Efficacy and Safety of Elvitegravir, Cobicistat, Emtricitabine, and Tenofovir Alafenamide (E/C/F/TAF) in Virologically Suppressed Asian Adults with Renal Impairment

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Introduction

- Tenofovir alafenamide (TAF) is a novel prodrug of tenofovir (TFV) that results in >90% lower plasma TFV levels compared to tenofovir disoproxil fumarate (TDF).

- As a result, TAF has an improved renal and bone safety profile relative to TDF and is efficacious as demonstrated in multiple patient populations.
Prodrug Pharmacology
Tenofovir Disoproxil Fumarate and Tenofovir Alafenamide

TAF results in >90% lower TFV plasma levels¹,²,³

OAT, organic anion transporter; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV, tenofovir

3. Data on File
Introduction

The efficacy and safety of co-formulated E/C/F/TAF\(^1\) have been reported in HIV-suppressed adults with renal function impairment (eGFR\(_{CG}\) 30 to 69 mL/min) through Week 96\(^2\).

In this study, we aimed to investigate the efficacy and safety of E/C/F/TAF in HIV-suppressed Asian adults with renal impairment.

\(^{1}\) elvitegravir 150mg, cobicistat 150mg, emtricitabine 200mg, and TAF 10mg
\(^{2}\) Pozniak A, et al. JAIDS 2016;71(5):530-7
Study Design-Post hoc analysis of Study 112

Study 112: Phase 3, 144-week, multicentered, single-arm, open label study

HIV Suppressed Adults With Renal Impairment
eGFR_{CG} 30-69 mL/min

N=242

E/C/F/TAF QD

Key inclusion criteria
- HIV-1 RNA <50 c/mL for ≥6 months
- “Stable” eGFR for ≥3 months

Primary Endpoint
Change from baseline in eGFR at Week 24

Secondary Endpoints
Efficacy, safety, and tolerability observed through Week 144

QD=once daily

ClinicalTrials.gov Identifier: NCT01818596.
Study Design: Post hoc analysis of Study 112

Switch to E/C/F/TAF in Asian Adults with Renal Impairment (Week 96); Study 112 Sub

HIV Suppressed Adults With Renal Impairment
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Sub-analysis by Ethnic group

Asian N=34

Non-Asian N=206

Week 96

Week 144
Baseline Characteristics

242 participants switched to E/C/F/TAF: 14% (N=34) self-identified as Asian

### Pre-switch Regimens (N=242)

- **TDF** 65%
- **NNRTI** 42%
- **PI** 44%
- **INSTI** 24%
- **ABC** 22%
- **Other** 7%
- **None** 5%

### Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Asian N=34</th>
<th>Non-Asian N=206</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years</td>
<td>55</td>
<td>59</td>
</tr>
<tr>
<td>Female</td>
<td>27%</td>
<td>19%</td>
</tr>
<tr>
<td>Geography: Ex-US</td>
<td>94%</td>
<td>20%</td>
</tr>
<tr>
<td>Median Body Mass Index, kg/m²</td>
<td>20.5</td>
<td>24.8</td>
</tr>
<tr>
<td>Median CD4 count, cells/μL</td>
<td>498</td>
<td>652</td>
</tr>
<tr>
<td>Median eGFR&lt;sub&gt;CG&lt;/sub&gt;, mL/min</td>
<td>44</td>
<td>58</td>
</tr>
<tr>
<td>Proportion with eGFR&lt;sub&gt;CG&lt;/sub&gt; &lt;60 mL/min</td>
<td>91%</td>
<td>62%</td>
</tr>
<tr>
<td>Median UPCR, mg/g</td>
<td>267</td>
<td>145</td>
</tr>
<tr>
<td>Median spine BMD, g/cm²</td>
<td>0.94</td>
<td>1.08</td>
</tr>
<tr>
<td>Median hip BMD, g/cm²</td>
<td>0.84</td>
<td>0.92</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>18%</td>
<td>13%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>35%</td>
<td>40%</td>
</tr>
</tbody>
</table>

UPCR=Urine Protein to Creatinine Ratio

Switch to E/C/F/TAF in Asian Adults with Renal Impairment (Week 96); Study 112 Sub

Virologic Outcomes (HIV-1 RNA <50 copies/mL) at Week 96

Virologic Success

Participants, %

97  87

n= 33  179

Virologic Failure†

0  2

No Virologic Data‡

3  11

E/C/F/TAF maintained high rates of virologic suppression at Week 96

‡ Discontinuation due to adverse events/death (0 Asian; 13 non-Asian) or other reasons e.g. lost to follow-up, protocol violation (1 Asian; 9 non-Asian).
Switch to E/C/F/TAF in Asian Adults with Renal Impairment (Week 96); Study 112 Sub

