# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 201917Orig1s000

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# CLINICAL PHARMACOLOGY REVIEW

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| **NDA: 201-917** | Submission Date(s): November 22, 2010 |
| **Drug** | Telaprevir |
| **Trade Name** | To be determined |
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| **Applicant** | Vertex Pharmaceuticals |
| **Relevant IND(s)** | 71,832 |
| **Submission Type; Code** | Original NDA (NME) |
| **Formulation; Strength(s)** | 375 mg Tablet |
| **Indication** | Treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease, including cirrhosis, who are treatment naïve or who have been previously treated, including prior null responders, partial responders, and relapsers in combination with pegylated interferon and ribavirin. |
| **Dosage and Administration** | 750 mg q8h for 12 weeks in combination with pegylated interferon and ribavirin with response-guided therapy:<br><br>For patients who are treatment naïve or are prior relapsers:<br>o Patients with undetectable HCV RNA at weeks 4 and 12 receive an additional 12 weeks of peg-interferon alfa and ribavirin alone for a total treatment duration of 24 weeks.<br>o Patients with detectable HCV RNA at either weeks 4 or 12 receive an additional 36 weeks of peg-interferon alfa and ribavirin alone for a total treatment duration of 48 weeks.<br><br>For patients who have been previously treated (except prior relapsers):<br>o Combination treatment with telaprevir followed by peg-interferon alfa and ribavirin treatment alone for atotal treatment duration of 48 weeks. |

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## 1. Executive Summary

Telaprevir is a new molecular entity in the hepatitis C (HCV) protease inhibitor class. It is among the first direct-acting antivirals in the treatment of HCV. Telaprevir is a diastereomer (S-configuration) with a major metabolite that is the R-diastereomer (VRT-127394). VRT-127394 has 30-fold lower antiviral activity than telaprevir.

Telaprevir is intended for administration in combination with the current standard of care, which consists of pegylated interferon alpha and ribavirin, in the treatment of genotype 1 chronic HCV in adult patients with compensated liver disease (including cirrhosis) who are treatment naïve or who have been previously treated. The proposed dosing regimen for telaprevir is 750 mg q8h orally for 12 weeks, while treatment duration for pegylated interferon alpha and ribavirin will be response-guided and can either be a total of 24 weeks or 48 weeks. The following clinical rules will dictate pegylated interferon alpha (Peg-IFN) and ribavirin (RBV) treatment duration:

For patients who are treatment naïve or are prior relapsers:

- Patients with undetectable HCV RNA at weeks 4 and 12 receive an additional 12 weeks of peg-interferon alfa and ribavirin alone for a total treatment duration of 24 weeks.
- Patients with detectable HCV RNA at either weeks 4 or 12 receive an additional 36 weeks of peg-interferon alfa and ribavirin alone for a total treatment duration of 48 weeks.

For patients who have been previously treated (except prior relapsers):

- Treatment with telaprevir is followed by peg-interferon alfa and ribavirin treatment alone for a total treatment duration of 48 weeks.

The following is a list of studies conducted by the Applicant in direct support of this NDA:

- Fourteen *in vitro* studies investigating telaprevir's metabolism pathway, potential for CYP inhibition, potential for CYP induction, potential for P-gp transport, potential for P-gp inhibition, and plasma protein binding.
- Nine phase 1 studies including studies investigating the bioavailabilities of various formulations of telaprevir, single-ascending dose studies in healthy volunteers, a food effect study, and an ADME study.
- Two hepatic impairment studies: one conducted in patients with mild hepatic impairment and one conducted in patients with moderate hepatic impairment.
- One renal impairment study conducted in patients with severe renal impairment given a single dose of telaprevir.
- Two thorough QTc studies
- Fifteen drug interaction studies (evaluating 22 drugs) in which interactions between telaprevir and a probe CYP3A substrate, a model CYP3A inhibitor, a

model CYP3A inducer, a sensitive P-gp substrate, and commonly co-administered drugs were evaluated.

- Six phase 2 studies in which the safety and efficacy of several combinations of different treatment durations of telaprevir (12 weeks and 24 weeks) and Peg-IFN/RBV (12 weeks, 24 weeks, 48 weeks) were investigated.
- Three phase 3 studies in which the safety and efficacy of either 8 weeks or 12 weeks of telaprevir treatment and either 24 weeks or 48 weeks of Peg-IFN/RBV were investigated.

The following clinical studies pertinent to clinical pharmacology are either planned or were ongoing at the time of the NDA submission:

- A phase 1 study investigating the intra-hepatic and plasma HCV viral kinetics in subjects treated with telaprevir, Peg-IFN, and RBV
- A phase 2a study to assess the efficacy and safety of telaprevir, Peg-IFN, and RBV treatment in subjects who are co-infected with HCV and HIV-1 and who are treatment-naïve for HCV (either not receiving HARRT or are receiving stable HARRT).
- A phase 1 study investigating the drug interaction potential between telaprevir and buprenorphine.
- A phase 1 study investigating the drug interaction potential between telaprevir and raltegravir.
- A phase 3 study investigating the safety and efficacy of telaprevir 1125 mg BID as compared with 750 mg q8h.

## 1.1 Recommendations

The Office of Clinical Pharmacology has reviewed this NDA submission and finds it acceptable from a clinical pharmacology perspective. The clinical pharmacology review team agrees with the response-guided regimens proposed by the Applicant, with the exception of the following treatment stopping rule:

- Patients with HCV RNA >1000 IU/mL (instead of (b) (4), as proposed by the Applicant) at Week 4 should discontinue telaprevir and continue Peg-IFN/RBV treatment. Patients with HCV RNA >1000 IU/mL (instead of (b) (4), as proposed by the Applicant) at Week 12 should discontinue Peg-IFN/RBV.

## 1.2 Phase 4 Commitments/Requirements

The Pharmacogenomics reviewer recommends that the Applicant complete the following study as a PMC:

- Conduct a genome-wide association study (GWAS) to identify factor(s) associated with severe skin reactions to telaprevir/peginterferon/ribavirin using cases from existing DNA substudies and appropriately selected controls.

## 1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Telaprevir is an NS3•4A protease inhibitor with demonstrated antiviral activity against HCV genotypes 1, 2, 3, and 4. The Applicant's proposal of a 750 mg dose given every 8 hours is reasonable. Analyses of the relationships between exposure, safety, and efficacy in phase 2 and phase 3 studies indicate that the telaprevir exposure obtained with a dose of 750 mg q8h co-administered with Peg-IFN-alfa and RBV provided a desirable balance between safety and efficacy in both treatment-naïve and prior treatment-failure subjects.

Telaprevir demonstrates non-linear, time-dependent, and population-specific PK. At *single* doses between 375 and 1875 mg in healthy volunteers, AUC increased more than dose proportionally, while Cmax increased more than dose proportionally between the 375- and 750-mg doses (Table 1.3-1). Telaprevir plasma concentrations accumulate following multiple dosing, with a concurrent decrease in clearance. In addition, clearance decreases with increasing single doses. In healthy subjects, the accumulation ratio for $AUC_\tau$ at the therapeutic dose (750 mg Q8h) is approximately 2-3 between a single dose and steady-state. Following multiple dosing in HCV-infected patients, telaprevir exposure increases until maximal $C_{trough}$ is reached between days 2 and 3 followed by a decrease in exposures until steady-state is reached by day 7. Overall, the accumulation ratio for $AUC_\tau$ is approximately 1.8 between day 1 and day 14 in patients. The major metabolite of telaprevir (also the R-diastereomer), VRT-127394, exhibited very similar PK characteristics as telaprevir in nearly all instances; however its potency is ~30-fold lower than telaprevir's.

Table 1.3-1 Telaprevir PK Parameters Following a Single Dose in **Healthy Volunteers** Using the 375-mg Tablet in Study 017

| PK Parameter | 375 mg (N=19) | 750 mg (N=19) | 1125 mg (N=18) | 1500 mg (N=9) | 1875 mg (N=9) |
|---|---|---|---|---|---|
| $C_{max}$ (ng/mL) | 539.79 | 1740.84 | 2346.67 | 3232.22 | 3259.44 |
| | (217.75) | (785.28) | (917.21) | (1496.90) | (1661.71) |
| $AUC_{0\text{-last}}$ (hr*ng/mL) | 3084.24 | 11102.16 | 18297.72 | 25991.47 | 30393.76 |
| | (1513.28) | (6692.22) | (8941.90) | (14006.59) | (17129.77) |
| $AUC_{0\text{-}\infty}$ (hr*ng/mL) | 3146.52 | 11749.10[b] | 19362.18[c] | 24250.23[d] | 34944.13[e] |
| | (1579.56) | (7484.56) | (11199.97) | (10194.68) | (22574.69) |
| $t_{max}$ (hr)[a] | 5 (3.55,6) | 5 (3.5,12) | 5 (3.5,12) | 5 (3,8) | 5 (2.5,8) |
| $t_{1/2}$ (hr) | 3.23 | 3.96[b] | 5.44[c] | 6.49 | 8.31 |
| | (0.70) | (1.10) | (1.79) | (2.20) | (3.30) |
| Cl/F (L/hr) | 157.43 | 100.61 | 77.96 | 68.88 | 92.83 |
| | (98.82) | (85.44) | (55.60) | (40.39) | (115.75) |
| Vz/F (L) | 692.80 | 522.53 | 560.09 | 574.30 | 1102.52 |
| | (367.89) | (342.80) | (293.69) | (281.23) | (1634.82) |

