Efficacy, safety and pharmacokinetic results of an ongoing international phase 3 study comparing elvitegravir/cobicistat/emtricitabine/tenofovir DF (Quad) with ritonavir-boosted atazanavir plus emtricitabine/tenofovir DF in treatment naïve HIV-1 infected subjects at 48 weeks

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Background

- Elvitegravir (EVG)/ cobicistat (COBI)/emtricitabine (FTC)/tenofovir DF (TDF) has been coformulated as the first integrase inhibitor-containing single-tablet regimen “Quad”
  - EVG is a potent once-daily HIV integrase inhibitor (150 mg)
  - COBI is a pharmacoenhancer lacking anti-HIV activity (150 mg)
  - FTC/TDF is a preferred first line NRTI combination (200 mg/300 mg)\(^1\)\(^-\)\(^3\)
- Recommended initial HIV regimen\(^1\)\(^-\)\(^3\)
  - Efavirenz (EFV)/FTC/TDF
  - Atazanavir/ritonavir (ATV/r) + FTC/TDF
  - Darunavir/ritonavir (DRV/r) + FTC/TDF
  - Raltegravir (RAL) + FTC/TDF

\(^1\) [http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf](http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf)
\(^2\) Thompson et al, JAMA, 2010;304(3):321-333
\(^3\) EACS Guidelines for the Clinical Management and Treatment of HIV-Infected Adults in Europe. Version 6.0 - October 2011

Study Design

- Randomized, double-blind, double-dummy, active-controlled, non-inferiority study
- Eligibility criteria
  - Treatment naïve
  - Genotypic sensitivity to ATV, FTC, and TDF
  - HIV-1 RNA > 5,000 c/mL
  - eGFR ≥ 70 mL/min (Cockcroft-Gault equation)
- Primary endpoint
  - HIV-1 RNA < 50 c/mL at Week 48 (Amplicor HIV-1 Monitor Test, version 1.5)
  - FDA snapshot algorithm
  - Prespecified primary analysis of non-inferiority margin 12%
- Exploratory analysis of PK/PD relationship

Study Design
236-0103

- Treatment naive (N = 700 planned)
  - International
  - Randomized 1:1
  - Stratification by HIV-1 RNA (>100,000 c/mL)

Quad QD
ATV/r+FTC/TDF Placebo QD

Quad Placebo QD
ATV/r + FTC/TDF QD

Primary Endpoint: Proportion with HIV-1 RNA < 50 c/mL at Week 48
- FDA snapshot analysis, 12% non-inferiority margin
- HIV-1 RNA: Amplicor HIV-1 Monitor Test, version 1.5

Conducted in parallel with Study 236-0102 comparing Quad to EFV/FTC/TDF

Baseline Characteristics
236-0103

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Quad (n=353)</th>
<th>ATV/r + FTC/TDF (n=355)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), Mean</td>
<td>38</td>
<td>39</td>
</tr>
<tr>
<td>Male</td>
<td>92%</td>
<td>89%</td>
</tr>
<tr>
<td>Non-White</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black or African Descent</td>
<td>29%</td>
<td>22%</td>
</tr>
<tr>
<td>Asymptomatic HIV Infection</td>
<td>81%</td>
<td>83%</td>
</tr>
<tr>
<td>HBV – HCV Seropositive</td>
<td>1% – 5%</td>
<td>2% – 3%</td>
</tr>
<tr>
<td>HIV-1 RNA (log_{10} c/mL), Median</td>
<td>4.88</td>
<td>4.86</td>
</tr>
<tr>
<td>HIV-1 RNA &gt; 100,000 c/mL</td>
<td>43%</td>
<td>40%</td>
</tr>
<tr>
<td>CD4 count (cells/mm³), Mean</td>
<td>364</td>
<td>375</td>
</tr>
<tr>
<td>&lt; 200</td>
<td>15%</td>
<td>11%</td>
</tr>
<tr>
<td>201 to ≤ 350</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td>351 to ≤ 500</td>
<td>35%</td>
<td>34%</td>
</tr>
<tr>
<td>&gt; 500</td>
<td>16%</td>
<td>20%</td>
</tr>
</tbody>
</table>
Subject Disposition Through Week 48  
236-0103

<table>
<thead>
<tr>
<th>Screened (N = 1017)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QUAD Randomized and Treated (N = 353)</td>
</tr>
<tr>
<td>91% Continuing (N = 320)</td>
</tr>
<tr>
<td>9% Discontinued (N = 33)</td>
</tr>
<tr>
<td>Adverse event</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Lack of efficacy</td>
</tr>
<tr>
<td>Investigator’s discretion</td>
</tr>
<tr>
<td>Withdrew consent</td>
</tr>
<tr>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>Subject non-compliance</td>
</tr>
<tr>
<td>Protocol violation</td>
</tr>
</tbody>
</table>

| ATV/r + FTC/TDF Randomized and Treated (N = 355) |
| 89% Continuing (N = 315) |
| 11% Discontinued (N = 40) |
| Adverse event | 16 |
| Lack of efficacy | 1 |
| Investigator Discretion | 3 |
| Withdrew consent | 6 |
| Lost to follow-up | 7 |
| Subject non-compliance | 5 |

