I. The effect of CYP3A inhibitors and inducers on the pharmacokinetics of telaprevir

II. Telaprevir binding to isolated human plasma proteins and protein binding displacement interactions between telaprevir and warfarin

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Author Disclosures

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

Drs. Lachau-Durand and van Heeswijk are employees of Tibotec BVBA.

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

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The effect of CYP3A inhibitors and inducers on the pharmacokinetics of telaprevir

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Introduction

• Telaprevir (TVR) is a substrate and an inhibitor of CYP3A

• NonCYP-mediated pathways, such as amide hydrolysis and reduction, also play a role in the metabolism of telaprevir and may predominate after multiple dosing

• Studies were conducted to examine the effects of CYP inhibitors and inducers on telaprevir metabolism
  – Ketoconazole (strong CYP3A inhibitor)
  – Rifampin (strong CYP3A inducer)
  – Efavirenz (moderate CYP3A inducer)
**Study Design: Ketoconazole**

**Effect of single dose ketoconazole (400 mg) on single dose TVR (750 mg)**
- Open label, randomized crossover design
  - 17 male healthy volunteers
  - TVR 750 alone (with food) or with 400 mg ketoconazole

**Effect of single dose ketoconazole (400 mg) on multiple dose TVR**
- Randomized, double-blind crossover (≥5 day w/o) in healthy males
  - 1250 mg + 3 dose of 750 mg q8h TVR alone
  - 400 mg ketoconazole alone
  - 1250 mg q8h TVR 4 doses + 400 mg ketoconazole with 4th dose
  - Some volunteers also received 200 mg ketoconazole dose with or without 1250 mg q8h TVR
  - All doses taken with food
After a Single TVR Dose, TVR Levels Increased with Ketoconazole

GLS Mean Ratio (90% CI)

$C_{\text{max}}$: 1.24 (1.10, 1.41)

$AUC_\infty$: 1.62 (1.45, 1.81)
No Apparent Effect of Ketoconazole After Multiple-Dose Telaprevir (1250 vs 750 q8h)

- Higher predose TVR levels after the 1250 mg q8h dose and similarity of the effect of 200 mg and 400 mg ketoconazole doses on TVR suggests that the 67% higher dose of TVR likely caused the modest increase in TVR exposure.
- Ketoconazole (400 mg) AUC was increased by 1.5-fold with TVR.

**GLS Mean Ratio**

- $C_{\text{max}}$: 1.17 (1.12, 1.23)
- AUC: 1.21 (1.16, 1.26)
- $C_{\text{min}}$: 1.20 (1.13, 1.26)
Ritonavir Also Did Not Boost TVR Exposure After Multiple Doses of Both Drugs (PK-15)
Study Design: Rifampin

- Evaluate effect of steady state rifampin on PK of single dose TVR
- 16 male/female volunteers
Significantly Lowered Exposure of TVR with Rifampin

GLS Mea

$C_{\text{max}}$ 0.14 (0.11; 0.18)

AUC 0.08 (0.07; 0.11)
Study Design: Efavirenz

N=28

- Telaprevir 750 mg q 8h
- 7-day w/o
- Efavirenz 600 mg QD
- Telaprevir 750 mg q 8h

Day 1
- Day 10
  - TVR PK
- Day 17
- Day 27
  - EFV PK
- Day 37
  - EFV PK
  - + TVR PK

Comparisons: TVR PK on Days 10 and 37; EFV PK on Days 27 and 37
Effect of Efavirenz on Telaprevir (750 mg q8h) at Steady State and Vice Versa

GLS Mean Ratio (90% CI)

C<sub>max</sub> 0.91 (0.82; 1.02)
AUC 0.74 (0.65; 0.84)
C<sub>min</sub> 0.53 (0.44; 0.65)

GLS Mean Ratio (90% CI)

C<sub>max</sub> 0.84 (0.76; 0.93)
AUC 0.93 (0.87; 0.98)
C<sub>min</sub> 0.98 (0.94; 1.02)
Conclusions

• CYP3A inducers can reduce telaprevir exposures to varying degrees based on their potency
  – Rifampin is contraindicated\(^1\)
  – With efavirenz, a telaprevir dose of 1125 mg q8h is being tested

• CYP3A inhibitors can increase telaprevir exposures
  – Due to auto-inhibition of CYP3A by telaprevir, effect likely to be greater initially than at steady state of telaprevir
  – Ketoconazole levels were increased by telaprevir
  – High doses (>200 mg/day) of ketoconazole or itraconazole are not recommended\(^1\)

\(^1\)INCIVEK\(^TM\) US Prescribing Information. Vertex Pharmaceuticals Incorporated.
Telaprevir binding to isolated human plasma proteins and protein binding displacement interactions between telaprevir and warfarin

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Introduction

- In clinical studies, formic acid is added to plasma samples upon collection to stabilize epimerization of telaprevir and its diastereomer, VRT-127394

- Acidification with formic acid can denature plasma proteins, so precise determination of telaprevir protein binding from clinical studies is not possible

- In this *in vitro* study, we determined:
  - Extent of $^{14}$C-telaprevir binding to plasma proteins
  - Binding to human serum albumin (HSA), α1 acid glycoprotein (AAG), human gamma globulin (HGG)
  - Potential for protein displacement interactions between telaprevir and warfarin in human plasma
Methods

• Ultrafiltration
• Telaprevir concentration range: 0.1 – 20 µM
• Binding to albumin, $\alpha_1$-acid glycoprotein (AAG), human gamma globulin (HGG) at 3 different concentrations of proteins
• Displacement of warfarin by TVR and vice-versa
Results and Conclusions

- $^{14}$C-telaprevir moderately bound to plasma proteins (~59.1 to 75.6%) with mild concentration-dependent decrease

- Binding to human serum albumin (HSA) or $\alpha_1$ acid glycoprotein (AAG) was low to moderate and concentration-dependent (TVR & protein)

- Binding to human gamma globulin (HGG) was low and concentration-independent

- Mean binding to HSA or AAG was lower than that in human plasma, suggesting that both proteins may be involved

- Telaprevir did not affect the protein binding of warfarin

- Warfarin displaced telaprevir from binding sites, particularly at lower telaprevir concentrations
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