Table 1.3-2 Telaprevir and VRT-127394 $AUC_{last}$ Values (ng*hr/mL) for **HCV-Infected** Subjects Dosed with the 250-mg Tablet in Study 101**

| Analyte, Time Point | VX-950 Dose | N | $t_{last}$ | Median | Mean | CV |
|---|---|---|---|---|---|---|
| **VX-950, Day 1** | 450 | 10 | 8 | 5512 | 5593 | 51% |
| | 750 | 8 | 8 | 5612 | 5699 | 39% |
| | 1250[a] | 10 | 8 | 7135 | 7194 | 30% |
| | | | 12 | 9224 | 9426 | 29% |
| **VX-950, Day 14** | 450 | 10 | 8 | 9276 | 9626 | 37% |
| | 750 | 8 | 8 | 9476 | 10078 | 36% |
| | 1250[a] | 10 | 8 | 11231 | 11021 | 29% |
| | | | 12 | 13923 | 13867 | 26% |
| **VRT-127394, Day 1** | 450 | 10 | 8 | 2501 | 2360 | 43% |
| | 750 | 8 | 8 | 2039 | 2254 | 43% |
| | 1250[a] | 10 | 8 | 2194 | 2372 | 29% |
| | | | 12 | 3489 | 3557 | 28% |
| **VRT-127394, Day 14** | 450 | 10 | 8 | 5088 | 5705 | 50% |
| | 750 | 8 | 8 | 6129 | 6174 | 34% |
| | 1250[a] | 10 | 8 | 5606 | 5469 | 27% |
| | | | 12 | 7196 | 7291 | 23% |

[a] AUC data for the 1250 mg group are shown for a $t_{last}$ of 8 hours to facilitate comparison with the other dose groups and for a $t_{last}$ of 12 hours because that was the dosing interval for the 1250 mg group. $t_{last} = 8$ then $AUC_{last} = AUC_{0-8}$ ; $t_{last} = 12$ then AUClast = $AUC_{0-12}$

**The 450-mg and 750-mg doses were given q8h and the 1250-mg dose was given q12h.

**Absorption**

Telaprevir is most likely absorbed in the small intestine, with no evidence of absorption in the colon. The absolute bioavailability of telaprevir has not been determined in humans. Based on popPK analyses in phase 2 studies, the absorption of telaprevir was characterized by 2 phases: an initial slow phase followed by a rapid phase. In almost all phase 1 and phase 2 studies, initial absorption of telaprevir was preceded by a lag time of an average of 0.2 hours. Telaprevir's absorption is also influenced by P-gp transporter efflux.

Food affects the bioavailability of telaprevir. A 3- to 4-fold increase in the AUC and $C_{max}$ of telaprevir was observed when the 375-mg tablet formulation that was used in the phase 3 studies was administered to healthy subjects as a single 750-mg dose in the fed state (standard breakfast: approximately 533 Kcal, 189 Kcal from fat) compared to the fasted state.

**Distribution**

Telaprevir is approximately 59% to 76% bound to human plasma proteins, mainly to α-1-acid glycoprotein (AAG) and human serum albumin (HSA) at concentrations ranging from 0.1 µM to 20 µM. The protein binding is concentration-dependent and decreases with increasing telaprevir concentrations at all concentrations of HSA and AAG.

The mean V/F of telaprevir in healthy subjects in phase 1 studies is approximately 377 L, suggesting a large volume of distribution, with extensive penetration of telaprevir into tissues beyond systemic circulation. The V/F of telaprevir was estimated from popPK analyses of phase 2 and phase 3 studies in HCV-infected patients to be between 212 and 673 L.

**Metabolism**

Telaprevir is mainly metabolized via phase 1 metabolism pathways, namely oxidation, hydrolysis, and reduction of the parent drug. The primary CYP isoform responsible for telaprevir metabolism is CYP3A4. A different metabolite profile exists following either a single dose of telaprevir or following multiple doses to steady-state. Following a single dose of telaprevir, VRT-127394 (the *R*-diastereomer of telaprevir) was the only metabolite present at greater than 10% of total drug-related material. However, following administration of multiple doses of telaprevir (in combination with Peg-IFN and RBV) in HCV-infected patients, pyrazinoic acid (PZA), VRT-127394, and VRT-0922061 were all predominant metabolites that were present at >10% of total drug-related material at steady-state. In addition to CYP-mediated metabolism, there is some evidence that proteolytic enzymes are involved in the metabolism of telaprevir.

**Elimination**

Telaprevir and its metabolites are primarily excreted through feces, with minimal renal elimination. After oral administration of $^{14}$C-telaprevir, more than 81.6% of the administered dose was excreted in feces, with unchanged telaprevir and VRT-127394 accounting for 31.8% and 18.7% of excreted drug-related material in feces, respectively. Only 1.00% of the administered dose was excreted in urine, of which only 0.11% of the administered dose of unchanged telaprevir could be detected. Approximately 8.15% of the administered dose was recovered in expired air.

**Specific Populations**

*Race*

No dedicated studies on the influence of race were conducted with telaprevir. However, based on the Applicant's popPK analysis across studies 104, 104EU, 106, C208, 108, 111, and C216 to investigate the influence of various covariates on telaprevir exposure, race was not found to be a significant covariate on the clearance of telaprevir.

*Gender*

No dedicated studies on the influence of gender were conducted with telaprevir. However, based on the Applicant's popPK analysis of phase 2 and phase 3 studies, gender was not found to be a significant covariate on the clearance of telaprevir in either study.

*Age*

No dedicated studies of the elderly population were conducted with telaprevir. However, the Applicant's popPK analysis of studies 104, 104EU, 106, C208, 108, 111, and C216 included 35 subjects ≥65 years of age. The results of the Applicant's analysis indicated that distributions of CL/F for subjects at the extremes of the age range lie entirely within 20% of the typical reference value. Furthermore, there was no relationship between inter-individual variability in CL/F estimates and

age. Subgroup analyses for efficacy indicate that elderly patients appear to respond to telaprevir/Peg-IFN/RBV treatment less well. In addition, old age may be associated with a higher risk of rash and Hgb toxicity. However, the exposure-safety relationship seems to be independent of age. Therefore, no dose adjustment is necessary based on age. Nonetheless, caution should be exercised in the administration and monitoring of telaprevir in geriatric patients.

*Hepatic Impairment*

Clearance of telaprevir in subjects with mild hepatic impairment (C-P class A) did not change significantly as compared with healthy subjects. However, clearance was *increased* (with a corresponding decrease in exposure) in subjects with moderate hepatic impairment (C-P class B) relative to healthy subjects. Due to the results of the study in moderately hepatically impaired subjects, the effect of severe hepatic impairment on telaprevir exposure was not studied. There is no dose adjustment recommended for patients with mild hepatic impairment. In addition, there was no effect of cirrhosis on telaprevir PK in the phase 3 studies. Telaprevir use is not recommended for patients with moderate or severe hepatic impairment. In addition, the use of Peg-IFN and RBV are contraindicated in patients with moderate and severe hepatic impairment.

*Renal Impairment*

The results of the renal impairment study (reduced study design) conducted by the Applicant were inconclusive. The renal impairment study included only a single dose of telaprevir. The results from this study indicate that following a single dose of telaprevir in patients with severe renal impairment, mean telaprevir $AUC_{inf}$ increased by 21% and Cmax increased by 3%, compared to subjects with normal renal function. Due to telaprevir's non-linear PK, a multiple-dose study would have more accurately characterized the effect of renal impairment on telaprevir steady-state exposure. However, an additional study is not needed at this time. Based on the limited amount of telaprevir that is eliminated renally, the relatively small magnitude of change from the single-dose study in severely renally impaired subjects, and telaprevir's accumulation ratio, it is unlikely that the magnitude of increase in telaprevir exposure following multiple doses would be great enough to warrant a dose adjustment in patients with renal impairment. Furthermore, because anemia (the only toxicity that is associated with telaprevir exposure) is more strongly associated with RBV exposure than TVR exposure, anemia would most likely be managed by lowering the RBV dose.

**Drug Interactions**

Based on *in vitro* studies, telaprevir is a demonstrated inhibitor of CYP3A and a substrate for both CYP3A metabolism and P-gp transport. Several drug interaction studies have been conducted by the Applicant to characterize the *in vivo* interaction between telaprevir and several probe substrates, probe inhibitors, probe inducers, as well as drugs that are likely to be co-administered. Results from these studies and the corresponding recommendations are presented below.

**Table 1.3-2 Drug Interactions: Summary of Pharmacokinetic Parameters for Telaprevir in the Presence of Co-administered Drugs***

| Drug | Dose and Schedule | | N | Effect on Telaprevir PK[a] | LS Mean Ratio (90% CI) of Telaprevir PK With/Without Coadministered Drug | | | Clinical Comment/Outomce |
|---|---|---|---|---|---|---|---|---|
| | Drug | Telaprevir | | | $C_{max}$ | AUC or $C_{avg,ss}$[b] | $C_{min}$ | |
| Escitalopram | 10 mg qd for 7 days | 750 mg q8h for 14 days | 13 | ↔ | 1.00 (0.95; 1.05) | 0.93 (0.89; 0.97) | 0.91 (0.86; 0.97) | Doses of escitalopram may need to be adjusted. |
| Esomeprazole | 40 mg qd for 6 days | 750 mg single dose | 24 | ↔ | 0.95 (0.86; 1.06) | 0.98 (0.91; 1.05) | NA | None |
| Ketoconazole | Ketoconazole 400 mg single dose | 750 mg single dose | 17 | ↑ | 1.24 (1.10; 1.41) | 1.62 (1.45; 1.81) | NA | Limit KETO dose to 200 mg/day |
| Oral Contraceptive | Norethindrone / ethinyl estradiol 0.5 mg/0.035 mg qd for 21 days | 750 mg q8h for 21 days | 23 | ↔ | 1.00 (0.93; 1.07) | 0.99 (0.93; 1.05) | 1.00 (0.93; 1.08) | Use 2 alternative forms of contraception |
| Rifampin | 600 mg qd for 8 days | 750 mg single dose | 16 | ↓ | 0.14 (0.11; 0.18) | 0.08 (0.07; 0.11) | NA | CONTRAINDICATED |
| **Anti-HIV Drugs** | | | | | | | | |
| Atazanavir (ATV)/ritonavir (rtv) | 300 mg ATV/ 100 mg rtv qd for 20 days | 750 mg q8h for 10 days | 14 | ↓ | 0.79 (0.74; 0.84) | 0.80 (0.76; 0.85) | 0.85 (0.75; 0.98) | None |
| Darunavir (DRV)/ritonavir (rtv) | 600 mg DRV/ 100 mg rtv bid for 20 days | 750 mg q8h for 10 days | 11 (N=14 for $C_{max}$) | ↓ | 0.64 (0.61; 0.67) | 0.65 (0.61; 0.69) | 0.68 (0.63; 0.74) | Not recommended for use with telaprevir |
| Efavirenz | 600 mg qd for 20 days | 750 mg q8h for 10 days | 21 | ↓ | 0.91 (0.82; 1.02) | 0.74 (0.65; 0.84) | 0.53 (0.44; 0.65) | None |
| Fosamprenavir (fAPV)/ ritonavir (rtv) | 700 mg fAPV/ 100 mg rtv bid for 20 days | 750 mg q8h for 10 days | 18 | ↓ | 0.67 (0.63; 0.71) | 0.68 (0.63; 0.72) | 0.70 (0.64; 0.77) | Not recommended for use with telaprevir |
| Lopinavir (LPV)/ritonavir (rtv) | 400 mg LPV/ 100 mg rtv bid for 20 days | 750 mg q8h for 10 days | 12 | ↓ | 0.47 (0.41; 0.52) | 0.46 (0.41; 0.52) | 0.48 (0.40; 0.56) | Not recommended for use with telaprevir |
| Ritonavir | 100 mg single dose | 750 mg single dose | 14 | ↑ | 1.30 (1.15; 1.47) | 2.00 (1.72; 2.33) | NA | None |
| Ritonavir | 100 mg q12h for 14 days | 750 mg q12h for 14 days | 5 | ↓ | 0.85 (0.63; 1.13) | 0.76[b,c] (0.60; 0.97) | 0.68 (0.57; 0.82) | None |
| Tenofovir disoproxil fumarate (TDF) | 300 mg qd TDF for 7days | 750 mg q8h for 7 days | 16 | ↔ | 1.01 (0.96; 1.05) | 1.00 (0.94; 1.07) | 1.03 (0.93; 1.14) | Increase clinical and laboratory monitoring for tenofovir-associated AEs (due to effect on TDF PK) |

