Pharmacokinetics of EVG/COBI/FTC/TDF Single Tablet Regimen following Treatment with EFV/FTC/TDF (Atripla®) in Healthy Subjects

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Abstract #O_21
Introduction

EVG/COBI/FTC/TDF Single Tablet Regimen (QUAD STR)
- Once-daily, Integrase Inhibitor-based STR for HIV-1 treatment
- QUAD efficacy and safety profile
  - Robust and durable efficacy in Phase 3 studies vs EFV/FTC/TDF (ATR) or Atazanavir (ATV)/r plus FTC/TDF (Truvada®)\(^1,2\)
  - Lesser incidence of CNS-adverse events (AE), lipid changes (total cholesterol, LDL) versus efavirenz (EFV)
- Switch from ATR to QUAD may be beneficial given EFV AE profile and teratogenicity
- Switch PK considerations
  - EVG metabolized by CYP3A (blocked by COBI), and UGT1A1/3
  - EFV a known inducer of CYP3A and UGT enzymes
  - EFV PK affected by CYP2B6 genetic polymorphisms
- Switch from ATR to RPV/FTC/TDF shown to maintain virologic suppression\(^3\)

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\(^1\) Sax P, et al., CROI 2012
\(^2\) DeJesus E, et al., CROI 2012
\(^3\) Mills T, et al. ICAAC 2011

Presented at the 13th Int. Workshop on Clin. Pharmacology of HIV Pharmacology – 2012, Barcelona Spain
EFV/FTC/TDF to QUAD Switch PK Assessment

Study Design

n = 32; 8 subjects CYP2B6 poor metabolizer genotype (516 G>T (homozygous TT))

• QUAD administered with food; EFV/FTC/TDF administered fasted
• EVG, metabolites GS-9200 (glucuronide) and GS-9202 (oxidative), COBI, FTC, TFV and EFV PK determined

Period 1 (Day 1-7) → 1 week → Period 2 (Day 15-28) → Period 3 Day 29-62 (5 wks) → Follow up 7 days
Demographics and Safety

Demographics

- 32 subjects enrolled; 29 completed study
  - 16 males, 16 females
  - Race: 22 White, 10 Black
  - Mean (range) age: 38 yrs (22 – 45); weight: 74.0 kg (53.4 – 102.7)

- EFV Poor metabolizers
  - 5 male, 3 female; 5 White, 3 Black; 7/8 hispanic/latino ethnicity

Safety

- Two subjects discontinued on EVG/COBI/FTC/TDF
  - One due to flank pain and abdominal pain lower (Grade 3 AE; Period 1)
  - One due to vomiting (Grade 1 AE; Period 3)

- One subject discontinued on EFV/FTC/TDF
  - Rash (Grade 2 AE; Period 2)

- No Grade 4 or other Grade 3 AEs or serious AEs observed
EVG PK pre- and post-ATR Switch to QUAD

- AUC$_{\text{tau}}$ 29% to 37% ↓
- C$_{\text{trough}}$ 55% to 67% ↓

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (90% CI)</th>
<th>QUAD Post-switch 1 week</th>
<th>QUAD Post-switch 2 weeks</th>
<th>GMR (90% CI) Post- vs Pre-switch</th>
<th>GMR (90% CI) Post- vs Pre-switch</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{\text{tau}}$ (ng.hr/ml)</td>
<td>22100 (26)</td>
<td>14300 (36)</td>
<td>15800 (30)</td>
<td>63.1 (59.8, 66.6)</td>
<td>70.8 (67.2, 74.7)</td>
</tr>
<tr>
<td>C$_{\text{max}}$ (ng/ml)</td>
<td>2020 (31)</td>
<td>1720 (45)</td>
<td>1820 (37)</td>
<td>81.5 (76.0, 87.4)</td>
<td>88.7 (82.7, 95.1)</td>
</tr>
<tr>
<td>C$_{\text{tau}}$ (ng/ml)</td>
<td>436 (38)</td>
<td>154 (69)</td>
<td>210 (51)</td>
<td>32.8 (28.3, 38.1)</td>
<td>44.5 (38.6, 51.4)</td>
</tr>
</tbody>
</table>