Changes in CD4 Count from Baseline to Week 96

Median baseline CD4 cell counts: 498 cells/μL for Asian and 652 cells/μL for Non-Asian

* P-values show statistical significance of Week 96 changes from baseline
## Adverse Events through Week 96

### Summary of Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Asian N=34</th>
<th>Non-Asian N=206</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse events in ≥ 10% of participants in either group, % (N)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>3% (1)</td>
<td>16% (32)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>16% (32)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3% (1)</td>
<td>14% (28)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>6% (2)</td>
<td>12% (25)</td>
</tr>
<tr>
<td>Back pain</td>
<td>3% (1)</td>
<td>11% (23)</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>6% (2)</td>
<td>10% (21)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>15% (5)</td>
<td>6% (12)</td>
</tr>
<tr>
<td><strong>Grade 3 or 4 AEs, % (N)</strong></td>
<td>12% (4)</td>
<td>16% (32)</td>
</tr>
<tr>
<td><strong>Discontinuations due to AEs, % (N)</strong></td>
<td>0</td>
<td>6% (12)</td>
</tr>
<tr>
<td><strong>Discontinuations due to renal AEs, N</strong></td>
<td>0</td>
<td>5†</td>
</tr>
</tbody>
</table>

† Details on 5 discontinuations due to declining eGFR were previously reported by Post F, et al. Poster #680, CROI February 2016.

- No proximal renal tubulopathy or Fanconi Syndrome in either group
- No discontinuations due to renal AEs among Asian participants
Estimated GFR by Cockcroft-Gault from BL to Week 96

Median eGFR_{CG} (mL/min)

- **Asian N=34**
- **Non-Asian N=206**

Estimated GFR_{CG} in Asian and non-Asian participants remained stable over 96 weeks after switching to E/C/F/TAF

* P-values show statistical significance of Week 96 changes from baseline
Quantitative Proteinuria at Baseline and Week 96

- After switching to E/C/F/TAF, Asian and non-Asian participants had decreases in all measures of proteinuria with no proximal renal tubulopathy or Fanconi’s syndrome.
- Two Asian participants with a history of TDF-associated Fanconi’s syndrome switched to E/C/F/TAF. Their renal function have remained stable without recurrence of tubulopathy for over two years (Figure 3).

* P-values show statistical significance of Week 96 changes from baseline.

UPCR=Urine Protein to Creatinine Ratio; UACR=Urine Albumin to Creatinine Ratio; β-2M:Cr=β-2-microglobulin to Creatinine Ratio; RBP:Cr=Retinol Binding Protein to Creatinine Ratio.
Cases with Hx of Fanconi’s syndrome during prior TDF use

Case 1: F/56

Relevant Past Medical History
- Stage 3 chronic kidney disease and TDF-associated Fanconi’s syndrome on prior TDF + 3TC + LPV + RTV
- Type 2 DM

Pre-Switch Regimen
- 3TC + EFV + LPV + RTV

Current Regimen
- E/C/F/TAF

Participant remains on E/C/F/TAF with stable renal function

DM=diabetes mellitus; 3TC=lamivudine; LPV=lopinavir; RTV=ritonavir

*Dipstick glucose negative and serum phosphorus in the normal range from baseline to Week 96.
Cases with Hx of Fanconi’s syndrome during prior TDF use

Case 2: M/66

Relevant Past Medical History
- Stage 3 chronic kidney disease and TDF-associated Fanconi’s syndrome on prior TDF + 3TC + EFV
- Type 2 DM (metformin + glipizide); HTN (enalapril)

Pre-Switch Regimen
- ABC + 3TC + EFV

Uncontrolled Diabetes (Day 422 to 758)
- Fasting glucose: 172–269 mg/dL
- Urine dipstick glucose: 1+ to 4+

Current Regimen
E/C/F/TAF

Participant remains on E/C/F/TAF with stable renal function

DM=diabetes mellitus; HTN=hypertension; 3TC=lamivudine; ABC=abacavir; EFV=efavirenz
Switching to E/C/F/TAF resulted in increases in spine and hip BMD in both Asian and non-Asian participants.

* P-values show statistical significance of Week 96 changes from baseline
Conclusions

Switching to E/C/F/TAF in Asian adults (N=34) with renal impairment was effective and safe similar to those of Non-Asian adults. (N=206)

- Maintained HIV suppression (97%) at Week 96
- No resistance emergence
- No discontinuations due to adverse events (inclusive of renal AEs)
- No recurrence of tubulopathy in 2 cases with prior TDF-associated tubulopathy

These data support the safe use of E/C/F/TAF in HIV-suppressed Asian adults with renal impairment.
References


Acknowledgments

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**Study 0112 investigators**


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