**Table 1.3-2 Drug Interactions: Summary of Pharmacokinetic Parameters for Telaprevir in the Presence of Co-administered Drugs***

| Drug | Dose and Schedule | | N | Effect on Telaprevir PK[a] | LS Mean Ratio (90% CI) of Telaprevir PK With/Without Coadministered Drug | | | Clinical Comment/Outomce |
|---|---|---|---|---|---|---|---|---|
| | Drug | Telaprevir | | | $C_{max}$ | AUC or $C_{avg,ss}$[b] | $C_{min}$ | |
| Tenofovir disoproxil fumarate (TDF) and efavirenz (EFV) | 600 mg EFV /300 mg TDF qd for 7 days | 1125 mg q8h for 7 days | 15 | ↓ | 0.86[c] (0.76; 0.97) | 0.82[c] (0.73; 0.92) | 0.75[c] (0.66; 0.86) | None |
| | 600 mg EFV /300 mg TDF qd for 7 days | 1500mg q12h for 7 days | 16 | ↓ | 0.97[c] (0.88; 1.06) | 0.80[b,c] (0.73; 0.88) | 0.52[c] (0.42; 0.64) | None |

NA: not available/ not applicable; N = Number of subjects with data; qd = once daily; bid = twice daily; q8h = every 8 hours; q12h = every 12 hours

[a] The direction of the arrow (↑ = *increase,* ↓ = *decrease,* ↔ = *no change*) indicates the direction of the change in PK

[b] $C_{avg,ss}$ = Average concentrations at steady state ($AUC_\tau/\tau$).

[c] Value with co-administered drug and telaprevir / value with telaprevir 750 mg q8h alone

*Data provided are under fed conditions unless otherwise noted.

**Table 1.3-3 Drug Interactions: Summary of Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Telaprevir**

| Drug | Dose and Schedule | | N | Effect on Drug PK[a] | LS Mean Ratio (90% CI) of Drug PK With/Without Telaprevir[b] | | | Clinical Comment/Outomce |
|---|---|---|---|---|---|---|---|---|
| | Drug | Telaprevir | | | $C_{max}$ | AUC | $C_{min}$ | |
| Alprazolam | 0.5 mg single dose | 750 mg q8h for 10 days | 17 | ↑ | 0.97 (0.92; 1.03) | 1.35 (1.23; 1.49) | NA | Clinical monitoring for alprazolam |
| Amlodipine | 5 mg single dose | 750 mg q8h for 7 days | 19 | ↑ | 1.27 (1.21; 1.33) | 2.79 (2.58; 3.01) | NA | Use with caution. Dose reduction for amlodidpine should be considered. Clinical monitoring is recommended. |
| Atorvastatin | 20 mg single dose | 750 mg q8h for 7 days | 19 | ↑ | 10.60 (8.74;12.85) | 7.88 (6.84; 9.07) | NA | CONTRAINDICATED |
| Cyclosporine A (CsA) | 100 mg single dose when administered alone; 10 mg single dose when coadministered with telaprevir (D8) | 750 mg q8h for 11 days | 9 | ↑ | 0.13 (0.11;0.16) **Dose norm.:** 1.32 (1.08;1.60) | 0.46 (0.39; 0.55) **Dose norm.:** 4.66 (3.90;5.51) | NA | Use of telaprevir is not recommended in patients with organ transplants |
| Digoxin | 2 mg single dose | 750 mg q8h for 11 days | 20 | ↑ | 1.50 (1.36; 1.65) | 1.85 (1.70; 2.00) | NA | Start with lowest dose of digoxin. Serum digoxin concentrations should be monitored and titrated for clinical effect |

**Table 1.3-3 Drug Interactions: Summary of Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Telaprevir**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Escitalopram | 10 mg qd, for 7 days | 750 mg q8h for 14 days | 13 | ↓ | 0.70 (0.65; 0.76) | 0.65 (0.60; 0.70) | 0.58 (0.52; 0.64) | Doses of escitalopram may need to be adjusted. |
| Ethinyl estradiol (EE), coadministered with norethindrone (NE) | 0.035 mg qd EE/ 0.5 mg qd NE for 21 days | 750 mg q8h for 21 days | 24 | ↓ | 0.74 (0.68; 0.80) | 0.72 (0.69; 0.75) | 0.67 (0.63; 0.71) | Use 2 alternative (barrier) forms of contraception |
| Ketoconazole | 400 mg single dose | 1250 mg q8h for 4 doses | 81 | ↑ | 1.23 (1.14; 1.33) | 1.46 (1.35; 1.58) | NA | Limit KETO dose to 200 mg/day |
| | 200 mg single dose | 1250 mg q8h for 4 doses | 28 | ↑ | 1.75 (1.51; 2.03) | 2.25 (1.93; 2.61) | NA | |
| *R*-Methadone | Methadone maintenance therapy (40 to 120 mg/daily) | 750 mg q8h for 7 days | 15 | ↓ | 0.71 (0.66; 0.76) | 0.71 (0.66; 0.76) | 0.69 (0.64; 0.75) | No initial dose adjustment. Clinical monitoring is recommended as maintenance dose of methadone may need to be adjusted. |
| *S*-Methadone | Methadone maintenance therapy (40 to 120 mg/daily) | 750 mg q8h for 7 days | 15 | ↓ | 0.65 (0.60; 0.71) | 0.64 (0.58; 0.70) | 0.60 (0.54; 0.67) | |
| Midazolam (iv) | 0.5 mg iv single dose | 750 mg q8h for 9 days | 22 | ↑ | 1.02 (0.8; 1.31) | 3.40 (3.04; 3.79) | NA | Co-administration should be done in controlled setting with proposer clinical monitoring and management. Dose reduction of midazolam should be considered especially if more than a single dose is administered. |
| Midazolam (oral) | 2 mg oral single dose | 750 mg q8h for 11 days | 21 | ↑ | 2.86 (2.52; 3.25) | 8.96 (7.75; 10.35) | NA | CONTRAINDICATED |
| Norethindrone (NE), coadministered with EE | 0.035 mg qd EE/ 0.5 mg qd NE for 21 days | 750 mg q8h for 7 days | 24 | ↔ | 0.85 (0.81; 0.89) | 0.89 (0.86; 0.93) | 0.94 (0.87; 1.0) | Use 2 alternative (barrier) forms of contraception (due to effect on EE component) |
| Tacrolimus | 2 mg single dose when administered alone; 0.5 mg single dose when coadministered with telaprevir (D8) | 750 mg q8h for 13 days | 9 | ↑ | 2.34 (1.68;3.25) **Dose norm.:** 9.35 (6.73;13.0) | 17.6 (13.2; 23.3) **Dose norm.:** 70.3 (52.9;93.4) | NA | Use of telaprevir is not recommended in patients with organ transplants |
| Zolpidem | 5 mg single dose | 750 mg q8h for 10 days | 19 | ↓ | 0.58 (0.52;0.66) | 0.53 (0.45; 0.64) | NA | Clinical monitoring and dose titration is recommended for zolpidem |

