Effect of the hepatitis C virus protease inhibitor telaprevir on the pharmacokinetics of amlodipine and atorvastatin

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Running title: amlodipine or atorvastatin and telaprevir interaction

Key words: telaprevir, protease inhibitor, amlodipine, atorvastatin, statins, calcium channel antagonist, pharmacokinetics

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Purpose: Telaprevir is a hepatitis C virus protease inhibitor that is both a substrate and an inhibitor of CYP3A. Amlodipine and atorvastatin are both substrates of CYP3A and are amongst the drugs most frequently used by patients with hepatitis C. This study was conducted to examine the effect of telaprevir on atorvastatin and amlodipine pharmacokinetics (PK).

Methods: This was an open-label, single sequence, non-randomized study enrolling 21 healthy male and female volunteers. A co-formulation of 5 mg amlodipine and 20 mg atorvastatin was administered on Day 1. Telaprevir was dosed as 750 mg q8h with food from Day 11 until Day 26 and a single dose of amlodipine/atorvastatin combination was re-administered on Day 17. Plasma samples were collected for determining the PK of telaprevir, amlodipine, atorvastatin, ortho-hydroxy atorvastatin, and para-hydroxy atorvastatin.

Results: When administration with or without telaprevir was compared, the least-squares mean ratios (90% confidence limits) for amlodipine were 1.27 (1.21; 1.33) for $C_{\text{max}}$ and 2.79 (2.58; 3.01) for $AUC_{0-\infty}$; and for atorvastatin were 10.6 (8.74; 12.9) for $C_{\text{max}}$ and 7.88 (6.84; 9.07) for $AUC_{0-\infty}$.

Conclusions: Telaprevir significantly increased the exposure to amlodipine and atorvastatin, consistent with the inhibitory effect of telaprevir on the CYP3A-mediated metabolism of these agents.
INTRODUCTION

Telaprevir is an orally administered inhibitor of the nonstructural 3/4A (NS3/4A) protease of the hepatitis C virus (HCV) (11). In recent phase 3 studies in patients with chronic hepatitis C (CHC), the addition of telaprevir as part of a combination with pegylated interferon and ribavirin regimen significantly increased the rates of sustained virologic response (8, 17, 23). Telaprevir was recently approved in the United States of America for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease (6).

Amlodipine is a dihydropyridine calcium channel antagonist used to treat high blood pressure and angina or coronary artery disease. Atorvastatin is a hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase inhibitor used to lower high cholesterol level and reduce the risk of heart attack and stroke. These two drugs are frequently prescribed for patients with CHC and are commercially available as a co-formulation (Caduet®, Pfizer Inc.) (1). Both amlodipine and atorvastatin are primarily metabolized by CYP3A (1). CYP3A-mediated metabolism converts atorvastatin into two major active metabolites, ortho-hydroxy atorvastatin and para-hydroxy atorvastatin, and three inactive lactone metabolites corresponding to each acid form (12). Both active acid metabolites are known to be equipotent to the parent drug and account for ~70% of total HMG-CoA reductase inhibitory activity of atorvastatin (5). Primarily excreted in the bile, atorvastatin is also a substrate for P-glycoprotein (P-gp) and organic anion transporter protein (OATP1B1/1B3) (1). Amlodipine is extensively metabolized, primarily involving oxidation to the pyridine derivative with subsequent oxidative deamination of the 2-aminoethoxyxymethyl side chain or deesterification at the 5-methoxycarbonyl group.
None of the metabolites have any significant calcium antagonist activity relative to amlodipine (20).

Telaprevir inhibits CYP3A-mediated metabolism at therapeutic concentrations, and may inhibit and/or saturate P-glycoprotein in the gut. Therefore, this study was designed to evaluate the drug-drug interaction between telaprevir and amlodipine and atorvastatin in healthy volunteers.