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COBI PK Pre- and Post-ATR Switch to QUAD

COBI PK post-ATR to QUAD switch
• $AUC_{\tau}$ 11% to 20% ↓

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (%CV)</th>
<th>QUAD Preswitch</th>
<th>QUAD Post-switch</th>
<th>GMR (90% CI) Post- vs Pre-switch</th>
<th>QUAD Post-switch</th>
<th>GMR (90% CI) Post- vs Pre-switch</th>
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<tr>
<td>$AUC_{\tau}$ (ng.hr/ml)</td>
<td>11800 (30)</td>
<td>10100 (45)</td>
<td>79.9 (74.6, 85.7)</td>
<td>10700 (38)</td>
<td>88.8 (82.9, 95.2)</td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>1540 (21)</td>
<td>1410 (32)</td>
<td>88.9 (84.1, 93.9)</td>
<td>1480 (25)</td>
<td>95.3 (90.2, 101)</td>
<td></td>
</tr>
<tr>
<td>$C_{\tau}$ (ng/ml)</td>
<td>46 (97)</td>
<td>23 (121)</td>
<td>51.8 (45.5, 59.0)</td>
<td>31 (120)</td>
<td>65.0 (57.5, 73.5)</td>
<td></td>
</tr>
</tbody>
</table>

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GS-9200 (EVG glucuronide) PK

- GS-9200 $AUC_{tau}$ 47% (1-week) and 37% (2-weeks) higher post-switch
- GS-9202 (metabolite inhibited by COBI) below limit of quantitation (BQL)

### GS-9200 PK Parameter Mean (%CV)

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<tr>
<th>GS-9200 PK Parameter Mean (%CV)</th>
<th>QUAD Preswitch</th>
<th>QUAD Post-switch 1 week</th>
<th>GMR (90% CI) Post- vs Pre-switch</th>
<th>QUAD Post-switch 2 weeks</th>
<th>GMR (90% CI) Post- vs Pre-switch</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AUC_{tau}$ (ng.hr/ml)</td>
<td>1710 (44)</td>
<td>2460 (43)</td>
<td>147 (134, 161)</td>
<td>2260 (37)</td>
<td>137 (125, 150)</td>
</tr>
<tr>
<td>$C_{max}$ (ng/ml)</td>
<td>164 (35)</td>
<td>294 (32)</td>
<td>181 (166, 196)</td>
<td>246 (28)</td>
<td>152 (140, 166)</td>
</tr>
<tr>
<td>$C_{tau}$ (ng/ml)</td>
<td>24 (71)</td>
<td>20 (102)</td>
<td>103 (92.4, 115)</td>
<td>22 (84)</td>
<td>96.9 (87.6, 107)</td>
</tr>
</tbody>
</table>

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EVG $C_{\text{trough}}$ post ATR-switch to QUAD

Days post-switch from ATR to QUAD

Ref. 3 5 7 8 10 12 14 15 18 21 28 35
n=8 n=5 n=2-3 n=1

IC$_{95}$

10 100 1000

EGV C$_{\text{trough}}$ (ng/ml)

BQL: data set to LLOQ/2

median (Q1, Q3); n=29

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EVG $C_{\text{trough}}$ in EFV CYP2B6 Poor Metabolizers

CYP2B6 Poor Metabolizer: 516 G>T, TT homozygous

Days post-ATR switch to QUAD

BQL: set to LLOQ/2

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EFV C_{trough} post-ATR to QUAD Switch

- EFV C_{trough} > IC_{90} for ~3 weeks after discontinuation
- EFV AUC 2-fold higher in PM vs non-PM
- EFV exposures comparable to historical data\(^1\)

<table>
<thead>
<tr>
<th>EFV PK Parameter</th>
<th>All Subjects (N=30)</th>
<th>PM (N=8)</th>
<th>Non-PM (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{AUC}_{\tau}) (ng(\cdot)h/mL)</td>
<td>65600 (54)</td>
<td>111000 (30)</td>
<td>49100 (35)</td>
</tr>
<tr>
<td>(C_{\text{max}}) (ng/mL)</td>
<td>3810 (44)</td>
<td>5860 (30)</td>
<td>3070 (27)</td>
</tr>
<tr>
<td>(C_{\tau}) (ng/mL)</td>
<td>2260 (62)</td>
<td>4050 (31)</td>
<td>1610 (44)</td>
</tr>
</tbody>
</table>

