Darunavir-Cobicistat-Tenofovir Alafenamide-Emtricitabine

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Disclosures

Dr. Kalapila has no financial conflicts of interest or disclosures.
Darunavir-Cobicistat-Tenofovir alafenamide-Emtricitabine (DRV-COBI-TAF-FTC)

**Dosing:** Once daily with food

- **Darunavir:** 800 mg (PI)
- **Cobicistat:** 150 mg (Booster)
- **Tenofovir alafenamide:** 10 mg (NRTI)
- **Emtricitabine:** 200 mg (NRTI)
Darunavir-Cobicistat-Tenofovir Alafenamide-Emtricitabine
Single-Tablet Regimen

• **Indication:** Complete regimen for treatment of HIV-1 in persons weighing ≥40 kg:
  - No prior antiretroviral treatment history, *or*
  - Virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable ART for ≥6 months and have no known resistance to darunavir or tenofovir

• **Testing Prior to Initiation**
  - Renal function
  - Serologic testing for hepatitis B (HBV) virus infection

• **With Renal or Hepatic Impairment**
  - Not recommended if estimated CrCl <30 mL/min
  - Not recommended with severe hepatic impairment (Child-Pugh C)
Darunavir-Cobicistat-Tenofovir Alafenamide-Emtricitabine
Mechanism of Action
Nucleoside Reverse Transcriptase Inhibitors (NRTIs): Mechanism of Action

HIV DNA

Human Nucleotides

Reverse Transcriptase

NTRIs
- Tenofovir alafenamide
- Emtricitabine

HIV RNA

Chain Termination
HIV Protease and Polypeptide Cleavage

Illustration: Cognition Studio, Inc. and David H. Spach, MD
Protease Inhibitors: Mechanism of Action

Illustration: Cognition Studio, Inc. and David H. Spach, MD
### Background
Randomized, double-blind, active-controlled, international, phase 3 study evaluating the efficacy and safety of the single-tablet regimen DRV-COBI-TAF-FTC compared with DRV-COBI + TDF-FTC for treatment-naïve individuals.

### Inclusion Criteria (n = 725)
- Age ≥ 18 years
- Antiretroviral naïve
- CD4 count > 50 cells/mm³
- HIV RNA ≥ 1,000 copies/mL
- eGFR ≥ 70 mL/min
- Genotypic sensitivity to DRV, TDF, and FTC
- No hepatitis B or C
- Not pregnant
- No AIDS-defining condition within 30 days

### Source
Week 48: Virologic Response by FDA Snapshot Analysis, ITT

Week 48: Change in Serum Creatinine and Estimated GFR

- Change in Serum Cr
  - DRV-COBI-TAF-FTC: 4.8
  - DRV-COBI + TDF-FTC: -5.9

- Change in eGFR (Cr)
  - DRV-COBI-TAF-FTC: 8.2
  - DRV-COBI + TDF-FTC: -9.3

- Change in eGFR (Cyst)
  - DRV-COBI-TAF-FTC: 5.3
  - DRV-COBI + TDF-FTC: 2.9

Abbreviations: Cr = creatinine (measured in µmol/L); eGFR = estimated glomerular filtration rate (measured in mL/min/1.73m², calculated using CKD-EPI); Cyst = cystatin C

### Mean Change in Markers of Proximal Tubulopathy at Week 48

<table>
<thead>
<tr>
<th></th>
<th>DRV-COBI-TAF-FTC (n = 362)</th>
<th>DRV-COBI + TDF-FTC (n = 363)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPCR (mg/g)</td>
<td>-22.42</td>
<td>-10.34</td>
</tr>
<tr>
<td>UACR (mg/g)</td>
<td>-2.45</td>
<td>-0.58</td>
</tr>
<tr>
<td>RBP:Cr (μg/g)</td>
<td>16.84</td>
<td>401.12</td>
</tr>
<tr>
<td>β2M:Cr (μg/g)</td>
<td>-100.58</td>
<td>837.63</td>
</tr>
</tbody>
</table>