METHODS

Volunteers

Twenty-one healthy male (n=15) and female (n=6) volunteers were enrolled at Covance Clinical Research Unit, Inc., Daytona Beach, Florida, USA. Female volunteers were of documented non-childbearing potential. At screening, volunteers were judged to be in good health on the basis of medical history, physical examination, and routine laboratory measurement results. Volunteers had ended any short-duration courses of prescription medications, herbal medications or dietary supplements (e.g., St. John’s Wort, ginkgo biloba, garlic supplements), vitamins, Seville oranges, grapefruit, or grapefruit juice, at least 14 days before the first dose of study drug. Prescription medications were not administered during the study. Volunteers had stopped over-the-counter medications no less than 2 days before the first administration of study drug. Occasional use of acetaminophen or ibuprofen was allowed during the study for the treatment of pain. Volunteers could not consume alcohol from 72 hours before first dose of study drug.
through the follow-up visit, and were nonsmokers (subjects who stopped smoking at least 6 months before screening were considered non-smokers). The protocol and informed-consent form were approved in accordance with national procedures. All volunteers provided written informed consent before participating in the study. The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local laws and regulations.

**Study Design**

This was a Phase 1, open-label, single-center, non-randomized study of telaprevir in combination with Caduet® tablets containing 5 mg of amlodipine and 20 mg of atorvastatin (amlodipine/atorvastatin). Volunteers received the following treatment: a single dose of amlodipine/atorvastatin alone on Day 1 followed by a wash-out period, telaprevir at doses of 750 mg q8h on Days 11 through 26, with a single dose of amlodipine/atorvastatin on Day 17. Outpatient visits occurred at Screening Visit (between 3 and 28 days before first dosing of study drug), on Days 3, 4, 6, 8, 12 through 14, 21 through 27, and at a final Safety Visit approximately 6 days after the last dose of study drug. Volunteers were confined in the clinical research unit from Days -1 to 2, 10 to 11, and 15 to 20.

**Drugs administered**

Telaprevir (375-mg tablets, Patheon, Mississauga, Ontario, Canada) was administered 750 mg q8h orally in the fed state (30 minutes after the start of a meal or snack).

Amlodipine/atorvastatin (25-mg fixed dose combination tablets containing 5-mg amlodipine and 20-mg atorvastatin; Pfizer Ireland Pharmaceuticals, Dublin, Ireland) was
administered orally as a single dose as per package insert, 30 minutes after the start of breakfast (1). During the study, compliance was assessed on an ongoing basis by counting returned dosage units and reviewing the volunteer logs. All volunteers were ≥90% compliant with the telaprevir dosing regimen, and all volunteers received their scheduled doses of amlodipine/atorvastatin (administered in the clinic).

Bioanalysis

Pharmacokinetic evaluations were based on the concentrations of amlodipine, atorvastatin, ortho-hydroxy atorvastatin, para-hydroxy atorvastatin, and telaprevir in plasma.

Plasma concentrations of amlodipine, atorvastatin, ortho-hydroxy atorvastatin, and para-hydroxy atorvastatin were determined at predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 120, 168, and 240 hours after a single dose of amlodipine/atorvastatin on Day 1, and at predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, and 72, 120, 168, and 240 hours after another single dose of amlodipine/atorvastatin on Day 17.

Neither amlodipine nor atorvastatin is an inhibitor of CYP3A while telaprevir is a potent inhibitor of CYP3A. Thus, the effect of amlodipine and atorvastatin on telaprevir PK was not anticipated. Therefore, telaprevir PK was only evaluated on Day 17, and was compared to that found historically. Plasma concentrations of telaprevir were determined at steady state at predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, and 8 hours after the morning dose of telaprevir on Day 17.

Analysis of all plasma samples was performed using validated LC/MS/MS methods at Covance Bioanalytical Services, LLC (8211 SciCor Drive, Suite B, Indianapolis, Indiana 46214 USA). Analytes and their internal standards (amlodipine-d4 maleic acid, ...
atorvastatin-d5 sodium salt, ortho-hydroxy atorvastatin-phenyl-d5, para-hydroxy atorvastatin-phenyl-d5, and d11-telaprevir) were extracted from human plasma by liquid-liquid extraction. After evaporation under nitrogen, the residue for all analytes was reconstituted and analyzed using liquid chromatography (normal phase) followed by tandem mass spectrometry (LC/MS/MS) with selected ion monitoring in the positive ion mode. Calibration curves were generated using weighted ($1/x^2$) linear least-squares regression. Standard curve range was from 0.0500 to 25.0 ng/mL for amlodipine (lower limit of quantitation [LLOQ] 0.0500 ng/mL), from 0.250 to 100 ng/mL for atorvastatin (LLOQ 0.250 ng/mL), from 0.250 to 100 ng/mL for para-hydroxy atorvastatin (LLOQ 0.250 ng/mL), from 0.250 to 100 ng/mL for ortho-hydroxy atorvastatin (LLOQ 0.250 ng/mL) and from 2.00 to 1000 ng/mL for telaprevir (LLOQ 2.00 ng/mL).

