Mean (%) Cₙ CAB LA Concentration-Time Profile by Treatment and UGT1A1 Predicted Activity Status**

**Figure 3. Oral Versus LA CAB Trough Overall Concentrations**

**References**