\(^1\) SUSTIVA USPI
EFV IC_{90}: Hamatake et al.. CROI 2008
EFV and EVG PK post-ATR to QUAD Switch

- Median EFV C_{trough} > IC_{90} through 4 weeks post ATR switch
- Median EVG C_{trough} post ATR-switch
  - 3-fold and 4-fold > IC_{95} at 1- and 2-weeks
  - 7 to 8-fold > IC_{95} by 5 weeks

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Time course of EFV and EVG $C_{\text{trough}}$ Change

- **3 Days Post Switch**
  - EFV < IC$_{95}$
  - EVG < IC$_{95}$

- **6 Days**
  - EFV < IC$_{90}$
  - EVG < IC$_{95}$

- **15 Days**
  - EFV post-Switch
  - EVG > IC$_{95}$
  - EFV > IC$_{90}$

- **35 Days**
  - EFV post-Switch
  - EVG < IC$_{95}$

**FTC and TFV Pharmacokinetics**

<table>
<thead>
<tr>
<th>FTC PK Parameter</th>
<th>EVG/COBI/FTC/TDF Day 7</th>
<th>EFV/FTC/TDF Day 28</th>
<th>EVG/COBI/FTC/TDF Day 35</th>
<th>EVG/COBI/FTC/TDF Day 42</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AUC_{\text{tau}}$ (ng·h/mL) Mean (%CV)</td>
<td>12700 (20)</td>
<td>10600 (21)</td>
<td>11800 (21)</td>
<td>12200 (22)</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL) Mean (%CV)</td>
<td>2050 (19)</td>
<td>2050 (24)</td>
<td>1910 (21)</td>
<td>1900 (22)</td>
</tr>
<tr>
<td>$C_{\text{tau}}$ (ng/mL) Mean (%CV)</td>
<td>102 (29)</td>
<td>69 (29)</td>
<td>96 (31)</td>
<td>101 (30)</td>
</tr>
<tr>
<td>$T_{1/2}$ (h) Median (Q1, Q3)</td>
<td>8.19 (6.68, 8.71)</td>
<td>8.48 (7.62, 10.1)</td>
<td>8.35 (7.73, 9.46)</td>
<td>8.53 (7.63, 9.20)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TFV PK Parameter</th>
<th>EVG/COBI/FTC/TDF Day 7</th>
<th>EFV/FTC/TDF Day 28</th>
<th>EVG/COBI/FTC/TDF Day 35</th>
<th>EVG/COBI/FTC/TDF Day 42</th>
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<tr>
<td>$AUC_{\text{tau}}$ (ng·h/mL) Mean (%CV)</td>
<td>3940 (20)</td>
<td>2280 (19)</td>
<td>3520 (24)</td>
<td>3470 (23)</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL) Mean (%CV)</td>
<td>442 (24)</td>
<td>314 (25)</td>
<td>403 (35)</td>
<td>383 (29)</td>
</tr>
<tr>
<td>$C_{\text{tau}}$ (ng/mL) Mean (%CV)</td>
<td>79 (25)</td>
<td>46 (21)</td>
<td>73 (29)</td>
<td>71 (26)</td>
</tr>
<tr>
<td>$T_{1/2}$ (h) Median (Q1, Q3)</td>
<td>14.4 (12.7, 15.9)</td>
<td>15.1 (12.6, 17.4)</td>
<td>14.6 (13.9, 16.1)</td>
<td>14.7 (13.2, 15.5)</td>
</tr>
</tbody>
</table>

- FTC and TFV PK comparable across treatments
Conclusions

• Following switch from EFV/FTC/TDF to QUAD
  – EVG exposures lower, primarily due to UGT induction by EFV
    • Effect more pronounced in EFV poor metabolizers
  – COBI AUC comparable to reference ~ 1 week post switch
  – TFV, FTC PK unaffected

• EVG and/or EFV exposure range associated with potent antiviral activity

• A Phase 3b study evaluating this regimen-switch in HIV-1 patients ongoing