The calibration curves and quality control data all met the pre-specified acceptance criteria for each batch of samples assayed.

**Pharmacokinetic Analyses**

PK analyses were carried out using WinNonlin, Version 5.0.1 (Pharsight Corporation, Mountain View, CA). Standard noncompartmental analyses for the computation of area under the concentration versus time curve (AUC) were conducted. The maximum observed concentrations ($C_{max}$) and time to achieve $C_{max}$ ($t_{max}$) were determined directly from the observed data. The AUC was computed using the linear trapezoidal rule between increasing concentrations and the log trapezoidal rule between decreasing concentrations. The AUC extrapolated to infinity ($AUC_{0-\infty}$) was computed as the cumulative AUC to the time ($t_{last}$) of the last quantifiable concentration ($C_{last}$), i.e. ($AUC_{last}$), plus the extrapolated AUC from $t_{last}$ to time infinity. $AUC_{last-\infty}$ was estimated
by dividing the $C_{\text{last}}$ by the terminal elimination rate constant ($\lambda z$). The terminal half-life ($t_{1/2}$) was calculated $\ln(2)/\lambda z$ and oral clearance ($\text{CL/F}$, where $F$ is the oral bioavailability) was calculated by dividing the dose by $(\text{AUC}_{0-\infty})$.

For all pharmacokinetic measurements and parameters, appropriate descriptive statistics were calculated, which included the arithmetic mean, arithmetic standard deviation (SD), and the number of volunteers.

The drug-drug interaction was assessed by Linear Mixed Effects Modeling method using WinNonlin. The PK parameters ($C_{\text{max}}$, $\text{AUC}_{\text{last}}$, $\text{AUC}_{0-\infty}$) of amlodipine and atorvastatin following a single dose of amlodipine/atorvastatin coadministered with telaprevir were compared to those parameters following a single dose of amlodipine/atorvastatin alone.

In the analysis, treatment effect (with or without telaprevir) was considered as a fixed effect and subject was a random effect. Geometric least square means for each treatment and 90% confidence interval (CIs) for the geometric least square mean ratio (GLSMR) were reported. The absence of an interaction was to be concluded if the 90% CIs for the ratio of the geometric least square means fell within the range of 0.80 and 1.25 for each PK parameter (2).

Safety Assessments

Adverse events and concomitant medications were monitored throughout the study. Vital signs were assessed at predose and at 4, 8, 10, and 24 hours postdose; 12-lead electrocardiograms (ECGs) were assessed at predose and at 8, 10 and 24 hours postdose for amlodipine/atorvastatin when administered alone and when administered in combination with telaprevir. Clinical chemistry and hematology were assessed at predose and on Days 10, 15, and 20. Urinalysis was assessed at predose. All safety assessments
were repeated at the safety follow-up visit conducted approximately 6 days following the last dose of the study medications.

RESULTS

Demographics and Disposition

Seventy-six percent of healthy volunteers were Caucasian (n=16), 19% Black or African American (n=4), and 5% American Indian/Alaskan Native (n=1), with a median age of 34 years (range 21 to 53 years) and a median BMI of 26.6 (range 20.7 to 30.1).

Twenty-one healthy volunteers were enrolled and plasma samples from at least 19 volunteers were available following all dosing occasions and were analyzed for amlodipine, atorvastatin, ortho-hydroxy atorvastatin, para-hydroxy atorvastatin, and telaprevir. Plasma samples from 2 volunteers for Day 17 were not available because they discontinued from the study after providing blood samples for Day 1 amlodipine/atorvastatin pharmacokinetics.