**Table 1.3-3 Drug Interactions: Summary of Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Telaprevir**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Anti-HIV Drugs** | | | | | | | | |
| Atazanavir (ATV), boosted with ritonavir (rtv) | 300 mg ATV/ 100 mg rtv qd for 20 days | 750 mg q8h for 10 days | 7 | ↔ | 0.85 (0.73; 0.98) | 1.17 (0.97; 1.43) | 1.85 (1.40; 2.44) | None |
| Darunavir (DRV), boosted with ritonavir (rtv) | 600 mg DRV/ 100 mg rtv bid for 20 days | 750 mg q8h for 10 days | 11 (N=14 for $C_{max}$) | ↓ | 0.60 (0.56; 0.64) | 0.60 (0.57; 0.63) | 0.58 (0.52; 0.64) | Not recommended for use with telaprevir |
| | 600 mg DRV/ 100 mg rtv bid for 24 days | 1125 mg q12h for 4 days | 15 | ↓ | 0.53 (0.47; 0.59) | 0.49 (0.43; 0.55) | 0.42 (0.35; 0.51) | |
| Efavirenz | 600 mg qd for 20 days | 750 mg q8h for 10 days | 21 | ↔ | 0.84 (0.76; 0.93) | 0.93 (0.87; 0.98) | 0.98 (0.94; 1.02) | None |
| Efavirenz (EFV), coadministered with tenofovir disoproxil fumarate (TDF) | 600 mg EFV /300 mg TDF qd for 7 days | 1125 mg q8h for 7 days | 15 | ↓ | 0.76[b] (0.68; 0.85) | 0.82[b] (0.74; 0.90) | 0.90[b] (0.81; 1.01) | None |
| | 600 mg EFV /300 mg TDF qd for 7days | 1500 mg q12h for 7days | 16 | ↓ | 0.80[b] (0.74; 0.86) | 0.85[b] (0.79; 0.91) | 0.89[b] (0.82; 0.96) | |
| Fosamprenavir (fAPV), boosted with ritonavir (rtv) | 700 mg fAPV/ 100 mg bid rtv for 20 days | 750 mg q8h for 10 days | 18 | ↓ | 0.65 (0.59; 0.70) | 0.53 (0.49; 0.58) | 0.44 (0.40; 0.50) | Not recommended for use with telaprevir |
| | 700 mg fAPV/ 100 mg bid rtv for 24 days | 1125 mg q12h for 4 days | 17 (N=18 for $C_{min}$) | ↓ | 0.60[b] (0.55; 0.67) | 0.51[b] (0.47; 0.55) | 0.42[b] (0.37; 0.47) | |
| Lopinavir (LPV), boosted with ritonavir (rtv) | 400 mg LPV/ 100 mg rtv b.i.d for 20 days | 750 mg q8h for 10 days | 12 | ↔ | 0.96 (0.87; 1.05) | 1.06 (0.96; 1.17) | 1.14 (0.96; 1.36) | Not recommended for use with telaprevir |
| Tenofovir disoproxil fumarate | 300 mg qd for 7 days | 750 mg q8h for 7 days | 16 | ↑ | 1.30 (1.16; 1.45) | 1.30 (1.22; 1.39) | 1.41 (1.29;1.54) | Increase clinical and laboratory monitoring for tenofovir-associated AEs |
| Tenofovir, on coadministration of tenofovir disoproxil fumarate (TDF) and efavirenz (EFV) | 600 mg EFV /300 mg TDF qd for 7 days | 1125 mg q8h for 7 days | 15 | ↑ | 1.22[b] (1.12; 1.33) | 1.10[b] (1.03; 1.18) | 1.17[b] (1.06; 1.28) | None |
| | 600 mg EFV /300 mg TDF qd for | 1500 mg q12h for 7 days | 16 | ↑ | 1.24[b] (1.13; 1.37) | 1.10[b] (1.03; 1.17) | 1.06[b] (0.98; 1.15) | |

**Table 1.3-3 Drug Interactions: Summary of Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Telaprevir**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 7 days | | | | | | | |

[a] The direction of the arrow (↑ = *increase,* ↓ = *decrease,* ↔ = *no change*) indicates the direction of the change in PK

[b] Value with co-administered drug and telaprevir / value with telaprevir 750 mg q8h alone

*Ongoing Studies*

The Applicant has submitted study protocols for 2 additional drug interaction studies. The first is investigating the potential PK interaction between telaprevir and buprenorphine in subjects on stable buprenorphine/naloxone maintenance therapy and the second is investigating the effect of a potential PK interaction between telaprevir and raltegravir.

**Exposure-Response**

Based on the Applicant's popPK analysis using sparse PK data from phase 2 and phase 3 studies, the estimated PK parameters are in good agreement with PK parameters derived from intensive PK sampling within the PK substudy in studies C216 and 108. Due to the high correlation between the modeled parameters, $C_{min,ss}$, $C_{max,ss}$, and $AUC_{\tau}$, no exposure parameter could be identified as the best predictor of any efficacy or safety endpoint; thus, any of these parameters could be used in relating exposure to response.

In general, the relationship between telaprevir exposure and all efficacy endpoints, including $SVR_{24planned}$, RVR, eRVR, VBT (viral breakthrough), and relapse, were shallow and statistically non-significant. Higher telaprevir exposure was weakly associated with increased $SVR_{24planned}$ (the primary efficacy endpoint in the pivotal trials). In reference to adverse events, the relationship between telaprevir and incidence of rash was shallow and non-signficant. On the contrary, higher telaprevir exposure was significantly associated with increased risk of anemia and Hgb toxicity, defined as Hgb <10 g/dL or any decrease from baseline >3.5 g/dL (refer to the pharmacometrics review in the appendix for further details).

**Pyrazinoic Acid Metabolite**

Following administration of multiple doses of telaprevir (in combination with Peg-IFN and RBV) in HCV-infected patients, pyrazinoic acid (PZA), VRT-127394, and VRT-0922061 were the 3 predominant metabolites that were present at >10% of total drug-related material at steady-state. The percent of PZA to total drug-related material was approximately 23%. The Applicant conducted an exploratory analysis using blood samples from a phase 2 study (104EU) investigating the relationship between all telaprevir metabolites and the incidence of rash. PZA was the only major metabolite that demonstrated a correlation between amount in plasma and incidence and severity of rash. The Applicant states that the subject number was too low and variability too high to make a firm conclusion regarding the role of PZA and rash. It was noted by the pharm/tox reviewer that PZA is also a metabolite of pyrazinamide and niacin, both of which cause rash However, the maximum steady-state levels of PZA in plasma following telaprevir administration is far lower (>10-fold lower) than PZA in plasma following administration of pyrazinamide. The

incidence of rash in patients administered pyrazinamide is 2-3%. In addition, the rash caused by telaprevir was clinically disctinct from that caused by pyrazinamide or niacin.Thus, the rash associated with telaprevir is unlikely to be mediated by PZA.

**QTc Prolongation**

Two studies were conducted to determine whether therapeutic and supratherapeutic doses of telaprevir prolonged the QTc interval. The first study was conducted using ketoconazole to achieve supratherapeutic exposures of telaprevir (study 008). The second study (study C136) was undertaken to include females in the study and a supratherapeutic dose without ketoconazole to boost telaprevir exposures since ketoconazole has been associated with QTc prolongation.

The CDER Interdisciplinary Review Team conducted an independent review of both studies and concluded that no significant QTc prolongation effect of telaprevir was detected from study C136. Their analysis showed that the maximum placebo-adjusted QTcF mean increase at the 1875 mg dose is 7.0 msec [90% CI: 4.2-9.9]. In addition, no significant concentration-QT relationship (P = 0.35) was established from that study. Therefore it was concluded that telaprevir does not prolong the QTc interval.

## 1.4 List of Abbreviations

| | |
|---|---|
| ESI | Event of special interest |
| eRVR | Extended rapid virologic response (undetectable HCV RNA at weeks 4 and 12 of treatment) |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| LC-MS/MS | Liquid chromatography-electrospray tandem dual mass spectrometry |
| LLOQ | Lower limit of quantification |
| Non-responder | Did not achieve an undetectable HCV RNA level during or at the end of a course of Peg-IFN/RBV therapy |
| Null responder | Did not achieve a 2-log drop in HCV RNA at week 12 of therapy |
| Partial responder | Achieved a ≥2-log drop in HCV RNA at week 12 of therapy but never achieved undetectable HCV RNA levels while on treatment |
| Peg-IFN | Peglated interferon alpha |
| P-gp | P-glycoprotein |
| PMC | Post-marketing commitment |
| PMR | Post-marketing requirement |
| QTc | Corrected QT interval |
| RBV | Ribavirin |
| Relapse | Having confirmed detectable HCV RNA during the follow-up period after previous undetectable HCV RNA at end of treatment |
| RVR | Rapid virologic response (undetectable HCV RNA at week 4) |
| SVR | Sustained virologic response |
| $SVR24_{planned}$ | Undetectable HCV RNA at 24 weeks after the last planned dose of study drug) |
| $SVR24_{actual}$ | Undetectable HCV RNA at 24 weeks after the last actual dose of study treatment |
| T/PR | Telaprevir + Peg-IFN + RBV treatment |
| T(DS)/PR | Telaprevir with a delayed start (by 4 weeks) in combination with Peg-IFN + RBV treatment |
| Pbo | Placebo |
| TVR, VX-950 | Telaprevir |
| ULOQ | Upper limit of quantification |
| Viral breakthrough (VBT) | An increase > 1 log in HCV RNA level from the lowest level reached, or a value of HCV RNA >100 IU/mL in subjects whose HCV RNA has previously become < 25 IU/mL during treatment |

## 2. Question-Based Review

### 2.1 General Attributes of the Drug

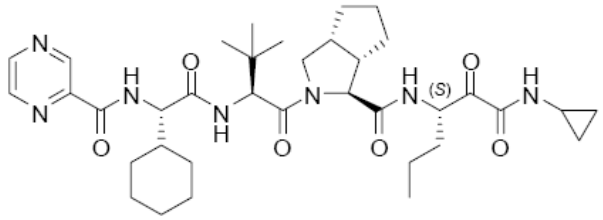
#### 2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to the clinical pharmacology and biopharmaceutics review?

Telaprevir (VX-950, TVR) is a small molecule α-keto amide peptidomimetic inhibitor of the hepatitis C virus NS3•4A protease. It is a single diastereomer with the S-configuration (also designated as the L-diastereomer) which can epimerize both *in vitro* and *in vivo* to the corresponding R-disastereomer (also designated as the D-diastereomer), VRT-127394.

*Structural Formula:* $C_{36}H_{53}N_7O_6$

*Chemical Name:* (1*S*,3a*R*,6a*S*)-2-[(2*S*)-2-({(2*S*)-2-cyclohexyl-2- [(pyrazin-2-ylcarbonyl)amino] acetyl}amino)-3,3-dimethylbutanoyl]-*N*-[(3*S*)-1-(cyclopropylamino)-1,2-dioxohexan-3-yl]-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrole- 1-carboxamide

*Chemical Structure:*




*Molecular Weight:* 679.85 g/mol

*Solubility Profile:* The following table lists the solubility of telaprevir in several solvents at 24 ± 3° C. In general, telaprevir is more soluble in organic solvents than aqueous ones.

| Solvent | Solubility in Solution (mg/mL) | Final pH | USP Definition[a] |
|---|---|---|---|
| Water | 0.0047 | 6.02 | Practically insoluble |
| 1% Sodium Lauryl Sulfate (SLS) | 0.45 | 7.27 | Very slightly soluble |
| 10% Vitamin E -TPGS | 0.099 | 5.20 | Practically insoluble |
| Acetone | 5.02 | Not applicable | Slightly soluble |
| Methylene Chloride | 366.0 | Not applicable | Freely soluble |
| PEG 400 | 0.42 | Not applicable | Very slightly soluble |
| Propylene Glycol | 0.73 | Not applicable | Very slightly soluble |

[a] Freely soluble: 100-1000 mg/mL, Slightly soluble: 1-10 mg/mL, Very slightly soluble: 0.1-1 mg/mL, Practically insoluble: <0.1 mg/mL

*Partition Coefficient:* The apparent log 1-octanol/aqueous partition coefficient (Po/w) values of telaprevir at room temperature (24±3° C) are 3.96 (pH 1), 3.87 (pH 5), and 4.00 (pH 7). The partition coefficient is pH independent, since telaprevir does not ionize between pH 1 and 7. The high apparent partition coefficient is consistent with the low aqueous solubility of the drug substance, suggesting the hydrophobic nature of telaprevir.

