The effect of telaprevir on the pharmacokinetics of CYP3A and P-gp substrates

Varun Garg, PhD

On behalf of Drs. N Adda, K Alves, G Chandorkar, J-E Lee, X Luo, F Smith, R van Heeswijk, and Y Yang
Author Disclosures

Drs. Adda, Alves, Garg, Luo, and Smith are employees and stockowners of Vertex Pharmaceuticals Incorporated.

Dr. van Heeswijk is an employee of Tibotec BVBA.

Dr. Chandorkar was an employee of Vertex at the time this work was performed. He is currently employed by Cubist Pharmaceuticals.

Dr. Yang was an employee of Vertex at the time this work was performed. He is currently employed by Acceleron Pharmaceuticals.

Dr. Lee was an employee of Vertex at the time this work was performed. She is currently employed at the U.S. FDA. The content of this work does not necessarily reflect any position of the U.S. FDA.
Introduction

• *In vitro* studies suggest that telaprevir is a substrate of P-glycoprotein (P-gp) and a substrate and inhibitor of CYP3A (IC$_{50}$ = 3.3 µM for midazolam and 18.9 µM for testosterone)

• Commonly used medications that are substrates of CYP3A:
  – Midazolam: Model substrate of CYP3A$^1$
  – Ethinyl estradiol (EE) and norethindrone (NE): components of oral contraceptives$^{2-3}$
  – Zolpidem and alprazolam: sedatives$^{4,5}$
  – Amlodopine: Calcium channel blocker$^6$
  – Atorvastatin: lipid-lowering agent$^6$

• Digoxin: Model substrate of P-gp$^1$

The Effect of telaprevir on the pharmacokinetics of midazolam and digoxin

V Garg¹, G Chandorkar¹, F Smith¹, K Alves¹, R van Heeswijk²

¹Vertex Pharmaceuticals Incorporated
²Tibotec BVBA
Study Design: Midazolam and Digoxin

- Sequential design
- 24 healthy male or female volunteers

Day 1 - D3

<table>
<thead>
<tr>
<th>Day 1</th>
<th>D3</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 mg IV midazolam</td>
<td>2.0 mg PO midazolam</td>
</tr>
<tr>
<td>0.5 mg PO midazolam</td>
<td></td>
</tr>
</tbody>
</table>

D8 - D23

- Telaprevir 750 mg q8h

<table>
<thead>
<tr>
<th>D8</th>
<th>D17</th>
<th>D19</th>
<th>D23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telaprevir 750 mg q8h</td>
<td>0.5 mg IV midazolam</td>
<td>2.0 mg PO midazolam</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.5 mg PO digoxin</td>
<td></td>
<td>0.5 mg PO digoxin</td>
</tr>
</tbody>
</table>
Effect on Midazolam (>5-fold for Oral)\(^1\)  
Suggests that Telaprevir is a Strong Inhibitor of CYP3A

### Intravenous midazolam

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Without telaprevir</th>
<th>With telaprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(_{\text{max}})</td>
<td>1.02 (0.8; 1.31)</td>
<td>2.86 (2.52; 3.25)</td>
</tr>
<tr>
<td>AUC</td>
<td>3.40 (3.04; 3.79)</td>
<td>8.96 (7.75; 10.35)</td>
</tr>
</tbody>
</table>

### Oral midazolam

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Without telaprevir</th>
<th>With telaprevir</th>
</tr>
</thead>
<tbody>
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\(^1\) FDA Draft Guidance for Industry. Drug Interaction Studies- Study Design, Data Analysis, and Implications for Dosing and Labeling; 2006
Effect on Digoxin Suggests that Telaprevir inhibits P-gp *in vivo*

**GLS Mean Ratio (90% CI)**
- $C_{\text{max}}$: 1.50 (1.36; 1.65)
- AUC: 1.85 (1.70; 2.00)

Digoxin renal clearance unaffected

Presented at the 6th International Workshop on Clinical Pharmacology of Hepatitis Therapy, 22-23 June 2011, Cambridge, USA
The effect of telaprevir on the pharmacokinetics of alprazolam and zolpidem in healthy volunteers

X Luo¹, R van Heeswijk², K Alves¹, V Garg ¹

¹Vertex Pharmaceuticals Incorporated
²Tibotec BVBA
Study Design: Group 1 (Zolpidem)

- Single sequence design to study effect of single and multiple doses of telaprevir
- 20 Healthy male or female volunteers

Day 1  |  Day 5  |  Day 15
--- | --- | ---
Zolpidem 5 mg po | Zolpidem 5 mg po | Zolpidem 5 mg po
Wash out | TVR 750 mg q8hr with food | PK up to 24 h
PK up to 24 h | PK up to 24 h | PK up to 24 h

Presented at the 6th International Workshop on Clinical Pharmacology of Hepatitis Therapy, 22-23 June 2011, Cambridge, USA
Mean PK Profiles of Zolpidem

Effect on Zolpidem
GLS Mean Ratio (90% CI)