Effect of Telaprevir on PK of Amlodipine

Mean plasma amlodipine concentration-time profile is shown in Figure 1, and PK parameters estimated from the noncompartmental analysis of amlodipine concentration data are shown in Table 1. Based on the ratio of the LS means, the mean C_{max} and the AUC_{0-\infty} for amlodipine were increased 1.27-fold and 2.79-fold, respectively, with coadministration of telaprevir (Table 1). The mean half-life of amlodipine increased from 41.3 hours to 95.1 hours and the mean apparent clearance (CL/F) decreased from 38.0 L/hr to 12.3 L/hr.
Effect of Telaprevir on PK of Atorvastatin and Metabolites

Mean plasma atorvastatin concentration-time profiles are shown in Figure 2, and PK parameters estimated from the noncompartmental analysis of atorvastatin concentration data are shown in Table 1. Based on the ratio of the LS means, the mean $C_{\text{max}}$ and the $AUC_{0-\infty}$ were markedly increased 10.6-fold and 7.88-fold, respectively, with coadministration of telaprevir (Table 1). The mean apparent clearance (CL/F) decreased from 685 L/hr to 83.8 L/hr. The mean (SD) half-life decreased from 9.44 (2.64) hours to 6.75 (1.55) hours when coadministered with telaprevir; the difference in half-life was not statistically significant.

The mean plasma concentration versus time profiles for ortho-hydroxy atorvastatin following amlodipine/atorvastatin administration on Day 1 and Day 17 are shown in Figure 3. Because a substantial number of sample concentrations for the 240-hour sampling interval were close to the LLOQ (both Day 1 and Day 17), the concentration-versus-time profile of ortho-hydroxy atorvastatin is limited to 24-hour postdose. As shown in Table 1, the variability for $C_{\text{max}}$ and $AUC_{0-\infty}$ on Day 17 is quite large. The extrapolated component for $AUC_{0-\infty}$ was over 25% in four volunteers on Day 17; furthermore, the AUC calculation was performed using imputed data by replacing the first BQL after $C_{\text{last}}$ with half of the LLOQ. Thus interpretation of these parameters should be made with caution, and further interpretation would not be clinically meaningful with limited data. Thus, GLSMRs were not calculated for this analyte.

Most of the concentrations of para-hydroxy atorvastatin were below the LLOQ, especially on Day 1. Only 2 volunteers showed detectable concentrations of para-hydroxy atorvastatin on Day 1. The $C_{\text{max}}$ of para-hydroxy atorvastatin in these 2
volunteers increased with telaprevir coadministration from 0.30 and 0.54 (mean of 0.42) ng/mL (Day 1) to 1.92 and 2.89 (mean of 2.40) ng/mL (Day 17).

**PK of Steady-State Telaprevir after Coadministration with Amlodipine and Atorvastatin**

Selected PK parameters were calculated for telaprevir at steady-state on Day 17 after coadministration with a single dose of amlodipine/atorvastatin. The mean (SD) $C_{\text{max}}$ of telaprevir was 3167 (778) ng/mL and the mean (SD) AUC$_{0-\text{last}}$ of telaprevir was 20471 (5317) hr·ng/mL. These values are similar to those observed historically (3).

**Safety**

There were no serious, life-threatening, or severe adverse events. One volunteer discontinued due to an adverse event (herpes zoster) during the telaprevir-alone period. This was considered possibly related to treatment, mild in severity, and resolved without intervention. With only 1 exception, all adverse events were considered to be of mild severity. The exception was diarrhea considered moderate for 1 volunteer during the telaprevir-amlodipine/atorvastatin combination period.