*Drug Product:* Telaprevir is formulated as an immediate release, film-coated tablet for oral administration. The manufacturing of the drug product occurs (b) (4) The final tablet is capsule-shaped, film-coated purple and debossed with the characters "V 375" on one side. The coated tablet is the intended commercial formulation; however, the uncoated tablet (identical core components) was used in all the phase 3 studies. Each tablet contains 375 mg of telaprevir drug substance, and has a total target weight of 1 g. The components and composition of the tablet are listed in the table below.

| Component | Quality Reference | Component Function | Amount per Tablet (mg) | Content (%w/w) |
|---|---|---|---|---|
| **Telaprevir** (b) (4) | | | | |
| Telaprevir drug substance | Section 3.2.S.4.1 | Active pharmaceutical ingredient | 375 | 37.3 |
| Hypromellose acetate succinate (HPMCAS) | USP/NF[c] | (b) (4) | | |
| Sodium lauryl sulfate (SLS) | USP/NF | | | |
| (b) (4) | USP/NF | | | |
| | USP/NF | | | |
| | USP | | | |
| Dibasic calcium phosphate, anhydrous | USP | | | |
| Microcrystalline cellulose | USP/NF | | | |
| Croscarmellose sodium | USP/NF | | | |
| Colloidal silicon dioxide | USP/NF | | | |
| Sodium stearyl fumarate | USP/NF | | | |
| (b) (4) | (b) (4) | | | |
| | USP | | | |
| **Total** | -- | -- | **1005.7** | **100.0** |

(b) (4)

### 2.1.2 What are the proposed mechanism(s) of action and therapeutic indications(s)?

Telaprevir is a potent slow-binding inhibitor of the active site of the HCV NS3•4A protease. The NS3•4A protease is a serine protease that is essential for the replication of HCV.

The Applicant is seeking an indication for telaprevir in combination with peginterferon-alfa and ribavirin, for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease, including cirrhosis, who are treatment naïve or who have been previously treated, including prior null responders, partial responders, and relapsers.

### 2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed dosage regimen of telaprevir is oral administration of 750 mg (2 x 375-mg tablets) taken 3 times a day (7-9 hours apart) with food for 12 weeks.

## 2.2 General Clinical Pharmacology

### 2.2.1 What are the design features and results of the clinical pharmacology and clinical studies used to support dosing or claims?

The Applicant conducted a total of 29 phase 1 studies (including 27 studies in healthy volunteers and 2 studies in HCV-infected patients), 6 phase 2 studies in HCV-infected patients, and 3 phase 3 studies in HCV-infected patients. Some key phase 1 studies relating to clinical pharmacology include the following:

- A single, ascending dose study in healthy volunteers
- A single-dose ADME study in healthy volunteers
- A food effect study using four different fed and fasted conditions in healthy volunteers
- A single-dose dose proportionality study with nested BE study in healthy volunteers
- A multiple, ascending dose study in healthy volunteers
- Two hepatic impairment studies (1 in subjects with mild hepatic impairment and 1 in subjects with moderate hepatic impairment)
- A renal impairment study in subjects with severe renal impairment
- Two thorough QTc prolongation studies in healthy volunteers
- Fifteen drug interaction studies with various probe substrates, model inhibitors/inducers of CYP3A and P-gp, and commonly co-administered drugs in healthy volunteers

The findings of the key phase 2 and phase 3 studies are summarized below.

Phase 2: Study VX05-950-102

This study was a single-arm, open-label study conducted to assess the safety, clinical activity, and pharmacokinetics of 28 days of combination dosing with telaprevir,

Peg-IFN-alfa-2a, and RBV. A total of 12 HCV-infected subjects who were treatment-naïve were included in the study. Following a 1250-mg telaprevir loading dose and 750 mg q8h in combination with the standard dose of Peg-IFN-alpha-2a (180 μg/week), and RBV (1000 to 1200 mg/day [weight-based dose regimen]), all subjects had undetectable HCV RNA levels at the end of the 28-day dosing period. The median change in HCV RNA ($log_{10}$ IU/mL) was -5.7997 (range: -6.989 to –4.635). Both sparse and intensive PK samples were collected. The absorption of telaprevir was characterized by 2 phases: an initial slow phase followed by a rapid phase. Absorption was preceded by a lag time of an average of 0.2 hours. The popPK estimates of clearance and volume of distribution were 28.4 L/hr and 212 L, respectively.

Phase 2: Study VX05-950-104 (PROVE1)

This was a 48-week, randomized, placebo-controlled, double-blind study in HCV-infected subjects who were treatment-naïve. A total of 260 subjects were planned for enrollment and randomization to receive either placebo or telaprevir (1250-mg telaprevir loading dose followed by 750 mg q8h) for 12 weeks in combination with Peg-IFN-alfa-2a (180 μg/wk) and ribavirin (1000 or 1200 mg/day) for 12, 24, or 48 weeks. The different treatment arms included the following:

| | | Treatments | | |
|---|---|---|---|---|
| **Treatment Group** | **Total Treatment Duration** | **Telaprevir 750 mg q8h** | **Peg-IFN-alfa-2a (180 μg/week) and RBV (1000 or 1200 mg/day, depending on body weight)** | **Number of Subjects** |
| T12/PR12 | 12 weeks | Weeks 1 through 12 | Weeks 1 through 12 | 20 |
| T12/PR24 | 24 weeks | Weeks 1 through 12 | Weeks 1 through 24 | 80 |
| T12/PR48 | 48 weeks | Weeks 1 through 12 | Weeks 1 through 48 | 80 |
| Pbo12/PR48 | 48 weeks | -- | Weeks 1 through 48 | 80 |

T = telaprevir; PR = Peg-IFN-alfa-2a and RBV, Pbo = placebo

The treatment in this study was response-guided: subjects in the T12/PR12 and T12/PR24 groups must have met the protocol-defined rapid viral response criterion ("RVR criterion;" undetectable HCV RNA from week 4 through week 10 in the T12/PR12 group, and undetectable HCV RNA from week 4 through week 20 in the T12/PR24 group) in order to stop treatment at 12 and 24 weeks, respectively. (The "RVR criterion" was not applicable to the T12/PR48 and Pbo12/PR48 groups.)

The efficacy analysis showed that the SVR rates for the T12/PR12, T12/PR24, T12/PR48, and Pbo12/PR48 groups were 35%, 61%, 67%, and 41%, respectively, indicating that the T12/PR24 and T12/PR48 groups were significantly more effective than the placebo group. On the contrary, the T12/PR12 group performed slightly worse than the placebo group.

Logistic regression modeling indicated that model-predicted telaprevir $C_{min,ss}$ was a predictor of severe rash and viral breakthrough, day 29 RBV plasma concentration was a predictor of SVR, gastrointestinal AEs, and grade 2 or greater decrease in hemoglobin, and that day 29 Peg-IFN-alfa-2a serum concentration was a predictor of RVR, eRVR, viral breakthrough, relapse, severe rash, gastrointestinal AEs, and grade 2 or greater decrease in hemoglobin.

Phase 2: Study VX05-950-104EU (PROVE 2)

This was a 48-week, randomized, partially placebo-controlled, partially double-blinded study in HCV-infected subjects who were treatment-naïve. A total of 323 subjects received placebo or telaprevir (1250-mg telaprevir loading dose followed by 750 mg q8h) in combination with Peg-IFN-alfa-2a (180 µg/wk), with and without RBV (1000 or 1200 mg/day) for 12 weeks, followed by Peg-IFN-alfa-2a and RBV for 0, 12, or 36 weeks. This trial (conducted exclusively in Europe) was performed nearly concurrently with PROVE1 with very similar treatment groups. The main differences in study design between PROVE1 and PROVE2 is the absence of the T12/PR48 group in PROVE2 and the addition of a T12/P12 group (without RBV). In addition the response-guided criteria were different between the two trials. The different treatment arms included the following:

| | | Treatments | | |
|---|---|---|---|---|
| **Treatment Group** | **Total Treatment Duration** | **Telaprevir (750 mg q8h)** | **Peg-IFN-alfa-2a (180 µg/week)** | **RBV (1000 or 1200 mg/day)a** |
| T12/PR12 | 12 weeks | Weeks 1 through 12 | Weeks 1 through 12 | Weeks 1 through 12 |
| T12/PR24 | 24 weeks | Weeks 1 through 12 | Weeks 1 through 24 | Weeks 1 through 24 |
| T12/P12 | 12 weeks | Weeks 1 through 12 | Weeks 1 through 12 | -- |
| Pbo12/PR48 | 48 weeks | -- | Weeks 1 through 48 | Weeks 1 through 48 |

T: telaprevir; P: Peg-IFN-alfa-2a; PR: Peg-IFN-alfa-2a and RBV; Pbo: placebo.
a RBV dose depended on body weight.

Treatment in this study was response-guided: subjects in the T12/P12, T12/PR12, and T12/PR24 groups must have met the protocol-defined viral response criterion (undetectable HCV RNA at week 10 in the T12/P12 and T12/PR12 groups, and undetectable HCV RNA at week 20 in the T12/PR24 group) in order to complete treatment at 12 weeks (T12/P12 and T12/PR12 groups) and 24 weeks (T12/PR24 group), respectively. The viral response criterion was not applicable to the Pbo12/PR48 group.

The efficacy analysis showed that the SVR rates for the T12/PR12, T12/PR24, T12/P12, and Pbo12/PR48 groups were 60%, 69%, 36%, and 46%, respectively, indicating that the T12/PR24 group performed better than the T12/PR12 groups, although both groups were significantly more effective than the placebo group. On the contrary, the T12/P12 group performed considerably worse than the placebo group, indicating that RBV co-administration is crucial for attaining SVR in this population.