• **Single dose TVR**
  \[ C_{\text{max}}: 0.99 \ (0.88; 1.12) \]
  \[ \text{AUC}: 1.14 \ (0.96; 1.36) \]

• **Multiple dose TVR**
  \[ C_{\text{max}}: 0.58 \ (0.52; 0.66) \]
  \[ \text{AUC}: 0.53 \ (0.45; 0.64) \]
Study Design: Group 2 (Alprazolam)

- Single sequence design to study effect of multiple doses of telaprevir
- 20 healthy male or female volunteers

**Study Design: Group 2 (Alprazolam)**

Day 1

- Alprazolam 0.5 mg po
- PK up to 96 h

Day 7

- Wash out

Day 17

- TVR 750 mg q8hr with food
- Alprazolam 0.5 mg po
- PK up to 96 h

Day 20

- Alprazolam 0.5 mg po
- PK up to 96 h
PK Profiles of Alprazolam

Effect on Alprazolam
GLS Mean Ratio (90% CI)

$C_{\text{max}}$: 0.97 (0.92; 1.03)
AUC: 1.35 (1.23; 1.49)
The pharmacokinetic interaction between amlodipine or atorvastatin and the HCV protease inhibitor telaprevir

J-E Lee¹, R van Heeswijk², K Alves ¹, F Smith¹, V Garg ¹

¹Vertex Pharmaceuticals Incorporated
²Tibotec BVBA
Single sequence design to study effect of single dose of telaprevir
21 Healthy male or female volunteers
Mean (SE) PK Profiles of Amlodipine

Effect on Amlodipine
GLS Mean Ratio (90% CI)
$C_{\text{max}}$ 1.27 (1.21; 1.33)
AUC 2.79 (2.58; 3.01)
Mean (SE) PK Profiles of Atorvastatin

**Effect on Atorvastatin**

GLS Mean Ratio (90% CI)

- $C_{\text{max}}$ 10.60 (8.74; 12.85)
- AUC 7.88 (6.84; 9.07)

**Atorvastatin Metabolite**

Ortho(OH)atorvastatin

- $C_{\text{max}}$ decreased ~ 65%
- AUC decreased 70%
The pharmacokinetic interaction between telaprevir and an oral contraceptive containing ethinyl estradiol and norethindrone

V Garg, Y Yang, F Smith, N Adda, R van Heeswijk

1Vertex Pharmaceuticals Incorporated
2Tibotec BVBA
Study Design

Cycle 1

<table>
<thead>
<tr>
<th>Modicon (0.5 mg NE + 0.035 mg EE) QD</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1  7</td>
<td>21  28</td>
</tr>
<tr>
<td>PK Sampling</td>
<td>NE/EE</td>
</tr>
</tbody>
</table>

Cycle 2

<table>
<thead>
<tr>
<th>Telaprevir 750 mg q8h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modicon (0.5 mg NE + 0.035 mg EE) QD</td>
</tr>
<tr>
<td>Day 29  35</td>
</tr>
<tr>
<td>PK Sampling</td>
</tr>
</tbody>
</table>
Mean (SD) PK Profiles of Ethinyl Estradiol and Norethindrone

**Effect on Ethinyl Estradiol**

- Without telaprevir
- With telaprevir

**No Effect on Norethindrone**

- Without telaprevir
- With telaprevir

**GLS Mean Ratio (90% CI)**

- Ethinyl Estradiol:
  - $C_{\text{max}}$: 0.74 (0.68; 0.80)
  - AUC: 0.72 (0.69; 0.75)
  - $C_{\text{min}}$: 0.67 (0.63; 0.71)

- Norethindrone:
  - $C_{\text{max}}$: 0.85 (0.81; 0.89)
  - AUC: 0.89 (0.86; 0.93)
  - $C_{\text{min}}$: 0.94 (0.87; 1.0)

Presented at the 6th International Workshop on Clinical Pharmacology of Hepatitis Therapy, 22-23 June 2011, Cambridge, USA
Mean (SD) PK Profiles of Telaprevir

No effect of oral contraceptive (OC) on TVR exposure
Conclusions

• Exposure of alprazolam, amlodipine, atorvastatin, digoxin, and midazolam increased, while exposure of zolpidem decreased following coadministration of telaprevir.
  – Dose modifications may be required when using alprazolam, amlodipine, digoxin, and zolpidem in combination with telaprevir\(^1\)
  – Co-administration of oral midazolam or atorvastatin with telaprevir is contraindicated\(^1\)

• Exposure to ethinyl estradiol was decreased by 28% when coadministered with telaprevir.
  – Hormonal contraceptives may not be reliable during telaprevir dosing and for up to two weeks following cessation of telaprevir. During this time, 2 effective methods of nonhormonal contraception should be used.\(^1\)

\(^1\)INCIVEK™ US Prescribing Information. Vertex Pharmaceuticals Incorporated
Acknowledgements

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Midazolam/digoxin
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Jennifer Webster, Vertex Pharmaceuticals Incorporated

Amlodopine/atorvastatin
Frank Farmer, Jr., MD, Covance
Mahlet Woldermarian, Vertex Pharmaceuticals Incorporated