Thirteen (62%) volunteers reported an adverse event, and 10 (48%) volunteers reported an adverse event that was considered drug-related by the investigator. The most frequent adverse events that were considered to be related to the treatment occurred in the nervous system or the gastrointestinal system. Most frequent adverse events (considered either related or unrelated to study drug by the investigator) included: headache (occurred in 5 volunteers (24%) during the amlodipine/atorvastatin-alone period, 2 volunteers (10%) during the telaprevir-alone period, and 1 volunteer (5%) during the telaprevir-
amlodipine/atorvastatin combination period); dizziness (occurred in 2 volunteers (10%) during the telaprevir-alone period, and in 3 volunteers (15%) during the telaprevir-amlodipine/atorvastatin combination period); diarrhea (occurring in 1 volunteer (5%) during each of the 3 periods); nausea (occurring in 1 volunteer (5%) during the telaprevir-alone period, and in 2 volunteers (11%) during the telaprevir-amlodipine/atorvastatin combination period). Rash has been previously reported with telaprevir administration (6). A mild, papular rash was reported in a single volunteer (4.8%) on Day 24 during the period of coadministration of amlodipine/atorvastatin and telaprevir; the rash resolved without treatment or change to study drug dosing.

There were no clinically significant changes from baseline in clinical laboratory values, vital signs, ECG parameters, and physical examination. Creatine kinase levels elevation can be associated with increased statin levels (1). However, there were no clinically significant changes in creatine kinase reported as adverse events in any volunteers.

DISCUSSION

Potential drug-drug interactions between telaprevir and amlodipine and atorvastatin were investigated in healthy volunteers by comparing the pharmacokinetics of these drugs with and without coadministration of telaprevir. A formulation containing a combination of the amlodipine and atorvastatin (Caduet®) was used in this study for dosing convenience. No significant interaction between amlodipine and atorvastatin was expected.

A clinical drug-drug interaction study of telaprevir and midazolam showed that telaprevir increased the AUC of oral midazolam almost 9-fold (3), indicating that telaprevir is a potent inhibitor of CYP3A4. Amlodipine is a dihydropyridine calcium antagonist drug
and has been reported as a substrate and mild inhibitor of CYP3A from both in vitro liver microsomal incubation and clinical studies (9, 13). Atorvastatin, one of the most commonly prescribed HMG-CoA reductase inhibitor, is also a substrate of CYP3A (5). Adverse events such as rhabdomyolysis and myopathy have been reported with statins, and most of the statin drug interactions are attributed to metabolism catalyzed by cytochrome P450 (22). Thus clinically significant changes in pharmacokinetics of amlodipine and atorvastatin, administered as Caduet, were anticipated with coadministration of telaprevir.

Results from the current study indicate that telaprevir significantly inhibited the metabolism of both amlodipine and atorvastatin. Bioavailability of amlodipine has been reported to be ~60% (14). It is extensively metabolized by the liver and is very slowly cleared from the body (elimination half-life is ~45 hours). Its volume of distribution is known to be large (~21 L/Kg) with high level of binding to plasma protein to albumin (~98%) (15). When amlodipine was coadministered with telaprevir, its AUC$_{0-\infty}$ increased 2.79-fold and its C$_{\text{max}}$ increased 1.27-fold. The mean (SD) half-life increased from 41.3 (8.2) hours to 95.1 (23.6) hours and the mean (SD) apparent clearance (CL/F) decreased from 38.0 (11.8) L/hr to 12.3 (2.97) L/hr. The increased half-life associated with clearance decrease signifies the inhibitory effect of telaprevir on the metabolism of amlodipine. A similar magnitude of effect on amlodipine has been observed in other studies with antiviral agents that are CYP3A inhibitors. For example, combined dosing of indinavir and ritonavir increased the median amlodipine AUC$_{0-24}$ by 90% (n = 18) (4). The effect of telaprevir on atorvastatin disposition was more pronounced. Atorvastatin is given in the acid form and its C$_{\text{max}}$ is achieved quickly (1~2 hours postdose) (10).
Atorvastatin acid undergoes extensive first-pass metabolism in the gut and the liver, and thereby its oral bioavailability is only ~14%. Its volume of distribution has been reported to be ~380 L with a high degree of plasma protein binding, mainly to albumin (98%) (22).