A popPK analysis was performed for telaprevir using sparse PK data from all subjects. Both sparse and intensive PK samples were collected. The population CL/F and V/F values were estimated to be 31.6 L/hr and 347 L, respectively. Logistic regression modeling indicated that model-predicted telaprevir $C_{min,ss}$ was a predictor of RVR, eRVR, viral breakthrough, severe rash, and grade 2 or greater decrease in hemoglobin. Day 29 Peg-IFN-alfa-2a serum concentration was a predictor of viral breakthrough. Day 29 RBV plasma concentration was a predictor of RVR, eRVR, and grade 2 or greater decrease in hemoglobin.

Phase 2: Study VX06-950-106 (PROVE 3)

This study was a randomized, stratified, partially placebo-controlled, partially double-blind study in HCV-infected subjects who failed previous therapy with Peg-IFN/RBV (including relapsers, non-responders, subjects with viral breakthrough). A total

of 465 subjects received 1 of 4 treatments: Peg-IFN-alfa-2a and RBV for 48 weeks; telaprevir in combination with Peg-IFN-alfa-2a and RBV for 24 weeks followed by 24 weeks of Peg-IFN-alfa-2a and RBV given alone; telaprevir in combination with Peg-IFN-alfa-2a for 24 weeks; and telaprevir in combination with Peg-IFN-alfa-2a and RBV for 12 weeks followed by 12 weeks of Peg-IFN-alfa-2a and RBV given alone. Telaprevir was administered at a loading dose of 1125 mg as the first dose on day 1 followed by a dose of 750 mg every 8 hours (q8h). Peg-IFN/RBV was administered according to standard dosing recommendations in their respective labels. Randomization was stratified by race and prior viral response. The different treatment arms included the following:

| Treatment Group | Day 1 – Week 12 | Weeks 12 – 24 | Weeks 24 – 48 |
|---|---|---|---|
| T12/PR24 | telaprevir, Peg-IFN-alfa-2a/RBV | placebo, Peg-IFN-alfa-2a /RBV | not applicable |
| T24/PR48 | telaprevir, Peg-IFN-alfa-2a/RBV | telaprevir, Peg-IFN-alfa-2a/RBV | Peg-IFN-alfa-2a/RBV |
| T24/P24 | telaprevir, Peg-IFN-alfa-2 | telaprevir, Peg-IFN-alfa-2a | not applicable |
| Pbo24/PR48 | placebo, Peg-IFN-alfa-2/ RBV | placebo, Peg-IFN-alfa-2a/RBV | Peg-IFN-alfa-2a/RBV |

SVR rates in the total population were 51%, 53%, 24%, and 14% in the T12/PR24, T24/PR48, T24/P24, and Pbo/PR48 groups, respectively. SVR rates among subjects with cirrhosis were 53% in the T12/PR24 group, 45% in the T24/PR48 group, 18% in the T24/P24 group, and 8% in the Pbo12/PR48 group. SVR rates overall and in prior relapsers were comparable among subjects in the T/PR groups with and without cirrhosis. SVR rates in prior non-responders were lower among subjects in the T/PR groups with cirrhosis than in subjects without cirrhosis. Treatment with the T24/P24 regimen resulted in a lower SVR rate, higher breakthrough rate, and higher relapse rate compared to the T/PR treatment groups, suggesting that RBV was necessary to increase viral suppression and decrease the rate of breakthrough and of relapse.

A popPK analysis was done for telaprevir using sparse PK data from all subjects. The population apparent clearance and apparent volume of distribution values were estimated to be 37.5 L/hr and 499 L, respectively. Logistic regression modeling indicated that model-predicted telaprevir $C_{min,ss}$ was a predictor of RVR, eRVR, SVR, viral breakthrough, and hemoglobin grade ≥2. Day 29 Peg-IFN-alfa-2a serum concentration was also a predictor of RVR, eRVR, SVR, viral breakthrough, and hemoglobin grade ≥2. Day 29 RBV plasma concentration was found to be a predictor of relapse and hemoglobin grade ≥2.

Phase 2: Study VX-950-TiDP24-C208

This study was an open-label, randomized, multi-center trial in treatment-naïve subjects with chronic HCV infection who were randomized to receive 1 of 2 different dose regimens of telaprevir in combination with standard therapy Peg-IFN-alfa-2a (Pegasys®)and RBV (Copegus®) or Peg-IFN-alfa-2b (PegIntron®) and RBV (Rebetol®) at the standard doses. A total of 160 subjects (40 per treatment group) were planned to be enrolled. Subjects were randomized to 1 of 4 treatment groups:

-T12(q8h)/P(2a)R: telaprevir 750 mg q8h with Pegasys/Copegus

-T12(q8h)/P(2b)R: telaprevir 750 mg q8h with PegIntron/Rebetol

-T12(q12h)/P(2a)R: telaprevir 1125 mg q12h with Pegasys/Copegus
-T12(q12h)/P(2b)R: telaprevir 1125 mg q12h with PegIntron/Rebetol

All subjects received 12 weeks of telaprevir treatment in combination with standard therapy (i.e., Peg-IFN and RBV). At week 12, telaprevir dosing ended and subjects continued on standard therapy only. The total duration of treatment depended on the subjects' individual on-treatment viral response and was maximally 48 weeks:

1. Peg-IFN and RBV treatment was stopped at week 24 if a subject's HCV RNA was undetectable (i.e., no HCV RNA was detected in the subject's plasma samples) from week 4 through week 20.
2. Peg-IFN and RBV treatment was continued up to week 48 if a subject did not have undetectable HCV RNA at week 4 (i.e., the subject did not have rapid viral response [RVR]), but the subject's HCV RNA level became undetectable at any visit after week 4 and remained undetectable until week 20.
3. In situations not captured by rules 1 and 2 (i.e., for different patterns of viral response), viral response was analyzed case by case, and the treatment duration of Peg-IFN and RBV was decided by the virology monitor.

SVR24 rates were similar in all 4 treatment groups (81.0 to 85.0%). At Week 4, 66.7 to 82.5% of the subjects had undetectable HCV RNA. There were no significant differences between the 4 treatment groups. The most frequently reported AEs were rash and pruritis (50-72% depending on the treatment group). A trend towards a positive relationship between the exposure to telaprevir and the severity of rash events and grades of treatment-emergent hemoglobin abnormalities was observed; however, very low numbers of subjects experienced a grade 3 rash event.

In the PK substudy, steady-state telaprevir Cmax was comparable for the q12h versus the q8h dosing regimen in the P(2a)R treatment groups (90% CI of the LSmeans ratio was within 0.80-1.25) and 11% higher for the q12h dosing regimen in the P(2b)R treatment groups. Telaprevir Cmin was 21% lower for the q12h dosing regimen in the P(2a)R treatment groups, while values were comparable in the P(2b)R treatment groups. Telaprevir $AUC_{24h}$ was 6% lower for the q12h regimen compared to the q8h regimen in the P(2a)R treatment groups. For the P(2b)R treatment groups, $AUC_{24h}$ was comparable for the q12h and q8h regimens. The population PK data for telaprevir were consistent with the results of the PK substudy.

Phase 3: Study VX07-950-108 (ADVANCE)

This study was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study conducted in treatment-naïve subjects with genotype 1, chronic hepatitis C virus (HCV) infection. The study compared 2 regimens of telaprevir dosed with Peg-IFN-alfa-2a and RBV against standard treatment, Peg-IFN-alfa-2a and RBV. Telaprevir was given in combination with Peg-IFN-alfa-2a and RBV for either the first 8 weeks (T8/PR group) or the first 12 weeks (T12/PR group). For subjects who achieved an extended rapid viral response (eRVR, defined as undetectable HCV RNA at week 4 and week 12), Peg-IFN-alfa-2a and RBV were dosed for a total of 24 weeks. For subjects who did not achieve eRVR, Peg-IFN-alfa-2a and RBV were dosed for a total of 48 weeks. A total of 1095 subjects were enrolled. The treatment arms were as follows:

| Treatment Group | Telaprevir Dosing Period | Telaprevir-matching Placebo Dosing Period | Peg-IFN-alfa-2a and RBV Dosing Period |
|---|---|---|---|
| | | | Treatment |
| T8/PR | Day 1 through Week 8 | Weeks 9 through 12 | Day 1 through Week 24–with eRVR<br>Day 1 through Week 48–without eRVR |
| T12/PR | Day 1 through Week 12 | --- | Day 1 through Week 24–with eRVR<br>Day 1 through Week 48–without eRVR |
| Pbo/PR48 | --- | Weeks 1 through 12 | Day 1 through Week 48 |

T: telaprevir; PR: Peg-IFN-alfa-2a and RBV; Pbo: placebo; eRVR: extended rapid viral response (undetectable HCV RNA at Week 4 and Week 12)

Telaprevir was administered orally in the fed state at a dose of 750 mg every 8 hours (q8h). Peg-IFN-alfa-2a was administered by subcutaneous injection once per week at a dose of 180 μg. RBV was administered orally twice daily at a dose of 1000 mg/day for subjects weighing <75 kg and 1200 mg/day for subjects weighing ≥75 kg.

$SVR_{24planned}$ rates, the primary efficacy endpoint, were significantly higher in both T/PR (T8/PR and T12/PR) groups compared to the Pbo/PR48 group: 68.7% versus 43.8% for T8/PR group versus Pbo/PR48 group ($P<0.0001$) and 74.7% versus 43.8% for T12/PR group versus Pbo/PR48 group ($P<0.0001$). Nausea, rash, pruritus, and anemia occurred at a higher incidence (≥5%) in both T/PR groups than in the Pbo/PR48 group.