91% Continuing (N = 320)  
9% Discontinued (N = 33)  

Primary Endpoint: HIV-1 RNA < 50 c/mL  
236-0103

QUAD was non-inferior to ATV/r + FTC/TDF at Week 48

95% CI for Difference

Favors ATV/r + FTC/TDF

Favors Quad

-1.9 3.0 7.8

Virologic Success  
Virologic Non-Suppression  
No W48 Data


Virologic Success by Subgroups

OVERALL
- Age
  - <40 years
  - ≥40 years
- Sex
  - Male
  - Female
- Race
  - White
  - Non-white
- Baseline HIV-1 RNA Level
  - ≤100,000 c/mL
  - >100,000 c/mL
- Baseline CD4 Count
  - ≤350 cells/mm³
  - >350 cells/mm³
- Study Drug Adherence
  - <95%
  - ≥95%

Differences in Percentages (95% CI)

Favors ATV/r + FTC/TDF
Favors QUAD

FDA snapshot at Week 48


HIV-1 RNA < 50 c/mL through Week 48 (M=F)

Quad: 92%
ATV/r + FTC/TDF: 88%
Diff: 3.5% (95% CI: -1.0 to 8.0)

Subjects with HIV-1 RNA <50 c/mL (%)

BL 2 4 8 12 16 24 32 40 48

Quad (n=): 353 353 353 353 353 353 353 353 353
ATV/r (n=): 355 355 355 355 355 355 355 355 355

Efficacy in Baseline HIV-1 RNA and CD4 Subgroups
236-0103

Virologic Success (%)

≤100,000 c/mL >100,000 c/mL CD4≤350 CD4>350
QUAD ATV/r + FTC/TDF

Efficacy by Baseline Demographics
236-0103

Virologic Success (%)

<40 ≥40 Male Female White Non-white
QUAD ATV/r + FTC/TDF

Mean Change from Baseline in CD4 Cells (cells/mm$^3$) 236-0103

Integrase, PI, NRTI Resistance Through Week 48 236-0103

<table>
<thead>
<tr>
<th>Subjects Analyzed for Resistance$^a$, n (%)</th>
<th>Quad (n=353)</th>
<th>ATV/r + FTC/TDF (n=355)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with Resistance to ARV Regimen, n (%)</td>
<td>12 (3)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Any Primary Integrase-R, n</td>
<td>5 (1)</td>
<td>0</td>
</tr>
<tr>
<td>E92Q</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>T66I</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Q148R</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>N155H</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Any Primary PI-R, n</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Any Primary NRTI-R, n</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>M184V/I</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>K65R</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$ Subjects who experienced either suboptimal virologic response (two consecutive visits with HIV-1 RNA ≥50 c/mL and <1 log$_{10}$ below baseline after Week 8), virologic rebound (two consecutive visits with HIV-1 RNA either ≥400 c/mL after achieving HIV-1 RNA <50, or >1 log$_{10}$ increase from nadir), or had HIV-1 RNA ≥400 c/mL at their last visit.

Virologic Success by EVG Exposure – Quad 236-0103

<table>
<thead>
<tr>
<th>EVG C_{trough} Quartile</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (ng/mL)</td>
<td>172.3</td>
<td>323.0</td>
<td>515.8</td>
<td>880.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Virologic Success (%)</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
</tr>
</thead>
<tbody>
<tr>
<td>96</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>94</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>98</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PK/PD Analysis Set, n=192


Summary of Adverse Events (AE) 236-0103

<table>
<thead>
<tr>
<th></th>
<th>Quad (n=353)</th>
<th>ATV/r + FTC/TDF (n=355)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 or 4 AE</td>
<td>13%</td>
<td>14%</td>
</tr>
<tr>
<td>Drug-related AE</td>
<td>45%</td>
<td>57%</td>
</tr>
<tr>
<td>SAE</td>
<td>7%</td>
<td>9%</td>
</tr>
<tr>
<td>Drug-related SAE</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>AE leading to DC of study drug</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Death, (n)</td>
<td>0</td>
<td>1% (3)^a</td>
</tr>
</tbody>
</table>

*Causes of death included septic shock, Pneumocystis jiroveci pneumonia, and cardiopulmonary arrest after overdose of recreational drugs.

