Confirmation of the Drug-drug Interaction Potential Between Cobicistat-boosted Antiretroviral Regimens and Hormonal Contraceptives

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Oral # 5
I am an employee of Gilead Sciences, Inc.
DHHS guidelines recommend offering effective and appropriate contraceptive methods to all HIV-infected women\(^1\)

Drug-drug interactions (DDIs) between ARVs and hormonal (“oral”) contraceptives (OCs) are well documented\(^2\) - \(^7\)

- OCs are extensively metabolized by CYP enzymes (including CYP3A, CYP2C9/19), UGT and SULT

**Background**

- Effect of COBI on OC (norgestimate/ethinyl estradiol [EE]) evaluated previously with EVG/COBI/FTC/TDF in healthy subjects and confirmed in HIV-infected women\(^1,2\)

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>EVG/COBI/FTC/TDF + norgestimate/EE(^1) n=13</th>
<th>EVG/COBI/FTC/TDF + levonorgestrel/EE(^3) n=20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norelgestromin</td>
<td>AUC(\tau) 130% ↑</td>
<td>110% ↑*</td>
</tr>
<tr>
<td></td>
<td>C(_{\text{max}}) 110% ↑</td>
<td></td>
</tr>
<tr>
<td>Norgestrel</td>
<td>AUC(\tau)</td>
<td>110% ↑*</td>
</tr>
<tr>
<td></td>
<td>C(_{\text{max}}) 60% ↑*</td>
<td></td>
</tr>
<tr>
<td>EE</td>
<td>AUC(\tau) 25% ↓</td>
<td>20% ↑*</td>
</tr>
<tr>
<td></td>
<td>C(_{\text{max}}) ↔ 10% ↑*</td>
<td></td>
</tr>
</tbody>
</table>

*Compared to historical data of levonorgestrel/EE administered alone\(^4\).

- Consistent with CYP3A inhibition by COBI

Background

♦ For RTV-boosted protease inhibitors, DDIs between ATV and DRV and OCs have been evaluated\(^1,2\)

♦ DDI with COBI-boosted ATV or DRV and OCs was not available
  – Phase I DDI study conducted as a regulatory request to confirm the magnitude and direction of a potential interaction with OCs

Aim

♦ Yaz® (DRSP/EE) is a combination oral contraceptive containing progestational and estrogenic compounds
  – Drospirenone (DRSP): 3 mg
  – Ethinyl Estradiol (EE): 20 µg

♦ Primary: to evaluate the effect of the PK enhancer COBI, plus ATV (ATV + COBI) or DRV (DRV + COBI) on the pharmacokinetics (PK) of DRSP/EE

♦ Secondary: safety and tolerability of administration of ATV + COBI or DRV + COBI when given alone or in combination with DRSP/EE
Study Design and Methods

- Phase I open-label, two cohort, fixed sequence study in healthy women

PK analysis:
- Plasma concentrations OCs (DRSP and EE) and ATV, DRV and COBI determined using validated LC/MS-MS assays
- Primary PK parameters (mean [%CV]) include AUC_{\text{∞}/\text{last}} (h·ng/mL) and C_{\text{max}} (ng/mL)
- Geometric least squares mean ratio (GMR; [Test Treatment vs Reference Treatment]) and 90% confidence intervals (CI) estimated using ANOVA; compared against lack of PK alteration bounds of 70–143%

- Safety assessed throughout the study

AUC_{\text{∞}/\text{last}}, area under plasma concentration-time curve from time 0 to ∞/last measurable concentration; C_{\text{max}}, maximal concentration; CV, coefficient of variation; LC/MS-MS, liquid chromatography tandem-mass spectrometry;
Results: Demographics

<table>
<thead>
<tr>
<th></th>
<th>DRV + COBI n=18</th>
<th>ATV + COBI n=18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed/enrolled, n</td>
<td>15/18*</td>
<td>14/18*</td>
</tr>
<tr>
<td>Median age, y (range)</td>
<td>28 (18–43)</td>
<td>30 (22–44)</td>
</tr>
<tr>
<td>Median body mass index, kg/m² (range)</td>
<td>26 (20–30)</td>
<td>26 (23–30)</td>
</tr>
<tr>
<td>Mean creatinine clearance, mL/min (range)</td>
<td>129 (95–186)</td>
<td>122 (96–171)</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>50</td>
<td>39</td>
</tr>
<tr>
<td>White</td>
<td>50</td>
<td>56</td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Ethnicity, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>39</td>
<td>50</td>
</tr>
</tbody>
</table>

*All discontinuations were due to Grade 1 maculopapular rash.
### Results: Safety

<table>
<thead>
<tr>
<th>AE by Preferred Term</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DRSP/EE</td>
<td>DRV + COBI</td>
<td>DRV + COBI + DRSP/EE</td>
</tr>
<tr>
<td>n=18</td>
<td>n=18</td>
<td>n=15</td>
<td>n=18</td>
</tr>
<tr>
<td>Any TEAEs</td>
<td>4</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Ocular icterus</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infrequent bowel movements</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Presyncope</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Rash maculo-popular</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Acne</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- All treatments were generally well tolerated
- 7 subjects discontinued due to Grade 1 maculopapular rash, a known AE of boosted PIs
- AEs were consistent with the known safety profiles of the approved products