Telaprevir concentrations were similar in the T8/PR and T12/PR groups. Peg-IFN-alfa-2a and RBV concentrations were similar in all treatment groups. Noncompartmental analysis (NCA) was performed on 41 intensive telaprevir PK profiles from 40 subjects. Median (minimum, maximum) telaprevir Cmin, Cavg, Cmax, and AUCτ were 1970 (39.3, 4160) ng/mL, 2730 (1010, 5480) ng/mL, 3400 (1450, 6870) ng/mL, and 21,800 (8120, 43,900) hr*ng/mL, respectively. A popPK analysis of telaprevir data was done on intensive and sparse PK assessments from 641 subjects. Apparent oral clearance and apparent volume of distribution were estimated to be 32.3 L/hr and 673 L, respectively. Logistic regression modeling indicated that model-predicted telaprevir $C_{avg,ss}$ was a predictor of RVR, eRVR, SVR, viral breakthrough, and grade 2 or higher hemoglobin decrease. Day 29 Peg-IFN-alfa-2a serum concentration was a predictor of RVR, eRVR, SVR, viral breakthrough, and grade 2 or higher hemoglobin decrease. Day 29 RBV plasma concentration was found to a predictor of grade 2 or higher hemoglobin decrease.

Phase 3: Study VX08-950-111 (ILLUMINATE)

This study was a phase 3, randomized, open-label, multicenter study conducted in treatment-naïve subjects with genotype 1, chronic hepatitis C. The study was designed to evaluate the SVR rates in subjects who achieved an eRVR (undetectable HCV RNA levels at week 4 and week 12 on treatment) with telaprevir in combination with Peg-IFN-alfa-2a and RBV and to evaluate the difference in SVR rates between T12/PR24 and T12/PR48 treatment regimens in subjects who achieve eRVR. Subjects who achieved an eRVR and completed the week 20 visit were randomized in a 1:1 ratio to stop all study treatment at week 24 (randomized withdrawal; T12/PR24/eRVR+ group) or to continue treatment with Peg-IFN-alfa-2a and RBV to week 48 (T12/PR48/eRVR+ group). Subjects who did not achieve an eRVR were assigned a total treatment with Peg-IFN-alfa-2a and RBV for 48 weeks (T12/PR48/eRVR- group). A total of 540 subjects were part of the full analysis set. The treatment arms were as follows:

| Treatment Group | Telaprevir Dosing Period | Peg-IFN-alfa-2a and RBV Dosing Period |
|---|---|---|
| T12/PR24/eRVR+ (randomized)[a] | Day 1 through Week 12 | Day 1 through Week 24 |
| T12/PR48/eRVR+ (randomized)[a] | Day 1 through Week 12 | Day 1 through Week 48 |
| T12/PR48/eRVR- (assigned)[b] | Day 1 through Week 12 | Day 1 through Week 48 |

[a] Subjects who achieved eRVR and completed the Week 20 visit were randomized in a 1:1 ratio to the T12/PR24/eRVR+group or the T12/PR48/eRVR+ group.

[b] Subjects who did not achieve eRVR, but completed the Week 20 Visit, were assigned to the T12/PR48/eRVR- group.

Telaprevir was administered orally in the fed state at a dose of 750 mg every 8 hours (q8h). Peg-IFN-alfa-2a was administered by subcutaneous injection once per week at a dose of 180 µg. RBV was administered orally twice daily at a dose of 1000 mg/day for subjects weighing <75 kg and 1200 mg/day for subjects weighing ≥75 kg.

The $SVR_{24planned}$ rates were 92.0% in the randomized T12/PR24/eRVR+ group and 87.5% in the randomized T12/PR48/eRVR+ group. The T12/PR24/eRVR+ treatment regimen is non-inferior to the T12/PR48/eRVR+ treatment regimen, as the lower limit of the 95% CI, -2.1%, was entirely to the right of the pre-defined non-inferiority margin of -10.5%. The key secondary endpoint, SVR week 72 rates, and the $SVR_{24actual}$ rates were consistent with the $SVR_{24planned}$ rates. During the telaprevir phase, the most commonly reported adverse events (>25% in any treatment group) were fatigue, pruritus, nausea, anemia, rash, headache, diarrhea, insomnia, and influenza-like illness.

Telaprevir, Peg-IFN-alfa-2a, and RBV concentrations were similar in all treatment arms. Empirical Bayes estimation of telaprevir data was performed on sparse PK assessments from 173 subjects to estimate telaprevir exposure variables for these subjects. Median (minimum, maximum) model-predicted telaprevir Cmin,ss, Cavg,ss, Cmax,ss, and AUCτ were: 2460 (1150, 4840) ng/mL, 2810 (1430, 5530) ng/mL, 3020 (1590, 6320) ng/mL, and 22,500 (11400, 44,200) hr*ng/mL, respectively.

Phase 3: Study VX-950-TiDP24-C216 (REALIZE)

This study was a randomized, double-blind, placebo-controlled phase 3 study in subjects with genotype 1 chronic HCV infection who failed prior treatment with Peg-IFN/RBV. The study was designed to compare the efficacy, safety, and tolerability of 2 regimens of telaprevir (with and without delayed start (DS) of telaprevir) combined with Peg-IFN-alfa-2a and RBV versus standard treatment (Peg-IFN-alfa-2a and RBV). For the DS group, Peg-IFN/RBV was started 4 weeks prior to initiation of telaprevir treatment. Telaprevir was administered at a dose of 750 mg every 8 hours (q8h) and Peg- IFN-alfa-2a and RBV at standard doses, i.e., 180 µg once weekly and 1000 or 1200 mg/day (weight-based), respectively. Subjects were randomized to one of the following treatments:

-Treatment group A (260 subjects: 140 prior relapsers and 120 prior non-responders): telaprevir in combination with Peg-IFN-alfa-2a and RBV for 12 weeks; followed by placebo in combination with Peg-IFN-alfa-2a and RBV for 4 weeks; followed by Peg-IFN-alfa-2a and RBV for 32 weeks.

-Treatment group B (260 subjects: 140 prior relapsers and 120 prior non-responders): placebo in combination with Peg-IFN-alfa-2a and RBV for 4 weeks;

followed by telaprevir in combination with Peg-IFN-alfa-2a and RBV for 12 weeks; followed by Peg-IFN-alfa-2a and RBV for 32 weeks.
-Treatment group C (control group, 130 subjects: 70 prior relapsers and 60 prior non-responders): placebo in combination with Peg-IFN-alfa-2a and RBV for 16 weeks; followed by Peg-IFN-alfa-2a and RBV for 32 weeks.

A total of 662 subjects completed treatment. The $SVR_{24planned}$ rates in prior relapsers were 83.4%, 87.9%, and 23.5% in the T12/PR48, T12(DS)/PR48, and Pbo/PR48 groups, respectively. The $SVR_{24planned}$ rates in prior non-responders were 41.3%, 41.5%, and 9.4% in the T12/PR48, T12(DS)/PR48, and Pbo/PR48 groups, respectively. The proportion of subjects achieving $SVR_{24planned}$ was statistically significantly higher in each of the telaprevir treatment groups (with and without delayed start) than in the placebo group for prior relapsers and prior non-responders separately (all P values <0.001). The most commonly reported adverse events (>25% in any treatment group) were fatigue, pruritus, headache, rash, and influenza-like illness.

This study included an intensive PK substudy with intensive sampling for 8 hours that took place on one day between 6 and 8 weeks post-initiation of treatment. Sparse PK samples were collected from all subjects throughout the dosing period and were used in the popPK analysis. The popPK analysis revealed no differences in telaprevir exposure were apparent between prior relapsers and prior non-responders, subjects with HCV genotype 1a, or 1b, or subjects with or without cirrhosis, while exposure was lower in the higher body weight quartiles, and in men compared to women. Telaprevir AUC was a significant predictor of $SVR_{24planned}$.

### 2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in the clinical pharmacology and clinical studies?

The primary endpoint in the phase 2 and phase 3 studies was proportion of subjects achieving SVR. SVR, or sustained virologic response, is defined as having undetectable plasma HCV RNA levels at both the end of treatment and at week 24 post-cessation of treatment. Other markers of response included extended rapid virological response (eRVR, undetectable HCV RNA at weeks 4 and 12 of treatment) and end-of-treatment (EOT) response.

### 2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

In most of the early phase 1 studies, both telaprevir and its R-disastereomer, VRT-127394, were measured in plasma. VRT-127394 is present at ~23% of telaprevir concentrations in total drug-related material at steady-state. However, as it became more clear that VRT-127394 played a minor role in the pharmacological activity of telaprevir (~30-fold lower activity than telaprevir), the Applicant no longer measured VRT-127394

plasma concentrations in some of the later drug interaction studies and in phase 2 and 3 studies.

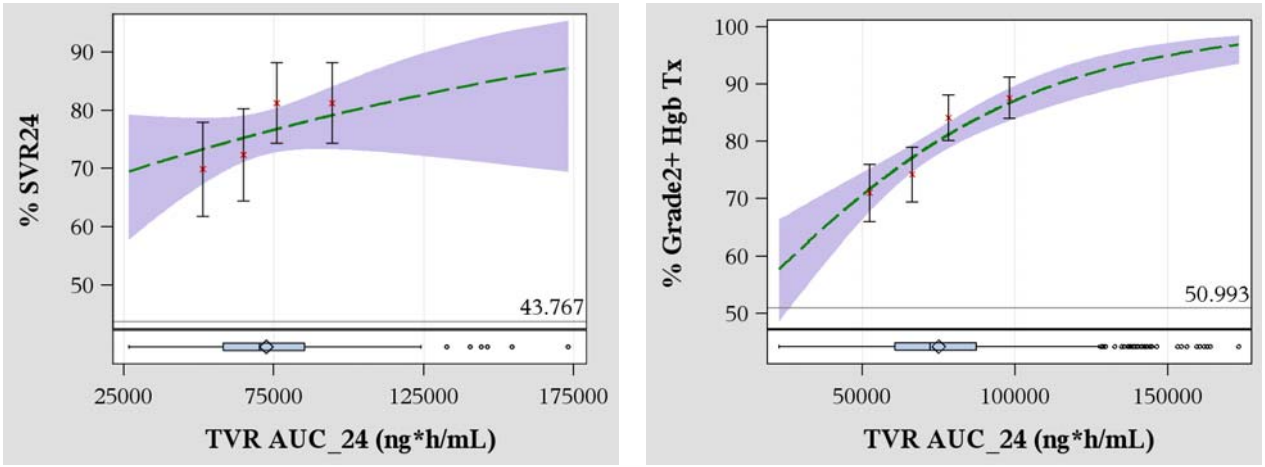
### 2.2.4 Exposure-response

#### 2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

The relationships between telaprevir exposure and all efficacy endpoints [SVR (sustained viral response), RVR (rapid viral response), eRVR (extended rapid viral response), VBT (viral breakthrough), and relapse] were shallow, and statistically non-significant. $SVR24_{planned}$(undetectable HCV RNA at the end of treatment (EOT) visit and at 24 weeks after the last planned dose of study treatment without any confirmed detectable in between) was the primary efficacy endpoint in the pivotal trials. As shown in Figure 2.2.4.1-1 (left), higher telaprevir exposure was weakly associated with increased $SVR24_{planned}$.