Upon coadministration of telaprevir with a single dose of amlodipine/atorvastatin, the atorvastatin AUC\(_{0-\infty}\) increased 7.88-fold and the atorvastatin C\(_{\text{max}}\) increased 10.6-fold. These results suggest that the primary effect of telaprevir on atorvastatin is to increase its bioavailability (F) by decreasing its first-pass metabolism by CYP3A and/or increasing its net absorption by inhibiting P-glycoprotein-mediated efflux back to the gut. The effect of telaprevir on the hepatic metabolism of atorvastatin does not appear to be significant in its overall disposition. A similar magnitude of effect on atorvastatin has been observed in studies using some other CYP3A inhibitors. For example, the AUC and C\(_{\text{max}}\) of atorvastatin were increased about 9-fold when it was coadministered with tipranavir/ritonavir at steady state (16).

With coadministration of telaprevir, the mean (SD) apparent clearance decreased from 685 (272) L/hr to 83.8 (32.7) L/hr and the apparent volume of distribution (V/F) decreased from 8984 (3431) L to 838 (405) L. The mean (SD) terminal half-life decreased from 9.44 (2.64) hours to 6.75 (1.55) hours with coadministration of telaprevir, although this difference was not statistically significant. Inhibition of atorvastatin metabolism would be expected to increase atorvastatin half-life. This unexpected result may be possibly caused by inhibition of transporters involved in the hepatic uptake of atorvastatin, such as organic anion-transporting polypeptide 1B1 (OATP 1B1), that could reduce the volume of distribution of atorvastatin to a similar or greater extent than the
decrease observed in systemic clearance. Such a mechanism has been hypothesized for the effect of cyclosporine (an inhibitor of OATP1B1) on rosuvastatin, a statin which is also a substrate of OATP1B1 and whose half-life was decreased by half upon coadministration of cyclosporine (19). Other statins that are substrates of OATP1B1 such as cerivastatin, fluvastatin and atorvastatin showed unaltered half-life while several-fold increases in AUC and $C_{\text{max}}$ were rendered when coadministered with cyclosporine (18). However, at this time, the effect of telaprevir on OATP1B1 is unknown.

The mean $AUC_{0-\infty}$ for ortho-hydroxy atorvastatin decreased by approximately 70% after telaprevir coadministration; however, most concentrations of para-hydroxy atorvastatin were below LLOQ, making noncompartmental analysis for this metabolite not feasible. In the 2 volunteers in which para-hydroxy atorvastatin was measurable before (Day 1) and after (Day 17) the co-administration of telaprevir, the concentrations of this metabolite increased about 6-fold. On Day 17, but not Day 1, several other volunteers had measurable concentrations of para-hydroxy atorvastatin. While these results were not anticipated, it has been reported that para-hydroxy atorvastatin, but not ortho-hydroxy atorvastatin, is also formed by CYP2C8 in addition to CYP3A (7). Therefore, in the presence of greater systemic exposure of atorvastatin during co-administration of telaprevir, it is plausible that more para-hydroxy atorvastatin may be formed via CYP2C8 and its plasma concentrations increased.

The PK of telaprevir was evaluated after coadministration at steady-state with a single dose of amlodipine/atorvastatin. The $C_{\text{max}}$ and $AUC_{\text{last}}$ were similar to the steady-state estimates obtained from other studies (21). This suggests that adequate exposure of
telaprevir was achieved in this study and a clinically significant effect of amlodipine or 
atorvastatin on telaprevir is unlikely.

The coadministration of multiple doses of telaprevir with one dose of amlodipine and 
atorvastatin administered in 2 periods was well-tolerated. There were no serious, life-
threatening, or severe adverse events, no volunteers were discontinued due to an adverse 
event, and most adverse events were mild. Frequently-reported adverse events included, 
headache, dizziness, diarrhea, and nausea, all of which have been reported in other 
clinical trials after administration of telaprevir alone (8, 17, 23). The low frequency and 
or lack of adverse events commonly associated with amlodipine and atorvastatin may be 
attributed to the single dose regimen of these drugs used in this study.