UPCR = urine protein to creatinine ratio; UACR = urine albumin to creatinine ratio; RBP:Cr = retinol binding protein to creatinine ratio; β2M:Cr = beta-2-microglobulin to creatinine ratio

Week 48: Percentage Change in Bone Mineral Density*

<table>
<thead>
<tr>
<th>Location</th>
<th>DRV-COBI-TAF-FTC</th>
<th>DRV-COBI + TDF-FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip</td>
<td>-2.7</td>
<td>-3.0</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>-0.7</td>
<td>-2.4</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>-0.3</td>
<td></td>
</tr>
</tbody>
</table>

*This is from a bone mineral density substudy (n = 113 participants in TAF arm, 99 in control arm)

## AMBER: Results

### Median Change in Fasting Lipid Parameters at Week 48

<table>
<thead>
<tr>
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<th>DRV-COBI-TAF-FTC (n = 362)</th>
<th>DRV-COBI + TDF-FTC (n = 363)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC (mg/dL)</td>
<td>28.6</td>
<td>10.4</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>17.4</td>
<td>5.0</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>4.3</td>
<td>1.5</td>
</tr>
<tr>
<td>TC:HDL ratio</td>
<td>0.2</td>
<td>0.08</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>23.9</td>
<td>14.2</td>
</tr>
</tbody>
</table>

TC = total cholesterol; LDL = low density lipoprotein; HDL = high density lipoprotein

Darunavir-Cobicistat-Tenofovir alafenamide-Emtricitabine
Summary of Key Studies

• **Trials in Treatment Naïve Adults**
  – AMBER: DRV-COBI-TAF-FTC versus DRV-COBI + TDF-FTC
    • DRV-COBI-TAF-FTC achieved a high virologic suppression rate and was non-inferior to DRV-COBI + TDF-FTC

DRV-COBI-TAF-FTC vs Continue Boosted PI + TDF-FTC

EMERALD: Design

**Background**: Randomized, open-label, active-controlled, international, phase 3 study evaluating the efficacy and safety of switching to the single-tablet regimen DRV-COBI-TAF-FTC versus continuing a boosted PI + TDF-FTC

**Inclusion Criteria** (n = 1,141)
- Age ≥18 years
- Antiretroviral experienced
- HIV RNA ≤50 copies/mL for >2 months*
- Taking a PI plus ritonavir or cobicistat
- Regimen stable for ≥6 months
- eGFR ≥50 mL/min
- No prior virologic failure on a DRV-based regimen
- Virologic failure on non-DRV-based regimen allowed
- Not pregnant or breastfeeding

*One HIV RNA 50-200 copies/mL within prior 12 months allowed

### EMERALD Study: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>DRV-COBI-TAF-FTC Switch Group (n = 763)</th>
<th>Boosted PI + TDF-FTC Continue Group (n = 378)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 Count (cells/mL)</td>
<td>630</td>
<td>624</td>
</tr>
<tr>
<td>Time since HIV diagnosis (years)</td>
<td>9.3</td>
<td>8.9</td>
</tr>
<tr>
<td>Time since first ART (years)</td>
<td>6.2</td>
<td>5.8</td>
</tr>
<tr>
<td>Previous use of &gt;5 ARV’s</td>
<td>59</td>
<td>58</td>
</tr>
<tr>
<td>Previous virologic failure</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Boosted darunavir at screening (%)</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Boosted atazanavir at screening (%)</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Boosted lopinavir at screening (%)</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

DRV-COBI-TAF-FTC vs Continue a Boosted PI + TDF-FTC

EMERALD: Results

Week 48: Virologic Response by FDA Snapshot Analysis, ITT

## EMERALD Study Virologic Outcomes

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</tr>
</thead>
<tbody>
<tr>
<td>Virologic rebound rate through 48 weeks*</td>
<td>2.5%</td>
<td>2.1%</td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/mL at 48 weeks</td>
<td>94.9%</td>
<td>93.7%</td>
</tr>
<tr>
<td>HIV RNA ≥50 copies/mL at 48 weeks</td>
<td>0.8%</td>
<td>0.5%</td>
</tr>
<tr>
<td>No virologic data at 48 weeks</td>
<td>4.3%</td>
<td>5.8%</td>
</tr>
</tbody>
</table>

