Bioavailability of two fixed-dose combination formulations of darunavir/cobicistat 800/150mg compared with darunavir 800mg and ritonavir 100mg co-administered as single agents

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**Introduction**

- **DRV** is a HIV-1 protease inhibitor approved for treatment-naïve and -experienced patients
  - boosted with low-dose RTV (rtv)
    - 800/100mg qd
    - 600/100mg bid

- **COBI (GS-9350)** is a potent, mechanism-based inhibitor of CYP3A, and compared with RTV showed
  - no antiviral activity
  - greater CYP450 enzyme inhibition specificity
  - less induction liability
  - improved physicochemical properties – amenable for co-formulation

DRV = darunavir; RTV = ritonavir; COBI = cobicistat
Multiple-dose pharmacokinetics of DRV 800mg with COBI 150mg (as single agents) versus RTV 100mg: GS-US-216-0115

<table>
<thead>
<tr>
<th></th>
<th>DRV + COBI</th>
<th>DRV + RTV</th>
<th>GMR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{\tau} (ng\cdot h/mL)</td>
<td>81,100 (31.0)</td>
<td>80,000 (34.0)</td>
<td>102 (97.4–106)</td>
</tr>
<tr>
<td>C_{\text{max}} (ng/mL)</td>
<td>7,740 (21.8)</td>
<td>7,460 (20.3)</td>
<td>103 (100–106)</td>
</tr>
<tr>
<td>C_{\tau} (ng/mL)</td>
<td>1,330 (66.8)</td>
<td>1,870 (83.3)</td>
<td>69.4 (59.0–81.7)</td>
</tr>
<tr>
<td>C_{0h} (ng/mL)</td>
<td>2,400 (50.7)</td>
<td>2,480 (34.3)</td>
<td>89.4 (80.4–99.4)</td>
</tr>
</tbody>
</table>
DRV tablet formulations

• Direct compression

• Dimensions (mm)
  – 75mg: 9.2 x 4.4 x 4.1
  – 150mg: 13.7 x 6.9 x 4.3
  – 300mg: 17.3 x 8.6 x 5.5
  – 400mg: 19.1 x 9.5 x 5.7
  – 600mg: 21.1 x 10.5 x 7.2

• Wet granulation process

• Dimensions (mm)
  – 800mg: 20.0 x 11.75 x 8.0
  – 800/150mg: 23.5 x 11.75 x 8.0

Presented at the 13th Int. Workshop on Clin. Pharmacology of HIV Pharmacology – 2012, Barcelona Spain
TMC114IFD1001: objectives

• Primary
  – compare, under fed and steady-state conditions, the relative oral bioavailability of two FDC formulation concepts of DRV/COBI 800/150mg (G003 and G004) to that of DRV/r 800/100mg co-administered as single agents

• Secondary
  – evaluate the short-term safety and tolerability of DRV/COBI and DRV/r in healthy volunteers

FDC = fixed-dose combination
TMC114IFD1001: study design

- Thirty-six healthy volunteers

Treatment A
- DRV/r 800/100mg qd
- 10 days
- ≥7 days washout

Treatment B
- DRV/COBI 800/150mg qd
  - G003
  - 10 days

Treatment C
- DRV/COBI 800/150mg qd
  - G004
  - 10 days

7-day follow-up for safety

△ DRV and RTV pharmacokinetics over 24 hours determined on Day 10

▲ DRV and COBI pharmacokinetics over 24 hours determined on Day 10

Plasma concentrations collected predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 9, 12, 16, 20 and 24 hours postdose

Safety and tolerability assessments were performed throughout the trial until at least 7 days after the last trial medication intake
Multiple-dose pharmacokinetics of DRV 800mg with COBI 150mg (FDC) versus RTV 100mg

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Multiple-dose pharmacokinetics and statistical analyses of DRV 800mg with COBI 150mg (FDC) versus RTV 100mg

<table>
<thead>
<tr>
<th>DRV pharmacokinetics (mean ± SD)</th>
<th>DRV/r 800/100mg qd, (n=32)</th>
<th>DRV/COBI 800/150mg qd as FDC (G003) (n=33)</th>
<th>DRV/COBI 800/150mg qd as FDC (G004) (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{0h}$, ng/mL</td>
<td>2,015 ± 852.3</td>
<td>1,504 ± 1,114</td>
<td>1,478 ± 933.8</td>
</tr>
<tr>
<td>$C_{24h}$, ng/mL</td>
<td>1,928 ± 717.9</td>
<td>1,493 ± 924.2</td>
<td>1,566 ± 885.1</td>
</tr>
<tr>
<td>$C_{min}$, ng/mL</td>
<td>1,506 ± 630.1</td>
<td>1,146 ± 783.3</td>
<td>1,224 ± 680.6</td>
</tr>
<tr>
<td>$C_{max}$, ng/mL</td>
<td>6,997 ± 1508</td>
<td>6,615 ± 1299</td>
<td>6,917 ± 1394</td>
</tr>
<tr>
<td>$AUC_{24h}$, ng•h/mL</td>
<td>78,090 ± 20,640</td>
<td>74,080 ± 19780</td>
<td>76,490 ± 20900</td>
</tr>
</tbody>
</table>

LS means (90% CI)

| $C_{0h}$, ng/mL | 0.65 (0.55-0.076) | 0.68 (0.57-0.80) |
| $C_{min}$, ng/mL | 0.69 (0.60–0.81) | 0.74 (0.63–0.86) |
| $C_{max}$, ng/mL | 0.97 (0.92–1.01) | 1.00 (0.96–1.04) |
| $AUC_{24h}$, ng•h/mL | 0.97 (0.92–1.02) | 0.99 (0.94–1.04) |

SD=standard deviation; LS = least squares

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Multiple-dose pharmacokinetics of COBI 150mg with DRV 800mg (FDC)

Plasma concentration of COBI (ng/mL) (mean ± SD)

Time (hours)

DRV/COBI 800/150mg qd as FDC (G003) (n=33)
DRV/COBI 800/150mg qd as FDC (G004) (n=33)

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Conclusions (1 of 2)

- Both DRV/COBI fixed-dose combination formulations achieved comparable values for $C_{\text{max}}$ and $\text{AUC}_{24\text{h}}$
- DRV $C_{\text{min}}$ and $C_{0\text{h}}$ was lower when combined with COBI than with RTV
  - this is not considered clinically relevant
    - no apparent relationship between DRV pharmacokinetics and antiviral activity/safety
    - DRV $C_{0\text{h}} < 550\text{ng/mL}$ not associated with loss of antiviral activity (based on limited data available)
    - modeling and simulation of DRV $C_{0\text{h}}$ suggests no decrease in antiviral activity with up to 50% reduction in DRV $C_{0\text{h}}$
- Results consistent with Gilead GS-US-216-0115 trial
Conclusions (2 of 2)

• Short-term administration of DRV/r or DRV/COBI was generally safe and well tolerated

• Both G003 and G004 appear to be suitable candidates for further development, and, on this basis, G004 was selected for further development
  – currently used formulation is G006, which is G004 with a pink coating
Acknowledgements and disclosures

• We would like to express gratitude to
  – Gilead Sciences, Inc.
  – the volunteers for their participation and support during the study
  – Janssen R&D team members, in particular Yaswant Dayaram and Eric Wong for their input into this presentation

• This study was sponsored by Janssen R&D

• Assistance in incorporating author comments was provided by Jackie Phillipson from Gardiner-Caldwell Communications; this support was funded by Janssen

• The authors have the following conflicts of interest to declare: TNK, MO, MT, KI, TVDC, VH, FT and RMWH are all full-time employees of Janssen