In summary, the results from this study suggest that telaprevir significantly increased 
exposure (C_{max} and AUC_{0-\infty}) of amlodipine and atorvastatin. **Atorvastatin** 
coadministration with telaprevir is contraindicated. When amlodipine is coadministered 
with telaprevir, caution should be used and dose reduction for amlodipine should be 
considered. Clinical monitoring is recommended. Please check INCIVEK™ package 
insert for full information and/or updates (6).
ACKNOWLEDGMENTS

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CONFLICT OF INTEREST/DISCLOSURE

This study was supported by Vertex Pharmaceuticals Incorporated (Vertex) and Tibotec BVBA (Tibotec). All authors were either employed by Vertex (VG, JEL, KA, FS, RK) or Tibotec (RvH) at the time of the study, and own stock in these companies.

JEL is currently employed by the U.S. Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993. Her contribution to this manuscript was based on her prior employment and the content of the work does not necessarily reflect any position of the U.S. Food and Drug Administration.

REFERENCES


Shitara Y. 2011. Clinical Importance of OATP1B1 and OATP1B3 in Drug-drug Interactions. Drug Metabolism and Pharmacokinetics 26:220-227


Figure Legends

Figure 1. Mean Plasma Concentration versus Time Profile of Amlodipine Following Oral Administration With and Without Telaprevir.

Error bars represent standard error of the mean.

Figure 2. Mean Plasma Concentration versus Time Profile of Atorvastatin Following Oral Administration With and Without Telaprevir.

Error bars represent standard error of the mean.

Figure 3. Mean Plasma Concentration versus Time Profile of Ortho-Hydroxy-Atorvastatin Following Oral Administration With and Without Telaprevir.

Error bars represent standard error of the mean.
Table 1. Effect of Telaprevir on the PK of Amlodipine, and Atorvastatin and its Metabolite Ortho-hydroxy-atorvastatin

<table>
<thead>
<tr>
<th>Substrate (Day of PK)</th>
<th>Interacting Drug</th>
<th>Subjects with PK Data</th>
<th>Arithmetic Mean (SD)</th>
<th>GLS Mean Ratioa</th>
<th>(90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cmax (ng/mL)</td>
<td>AUC∞ (ng.h/mL)</td>
<td>t1/2 (h)</td>
</tr>
<tr>
<td>AML 5 mg single dose (D1)</td>
<td>None</td>
<td>21</td>
<td>8.00 (6.00, 12.00)</td>
<td>2.75 (0.74)</td>
<td>142 (37)</td>
</tr>
<tr>
<td>AML 5 mg single dose (D17)</td>
<td>Telaprevir 750 mg q8h (D11-26)</td>
<td>19</td>
<td>12.00 (4.00, 23.85)</td>
<td>3.55 (0.87)</td>
<td>425 (83)</td>
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<tr>
<td>ATVS 20 mg single dose (D1)</td>
<td>None</td>
<td>21</td>
<td>1.50 (0.75, 6.00)</td>
<td>3.50 (1.93)</td>
<td>33.8 (13.6)</td>
</tr>
<tr>
<td>ATVS 20 mg single dose (D17)</td>
<td>Telaprevir 750 mg q8h (D11-26)</td>
<td>19</td>
<td>3.00 (1.50, 4.02)</td>
<td>38.5 (20.0)</td>
<td>277 (116)</td>
</tr>
</tbody>
</table>

Ortho-hydroxy-ATVS: [OHATVS]:

| ATVS 20 mg single dose (D1) | None | 21 | 4.00 (1.50, 10.0) | 2.95 (1.07) | 42.09 (12.76) | 10.16 (1.57) | NA | NA |
| OHATVS: ATVS 20 mg single dose (D1) | Telaprevir 750 mg q8h (D11-26) | 19 | 4.00 (1.00, 12.0) | 1.04 (1.44) | 12.64 (10.50) | 8.53 (2.36) | NA | NA | NA | NA |

Abbreviations: AML: amlodipine; ATVS: atorvastatin; NA: not available; OHATVS: ortho-hydroxy-atorvastatin

a Value for substrate with telaprevir/ value for substrate without telaprevir
b Tmax is median (min; max)
c Four volunteers had an extrapolated component of AUC∞ that was over 25% on Day 17; furthermore, the AUC calculation was performed using imputed data by replacing the first BQL after Clast with half of the LLOQ.
Nominal Time (hr)

Mean Concentration (ng/mL)

With telaprevir
Without telaprevir

0.10
1.00
10.0
0 10 20 30 40 50