*HIV RNA ≥50 copies/mL or premature discontinuation with last HIV RNA ≥50 copies/mL

DRV-COBI-TAF-FTC vs Continue a Boosted PI + TDF-FTC
EMERALD: Results

Week 48: Change in Serum Creatinine and Estimated GFR


Cr = creatinine (measured in µmol/L)
eGFR = estimated glomerular filtration rate (measured in mL/min/1.73 m², calculated using CKD-EPI)
Cyst = cystatin C
### DRV-COBI-TAF-FTC vs Continue a Boosted PI + TDF-FTC

**EMERALD: Results**

**Week 48: Change in Urinary Markers of Tubular Dysfunction**

<table>
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</tr>
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<tbody>
<tr>
<td>UPCR (mg/g)</td>
<td>-33.9</td>
<td>-6.43</td>
</tr>
<tr>
<td>UACR (mg/g)</td>
<td>-3.2</td>
<td>1.3</td>
</tr>
<tr>
<td>RBP:Cr (mg/g)</td>
<td>-630.5</td>
<td>1037.1</td>
</tr>
<tr>
<td>β2M:Cr (mg/g)</td>
<td>-1454.7</td>
<td>1371.3</td>
</tr>
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</table>

UPCR = urine protein to creatinine ratio; UACR = urine albumin to creatinine ratio; RBP:Cr = retinol binding protein to creatinine ratio; β2M:Cr = beta-2-microglobulin to creatinine ratio

EMERALD: Results

Week 48: Change in Bone Mineral Density

This is from a bone mineral density substudy (n = 209 participants in switch arm, 108 in control arm)

**DRV-COBI-TAF-FTC vs Continue a Boosted PI + TDF-FTC**

**EMERALD: Results**

<table>
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<tbody>
<tr>
<td>TC (mg/dL)</td>
<td>19.7</td>
<td>1.3</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>15.7</td>
<td>1.9</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>3.0</td>
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TC = total cholesterol; LDL = low density lipoprotein; HDL = high density lipoprotein

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    • DRV-COBI-TAF-FTC achieved a high virologic suppression rate and was non-inferior to DRV-COBI + TDF-FTC

• Trials In Adults with Virologic Suppression
  - EMERALD: Switch to DRV-COBI-TAF-FTC or stay on PI + TDF-FTC
    • DRV-COBI-TAF-FTC is safe and efficacious as a potential switch option for the treatment of HIV-1 infection in adults with viral suppression, if a single tablet regimen is needed

Darunavir-Cobicistat-Tenofovir Alafenamide-Emtricitabine
Adverse Effects

• **Gastrointestinal**
  - Diarrhea (9%) and nausea (6%) in persons taking darunavir with cobicistat

• **Hepatotoxicity**
  - Risk increased with pre-existing liver dysfunction, including chronic HBV or HCV

• **Skin Reactions**
  - Darunavir contains a sulfonamide moiety
  - Rash in approximately 8%
  - Stevens-Johnson syndrome in 0.1% of persons taking darunavir with cobicistat

• **Prior Sulfonamide Allergy**
  - Incidence and severity of rash similar with or without a history of sulfonamide allergy
  - History of sulfonamide allergy not a contraindication but monitoring recommended
• Oral, once-daily single tablet combination antiretroviral therapy with a high genetic barrier to resistance

• It is a large pill which, some individuals may find difficult to swallow

• It should not be used in patients with severe renal or severe hepatic impairment

• The medication is mostly associated with gastrointestinal adverse effects, such as diarrhea and nausea

• As an inhibitor of CYP3A, COBI can cause problematic interactions with drugs metabolized by CYP3A or drugs that induce or inhibit CYP3A
Acknowledgments

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