Evaluation of the Drug-Drug Interaction (DDI) Potential Between Cobicistat-Boosted Protease Inhibitors and Statins

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Disclosures

♦ I am an employee of Gilead Sciences, Inc.
Cobicistat (COBI) is a mechanism-based CYP3A inhibitor and pharmacokinetic (PK) booster\(^1,2,3\)

- COBI is an inhibitor of CYP3A, CYP2D6, P-gp, BCRP, and OATP1B1/1B3

**COBI approved for use with the HIV integrase strand transfer inhibitor elvitegravir (EVG) when given either as the single tablet regimen Stribild™ (EVG/COBI/emtricitabine [FTC]/tenofovir disoproxil fumarate) or Genvoya™ (EVG/COBI/FTC/tenofovir alafenamide)\(^1,2\)**

**COBI approved for use with the HIV protease inhibitors atazanavir (ATV) or darunavir (DRV)\(^3\)**

- DRV inhibits CYP3A and P-gp\(^4\)
- ATV inhibits CYP3A, UGT1A1, P-gp, BCRP, and OATP1B1/1B3\(^5\)

Background

Statins

- HMG-CoA reductase inhibitors, rosuvastatin (ROS; Crestor®) and atorvastatin (ATOR; Lipitor®) are commonly prescribed to treat hypercholesterolemia in HIV-infected individuals\(^1,2\)
  - **ROS** is a substrate of drug transporters\(^1\)
  - **ATOR** is a substrate for drug transporters and drug-metabolizing enzymes\(^7\)

<table>
<thead>
<tr>
<th>DDI mechanism</th>
<th>ROS</th>
<th>ATOR</th>
<th>DRV+COBI</th>
<th>ATV+COBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug transporters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-gp/BCRP</td>
<td>Substrate</td>
<td>Substrate</td>
<td>Inhibitor</td>
<td>Inhibitor</td>
</tr>
<tr>
<td>OATP1B1/1B3</td>
<td>Substrate</td>
<td>Substrate</td>
<td>Inhibitor</td>
<td>Inhibitor</td>
</tr>
<tr>
<td>Drug-metabolizing enzymes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP3A4</td>
<td>—</td>
<td>Substrate</td>
<td>Inhibitor</td>
<td>Inhibitor</td>
</tr>
</tbody>
</table>

- The risk of skeletal muscle adverse events (eg, myopathy) is increased during concomitant use of statins with strong CYP3A inhibitors\(^2,3\)

Aim

- **Primary**: To evaluate the effect of the COBI-boosted DRV (DRV + COBI) or COBI-boosted ATV (ATV + COBI) on the PK of ROS or ATOR.

- **Secondary**: To evaluate the safety and tolerability of administration of DRV + COBI or ATV + COBI when given alone or in combination with ROS or ATOR.
**Study Design**

- Randomized, fixed sequence, three periods, multiple cohort, open label, single center study in healthy subjects (n=16/cohort)
Methods

- Plasma concentrations determined using validated LC/MS-MS assays
- GMR, associated 90% CIs used to statistically compare exposures
- No effect boundaries were 70–143% for AUC and 50–200% for $C_{\text{max}}$

CI, confidence interval; GMR, geometric mean ratios; LC/MS-MS, liquid chromatography-tandem mass spectrometry.
## Results: Enrollment and Demographics

<table>
<thead>
<tr>
<th></th>
<th>DRV+COBI+ROS n=16</th>
<th>DRV+COBI+ATOR n=16</th>
<th>ATV+COBI+ROS n=16</th>
<th>ATV+COBI+ATOR n=16</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, n</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
<td>12</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td><strong>Median age, y (range)</strong></td>
<td>32 (18–45)</td>
<td>30 (19–43)</td>
<td>34 (21–45)</td>
<td>31 (20–44)</td>
</tr>
<tr>
<td><strong>Mean weight, kg (SD)</strong></td>
<td>78.8 (13.1)</td>
<td>81.7 (14.6)</td>
<td>80.1 (8.8)</td>
<td>79.3 (11.9)</td>
</tr>
<tr>
<td><strong>Race/ethnicity, n</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>12</td>
<td>9</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>White</td>
<td>4</td>
<td>7</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>3</td>
<td>3</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>
Results: Safety

- All treatments were generally well tolerated
- All subjects completed the study
- The majority of adverse events (AEs) that were related to study drug were mild in severity; no Grade 3 or 4 AEs were observed
- The most frequently reported AEs were ocular icterus and hyperbilirubinemia in the ATV-containing cohorts
- Common AEs also included headache and gastrointestinal disorders irrespective of treatment
Coadministration increased ROS AUC∞ and Cmax, consistent with the inhibitory effect of DRV+COBI on P-gp/BCRP and/or OATP1B1/1B3.
Results: Cohort 2
Effect of DRV+COBI on **ATOR** PK

- Coadministration increased ATOR AUC<sub>∞</sub> and C<sub>max</sub>, consistent with the inhibitory effect of DRV+COBI on CYP3A, P-gp/BCRP, and/or OATP1B1/1B3
Results: Cohort 3

Effect of ATV+COBI on ROS PK

Coadministration increased ROS AUC$_\infty$ and C$_{\text{max}}$, consistent with the potent inhibitory effect of ATV+COBI on OATP1B1/1B3 and P-gp/BCRP.
Results: Cohort 4
Effect of ATV+COBI on ATOR PK

Coadministration increased ATOR AUC∞ and Cmax, consistent with the potent inhibitory effect of ATV+COBI on CYP3A, OATP1B1/1B3, and/or P-gp/BCRP.
Conclusions

- All treatments were generally well-tolerated and all subjects completed the study.
- These study findings were consistent with the current dosing recommendations for ROS and ATOR upon coadministration with boosted DRV or ATV.

- It is recommended to initiate ROS or ATOR treatment with the lowest dose, and titrate to desired response while monitoring for safety.
- It is recommended not to exceed a dose of 10 mg ATOR daily and monitor for safety.
Acknowledgments

We extend our thanks to the study participants and study team. This study was funded by Gilead Sciences, Inc.