**Results: Effect of ATV + COBI on DRSP/EE PK**

- **ATV + COBI increased DRSP exposure**
  - Attributed to inhibition of CYP3A by COBI
  - Similar increase in DRSP exposures observed with CYP3A inhibitor ketoconazole

- **ATV + COBI did not impact EE PK (within no-effect boundary)**

Results: Effect of DRV + COBI on DRSP/EE PK

DRV + COBI increased DRSP exposure; attributed to inhibition of CYP3A by COBI

DRV + COBI reduced EE exposure; decreases in EE exposures observed with DRV/ritonavir (RTV)

May be attributed to induction (eg, P-gp, CYP2C9)

Conclusions

- All treatments were generally well tolerated; no new safety findings
  - DRSP exposure increased with ATV+COBI and DRV+COBI
  - EE exposure was unchanged with ATV+COBI and modestly decreased with DRV+COBI
  - Yaz prescribing information recommends clinical monitoring when used with strong CYP3A inhibitors due to potential for hyperkalemia\(^1,2\)
    - This recommendation remains when Yaz is administered with COBI-containing products

Acknowledgments

We extend our thanks to the study participants and study teams. These studies were funded by Gilead Sciences, Inc.
Backup
Results: Effect of ATV+CObI on DRSP PK

**PK Parameter**

<table>
<thead>
<tr>
<th>Mean (%)CV</th>
<th>ATV + CObI + DRSP/EE [Test] n=14</th>
<th>DRSP/EE [Reference] n=18</th>
<th>GMR% (90% CI) [Test/Reference]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUC_∞, h·ng/mL</strong></td>
<td>1118 (38)</td>
<td>466 (21)</td>
<td>230 (200, 264)</td>
</tr>
<tr>
<td><strong>C_{max}, ng/mL</strong></td>
<td>33 (23)</td>
<td>29 (20)</td>
<td>112 (105, 119)</td>
</tr>
</tbody>
</table>

- ATV + CObI increased DRSP exposure
  - Attributed to inhibition of CYP3A by CObI
  - Similar increase in DRSP exposures observed with CYP3A inhibitor ketoconazole¹

Results: Effect of DRV+COBI on EE PK

ATV + COBI did not impact EE PK (within no-effect boundary)

Results: Effect of DRV+COBI on DRSP PK

DRV + COBI increased DRSP exposure; attributed to inhibition of CYP3A by COBI

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>DRV + COBI + DRSP/EE [Test]</th>
<th>DRSP/EE [Reference]</th>
<th>GMR% (90% CI) [Test/Reference]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean AUC_{∞}, h·ng/mL</td>
<td>895 (24)</td>
<td>567 (24)</td>
<td>158 (147, 171)</td>
</tr>
<tr>
<td>Mean C_{max}, ng/mL</td>
<td>36 (21)</td>
<td>31 (20)</td>
<td>115 (105, 126)</td>
</tr>
</tbody>
</table>

Results: Effect of DRV+COBI on EE PK

DRV + COBI reduced EE exposure; decreases in EE exposures observed with DRV/ritonavir (RTV)\(^1\)

- May be attributed to induction (eg, P-gp, CYP2C9)

Study Design and Methods

**Study 2**

- A PK substudy was done in the WAVES open label extension phase to evaluate the effect of EVG/COBI/FTC/TDF on the PK of commonly used OCs\(^1,2\)

- Plasma concentrations determined using validated LC/MS/MS assays

- Primary PK parameters (mean [%CV]) include \(\text{AUC}_{\text{τ, last}}\) (h·ng/mL) and \(C_{\text{max}}\) (ng/mL)

- Norgestrell (NG) and EE exposures compared to historical data

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Results: Effect of DRV+COBI and ATV+COBI on DRSP PK

- DRV + COBI increased DRSP exposure; attributed to inhibition of CYP3A by COBI
- ATV + COBI increased DRSP exposure
  - Attributed to inhibition of CYP3A by COBI
  - Similar increase in DRSP exposures observed with CYP3A inhibitor ketoconazole

Results: Effect of DRV+COBI and ATV+COBI on EE PK

DRV + COBI reduced EE exposure; decreases in EE exposures observed with DRV/ritonavir (RTV)\(^1\)

- May be attributed to induction (eg, P-gp, CYP2C9)

ATV + COBI did not impact EE PK (within no-effect boundary)

Results: Effect of DRV + COBI and ATV + COBI on DRSP/EE PK

- DRV + COBI increased DRSP exposure; attributed to inhibition of CYP3A by COBI
- DRV + COBI reduced EE exposure; decreases in EE exposures observed with DRV/ritonavir (RTV)¹
  - May be attributed to induction of non-CYP3A pathways (ie, P-gp, CYP2C9)
- ATV + COBI increased DRSP exposure
  - Attributed to inhibition of CYP3A by COBI
  - Similar increase in DRSP exposures observed with CYP3A inhibitor ketoconazole¹
- ATV + COBI did not impact EE PK (within no-effect boundary)