Pharmacokinetic Interaction Between Norgestimate/Ethinyl Estradiol and EVG/COBI/FTC/TDF Single Tablet Regimen

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Introduction

• Elvitegravir (EVG) is an HIV-1 integrase inhibitor
• Cobicistat (COBI) is a potent, mechanism-based inhibitor of Cytochrome P450 3A (CYP3A)
• EVG and COBI have been co-formulated with NRTI backbone FTC/TDF into a single tablet (EVG/COBI/FTC/TDF: FDC) for HIV-1 treatment in treatment-naïve patients
  – FDC is presently being evaluated in Phase 3
• Ortho Tri-Cyclen Lo® is a combination oral contraceptive containing progestational and estrogenic compounds
  – Norgestimate: 0.180 mg, 0.215 mg and 0.250 mg
  – Ethinyl Estradiol: 25 µg
• Drug interactions between hormonal contraceptives and antivirals have been documented 1,2,3,4
Objectives

Primary Objective

- To determine the effect of EVG/COBI/FTC/TDF on the pharmacokinetics of Ortho Tri-Cyclen® Lo

Secondary Objective

- To evaluate the safety and tolerability of administration of EVG/COBI/FTC/TDF and Ortho Tri-Cyclen® Lo
Methods

- Open-label, fixed-sequence, two-parts study
  - Part A (lead-in): required for subjects not taking Ortho-Tri-Cyclen Lo®
  - Part B (main study): enrolled subjects who had taken Ortho-Tri-Cyclen Lo® for at least 1 full month prior to Day 1
Methods

• All treatments administered with a standard meal
  – 400 kcal and 13 grams of fat
• In Part B, PK samples collected over 24 hours on Day 21 of each cycle for EE, NGMN (NGM metabolite), and on Day 21 of the second cycle for EVG and COBI
• Plasma concentrations of EVG, COBI, EE and NGMN measured using LC/MS/MS
• PK parameters calculated by noncompartmental analysis (WinNonlin 5.3, Pharsight)
• Geometric least-squares mean ratios and 90% confidence intervals (Test: Reference) estimated using ANOVA for AUC_{inf}, and C_{max} of the EE and NGMN using 80-125% bounds
• EVG and COBI exposures descriptively compared to historical data
• Exploratory analysis of PD parameters progesterone, FSH and LH was carried out in both cycles
Results

Demographics
• 21 subjects enrolled
  – 19 enrolled in Part A; 16 subjects enrolled in Part B from Part A
  – 2 enrolled in Part B directly
  – 15 subjects completed the study
• Mean age (range): 30 years (19, 45)
• Mean weight (range): 64.4 kg (48.5, 83.3)
• Race:
  – White: 66.7%
  – Black: 19.0%
  – Asian: 9.5%
  – American Indian or Alaska Native: 4.8%
• Ethnicity
  – Hispanic/Latino: 33.3%
  – Non-Hispanic/Latino: 66.7%
Results

Safety

- No Grade 3 or 4 AE or SAE reported in the study
- All treatment-emergent AEs were Grade 1 or Grade 2
- No discontinuations due to AE

<table>
<thead>
<tr>
<th>Number (%) of Subjects with AE by System Organ Class and Preferred Term</th>
<th>Lead-in NGM/EE (N=19)</th>
<th>NGM/EE (N=18)</th>
<th>NGM/EE + FDC (N=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Treatment-Emergent AE</td>
<td>4 (21.1%)</td>
<td>9 (50.0 %)</td>
<td>15 (93.8 %)</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
<td>14 (87.5%)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>0</td>
<td>2 (11.1%)</td>
<td>13 (81.3%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>2 (11.1%)</td>
<td>6 (37.5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>5 (31.3%)</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td>3 (15.8%)</td>
<td>5 (27.8%)</td>
<td>12 (75.0%)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (10.5%)</td>
<td>3 (16.7%)</td>
<td>8 (50.0%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (5.3%)</td>
<td>2 (11.1%)</td>
<td>3 (18.8%)</td>
</tr>
</tbody>
</table>