## Common Adverse Events (All Grades)

### 236-0103

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Quad (n=353)</th>
<th>ATV/r + FTC/TDF (n=355)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>22%</td>
<td>27%</td>
</tr>
<tr>
<td>Nausea</td>
<td>20%</td>
<td>19%</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>15%</td>
<td>16%</td>
</tr>
<tr>
<td>Headache</td>
<td>15%</td>
<td>12%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14%</td>
<td>13%</td>
</tr>
<tr>
<td>Ocular icterus</td>
<td>1%</td>
<td>14%</td>
</tr>
</tbody>
</table>

* > 10% in either treatment group


## Common Adverse Events Leading to DC

### 236-0103

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Quad (n=353)</th>
<th>ATV/r + FTC/TDF (n=355)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Nausea</td>
<td>&lt;1%</td>
<td>1%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>&lt;1%</td>
<td>1%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>&lt;1%</td>
<td>1%</td>
</tr>
<tr>
<td>Jaundice</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Drug Eruption</td>
<td>0%</td>
<td>1%</td>
</tr>
</tbody>
</table>

*At least 2 subjects in either treatment group

*One subject from each treatment group discontinued due to renal adverse event; one subject in Quad group due to blood creatinine increased, one subject in ATV/r+FTC/TDF group due to nephropathy toxic.

Grade 3 and 4 Laboratory Abnormalities
236-0103

<table>
<thead>
<tr>
<th>Grade 3 or 4 Labs⁵</th>
<th>Quad (n=353)</th>
<th>ATV/r + FTC/TDF (n=355)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatine Kinase</td>
<td>6%</td>
<td>7%</td>
</tr>
<tr>
<td>Hematuria</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>AST</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Amylase</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>ALT</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>1%</td>
<td>58%</td>
</tr>
</tbody>
</table>

*At least 2% in either treatment group


Change from Baseline in Serum Creatinine¹
236-0103

- Increase in Cr consistent with MATE-1 inhibition of Cr secretion by RTV & COBI²

Change from Baseline in Fasting Lipids at Week 48
236-0103

|                  | QUAD (n=54) | ATV/r + FTC/TDF (n=66) | \( P \)  
|------------------|-------------|------------------------|------
| Total Cholesterol| 0.26        | 0.28                   | 0.27 |
| LDL              | 0.21        | 0.13                   | 0.13 |
| HDL              | 0.28        | 0.15                   | 0.13 |
| Triglyceride     | 0.26        | 0.09                   | 0.09 |


Bone Mineral Density at Week 48
236-0103

|                  | QUAD (n=54) | ATV/r + FTC/TDF (n=66) | \( P \)  
|------------------|-------------|------------------------|------
| Fracture events, (n) | 1% (3)      | 2% (6)                 | 0.51 |

Conclusions
236-0103

• High and comparable efficacy in Quad and ATV/r + FTC/TDF
  – Robust, durable, and consistent efficacy on all endpoints
  – High virologic suppression rates in all subgroups, including those with baseline HIV-1 RNA > 100,000 c/mL

• Quad was well-tolerated
  – Similar low rates of treatment discontinuation
  – Smaller increases in triglyceride in Quad
  – Discontinuations due to renal adverse events were 0.3% in ATV/r + FTC/TDF and 0.3% in Quad

Summary

• Full results of studies 236-0102 and 236-0103 submitted for peer-reviewed publication

• Health authority filings submitted in Europe, Australia, Canada, Switzerland, and the U.S. (FDA decision expected by August 27, 2012)
Study 236-0103 Investigators

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Elliott, Julian
Fritschi, Robert
Morey, Richard
Schmedt, Tina
Smith, Don

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Sampaio, Pedro

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Blaschki, Anders

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Norsdskaer, Supaporn

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Fife, Thomas
Fiala, Douglas
Flaxin, Jason
Furman, Stephen
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Gaffney, Joseph
Gege, Zarkungo, Patsa
Goebel, Robert
Hald, David
Hardy, Kevin
Horton, James
Hui, Gregory
Jones, Thomas
Khan, Homayoon
Kweek, Collin
Klein, Daniel
Kozai, Michael
LaMarca, Anthony
Lichtenstein, Kenneth
Lucas, Chris
Matsukawa, Osaka
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McCord, Cheryl
McCowan, Joseph
Michaels, Michael
McIvor, Gavin
Midsæter, Dorte
Mills, Anthony
Montanaro, Javier
Moxon, Karen
Mouza, Ronald
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Palmer, Philip
Parks, David
Parr, Gerald
Pollard, Richard
Preble, David
Ramgopal, Mall
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Reinhard, Jayaram
Rexing, Keith
Richter, Gary
Robbins, William
Roberts, Alison
Rodriguez, Jorge
Rouwendal, Peter
Sakr, Sonia
 Schneider, Stefan
Schneider, Sharon
Seltzer, Anna
Seidman, Michael
Shallit, Peter
Shellock, David
Shikuma, Cecilia
Shin, Joon
Sokol-Anderson, Marcia
Squires, Kathleen
Stephens, Jeffrey
Thomson, Melanie
Towner, William
Varghese, Thomas
Ward Douglas
Wheat, David
Wilk, Almree
Wills, Todd
Woolf, Michael
Yang, Bienvenido
Yuen, Benjamin
Zinczenko, Andrew
Zunec, Christine

Chin C, et al. BHIVA 2012, Birmingham, Oral 026