Presented at the 12th Int. Workshop on Clin. Pharmacology of HIV Therapy, 13-15 April 2011, Miami, Fl, USA
NGMN Pharmacokinetics

- NGMN exposure is increased with FDC plus NGM/EE versus NGM/EE alone
  - Increases in NGMN have been previously documented\(^1\)
  - Potential effect on NGMN clearance since formation is esterase mediated\(^5,6\)

\(n = 15, \text{ mean } (\%CV); \ FDC: \text{ EVG/COBI/FTC/TDF}\)

<table>
<thead>
<tr>
<th>NGMN Parameter</th>
<th>NGM/EE</th>
<th>NGM/EE + FDC</th>
<th>GMR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC\text{(t_\tau)} (pg·hr/ml)</td>
<td>21400 (17.1)</td>
<td>48300 (17.7)</td>
<td>226 (215, 237)</td>
</tr>
<tr>
<td>(C_{\text{max}}) (pg/ml)</td>
<td>2150 (15.4)</td>
<td>4460 (14.5)</td>
<td>209 (200, 217)</td>
</tr>
<tr>
<td>(C_{\tau}) (pg/ml)</td>
<td>510 (23.1)</td>
<td>1370 (24.7)</td>
<td>267 (243, 292)</td>
</tr>
</tbody>
</table>
EE Pharmacokinetics

- EE AUC\textsubscript{\text{tau}} and C\textsubscript{\text{tau}} are decreased with FDC plus NGM/EE versus NGM/EE alone
  - Decreases in EE exposures observed with PI/r\textsuperscript{1,2,4}
  - EE is metabolized by sulfation, oxidation and glucuronidation\textsuperscript{7}
  - EVG is a modest PXR activator; COBI has minimal effects on PXR (data on file)

mean ± SD, n = 15

<table>
<thead>
<tr>
<th>EE Parameter</th>
<th>NGM/EE</th>
<th>NGM/EE + FDC</th>
<th>GMR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC\textsubscript{\text{tau}} (pg·hr/ml)</td>
<td>1050 (32.1)</td>
<td>775 (26.1)</td>
<td>75.0 (69.4, 81.0)</td>
</tr>
<tr>
<td>C\textsubscript{\text{max}} (pg/ml)</td>
<td>106 (30.7)</td>
<td>98.6 (27.8)</td>
<td>94.1 (85.5, 104)</td>
</tr>
<tr>
<td>C\textsubscript{\text{tau}} (pg/ml)</td>
<td>25.8 (78.9)</td>
<td>13.7 (57.8)</td>
<td>56.5 (51.9, 61.5)</td>
</tr>
</tbody>
</table>

n = 15, mean (%CV); FDC: EVG/COBI/FTC/TDF

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EVG and COBI Pharmacokinetics

- EVG and COBI exposures are within the range of those reported in previous studies

<table>
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<th>Parameter</th>
<th>EVG</th>
<th>COBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AUC_{\text{tau}}$ (ng·hr/ml)</td>
<td>27000 (23.9)</td>
<td>10700 (29.5)</td>
</tr>
<tr>
<td>$C_{\text{tau}}$ (ng/ml)</td>
<td>415 (40.5)</td>
<td>25.6 (74.2)</td>
</tr>
<tr>
<td>$C_{\max}$ (ng/ml)</td>
<td>2700 (23.7)</td>
<td>1560 (19.7)</td>
</tr>
</tbody>
</table>

$n = 15$, mean (%CV)
Exploratory Pharmacodynamics

- Low endogenous progesterone
- Similar low FSH and LH in both treatments

Bars represent median (Q1, Q3)
Conclusions

• Study treatments were generally well-tolerated

• Increases in NGMN AUC\textsubscript{tau}, C\textsubscript{max} C\textsubscript{tau} with NGM/EE plus FDC versus NGM/EE alone

• EE AUC\textsubscript{tau} and C\textsubscript{tau} decreases with NGM/EE plus FDC versus NGM/EE alone

• EVG and COBI exposures were within the range of those reported in previous studies

OC is to contain 30 µg of EE if administered with FDC to assure adequate contraception
References