Multivariate logistic analyses indicated that RBV exposure was significantly correlated with eRVR and SVR. However, this correlation between RBV exposure and SVR did not exist in the sub-group of patients who achieved RVR, which accounted for approximately 70% of the telaprevir treatment population.

Figure 2.2.4.1-1. Higher Telaprevir Exposure Was Weakly Associated with Increased SVR (Left [a]), but Was Significantly Associated with Increased Risk of Hgb Tox (Right [b])



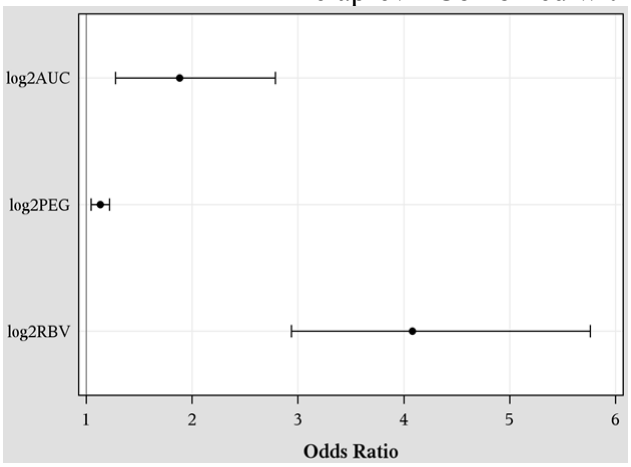

[a] Exposure-SVR analysis was conducted in the pooled naïve patients with T12/PR (RGT or 48 WK).
[b] Exposure-Hgb Tx was conducted in the pooled patients with T12/PR. Grade 2+ Hgb Tx was defined as Hgb < 10 g/dL or any decrease from baseline > 3.5 g/dL.

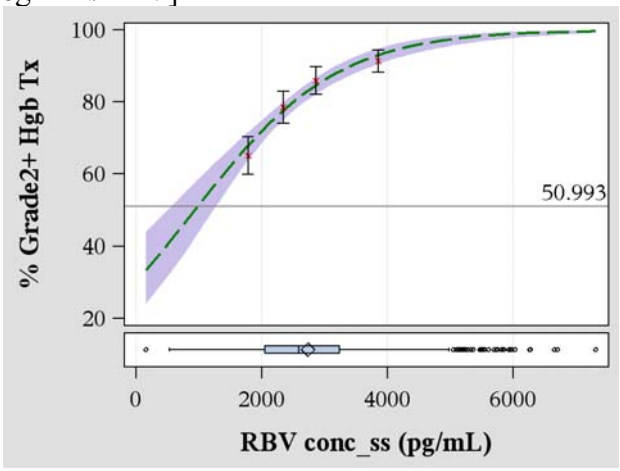
#### 2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

The relationship between rash toxicity and telaprevir, PegIFN, and RBV exposures were shallow, and statistically non-significant. However, higher telaprevir exposure was significantly associated with increased risk of anemia and Hgb toxicity, defined as Hgb < 10 g/dL or any decrease from baseline > 3.5 g/dL (Figure 2.2.4.1-1, right). From a multivariate logistic analysis, the odds ratio of Hgb toxicity associated with doubling of telaprevir exposure is 2.4 (95% CI: 1.6, 3.6), after adjusting for PegIFN and RBV exposure.

The exposure-response relationship between Hgb toxicity and RBV exposure is steepest compared to the relationship with respect to telaprevir or Peg-IFN exposure, with the odds ratio associated with doubling of RBV exposure as 5.2 (95% CI: 3.6, 7.5) [Figure 2.2.4.2-1].

Figure 2.2.4.2-1 RBV Exposure Effect on Hgb Toxicity [in Pooled Population with 12-week Telaprevir Combined with Peg-IFN/RBV]




In addition to exploring the relationship between telaprevir exposure and rash, the Applicant found a potential correlation between pyrazinoic acid (PZA) levels in plasma and rash in an exploratory analysis in a small number of subjects from three phase 2 studies. PZA levels were higher in subjects with rash than in subjects without rash and the levels appeared to increase with increased severity of rash. However, due to the small sample size and high inter-subject variability with respect to metabolite levels, there was insufficient power to conclude that the presence of rash was definitively correlated with pyrazinoic acid levels.

### 2.2.4.3 Does this drug prolong the QT or QTc interval?

A modest prolongation effect of telaprevir at a supratherapeutic dose of 1875 mg q8h on the QTcF interval was observed in healthy volunteers, based on the Applicant's analysis (with a placebo adjusted maximum mean increase of 8.0 msec [90% CI: 5.1-10.9]). The CDER IRT (interdisciplinary review team) conducted an independent review and concluded that no significant QTc prolongation effect of telaprevir was detected from the tQT study. Based on the IRT's analysis, the maximum placebo adjusted QTcF mean increase at the 1875 mg dose is 7.0 msec

[90% CI: 4.2-9.9]. In addition, no significant concentration-QT relationship (P = 0.35) was established from that study.

Plasma concentrations with the supratherapeutic dose of 1875 mg q8h in healthy volunteers were comparable to those observed in HCV patients who received telaprevir 750 mg q8h in combination with Peg-IFN and RBV. In principle, the worst-case scenario for telaprevir exposure would be a patient who takes telaprevir (in combination with Peg-IFN and ribavirin) with ketoconazole (24% increase in Cmax) with a high-fat meal (4% increase in Cmax). In addition, the test plasma concentration in the current tQT study may be insufficient to cover the worst case scenario at steady-state expected due to severe renal impairment (since the renal impairment study was conducted with only a single dose of telaprevir). The magnitude of increase in Cmax following multiple doses of telaprevir may be higher than the 3% increase observed with a single dose of telaprevir in subjects with severe renal impairment.

#### 2.2.4.4 Is the dose and dosing regimen selected by the Applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Yes, the dose and dosign regimend proposed by the Applicant is appropriate, based on known concentration-resonse relationships. The 750 mg q8h telaprevir dose in combination with Peg-IFN and RBV was consistently superior to the standard of care (SOC) in all of the phase 2 and phase 3 clinical trials. The following conclusions were made by the pharmacometrics reviewer:

- The exposure-response relationship indicated that the exposure range obtained with the 750 mg q8h telaprevir dosing seemed to establish a good balance between efficacy and safety in combination with Peg-IFN and RBV. A higher dose of telaprevir is clearly not desired due to the much stronger exposure-anemia relationship compared to the exposure-efficacy relationships (Figure 2.2.4.1-1).
- The exposure-response relationship between Hgb toxicity and RBV exposure is steepest compared to the relationship with respect to telaprevir or Peg-IFN exposure. Therefore, using dose reduction of RBV to manage Hgb toxicity and anemia is reasonable (Figure 2.2.4.2-1).
- 8-weeks of telaprevir treatment (shorter duration) does not provide an advantage over 12 weeks of treatment (longer duration) in selected subpopulation (Figure 2.2.4.4-1). Although in subgroup analyses treatment naïve patients with low baseline HCV RNA levels (<80000 IU/mL) may seem to achieve similar SVR with the shorter (8-week) TVR treatment compared to the 12-week TVR treatment (Figure 2.2.4.4-2), the breakthrough rate was higher with shorter duration.
- For prior relapse patients, the response-guided Peg-IFN/RBV treatment duration (24 weeks for patients who achieve eRVR and 48 weeks for those who do not) is reasonable, based on the following: 1) The SVR rates for prior relapse patients who achieve eRVR were high (>90%) with short (24 weeks)

or long (48 weeks) Peg-IFN/RBV duration based on cross-trial comparison; 2) Prior relapse patients may be considered a potential subset within treatment naïve population who are suitable for RGT ,and data from treatment naïve and experienced population can be bridged to derive dosing recommendations for prior relapse patients. (Please refer to the pharmacometrics review in the Appendix for full details of analysis)

- The response-guided Peg-IFN/RBV treatment duration proposed for treatment-naïve and prior relapse patients also is reasonable for prior partial or null responder patients based on the following: 1) The SVR rates for patients who achieve eRVR were similar (Partial responders~62-77% and null responders~62-71%) for each group with short (24 weeks) or long (48 weeks) Peg-IFN/RBV duration based on cross-trial comparison; 2) Prior partial and null responders may be considered potential subsets within the treatment naïve population who are suitable for RGT, and data from treatment naïve and experienced populations can be bridged to derive dosing recommendations for prior relapse patients. (Please refer to the pharmacometrics review in the Appendix for full details of analysis)
- Patients with HCV RNA > 1000 IU/mL (instead of (b) (4) as proposed by the Applicant) at Week 4 should discontinue telaprevir, and >1000 IU/mL at Week 12 should discontinue Peg-IFN/RBV treatment, based on the following: 1) there were about 2% of treatment naïve patients with 100-1000 IU/mL HCV RNA at Week 4. Among these patients, 26% achieved SVR. Therefore, TVR/Peg-IFN/RBV treatment should be continued in subjects with 100-1000 IU/mL HCV RNA at Week 4, especially when there is no other better choice available; 2) About 1% of treatment naïve patients had HCV RNA levels between 100 and 1000 IU/mL at Week 12. Among these patients, 25% achieved SVR. Therefore, Peg-IFN/RBV treatment can be continued in subjects with 100-1000 IU/mL HCV RNA at Week 12. (Please refer to the pharmacometrics review in the Appendix for full details of analysis)

Figure 2.2.4.4-1 Proportion of Patients Achieving SVR Was Numerically Higher in T12/PR Compared to T8/PR (Left), but Proportion of Patients with Grade 3 Rash ESI Was Also Higher in T12/PR (Right) [Study 108]

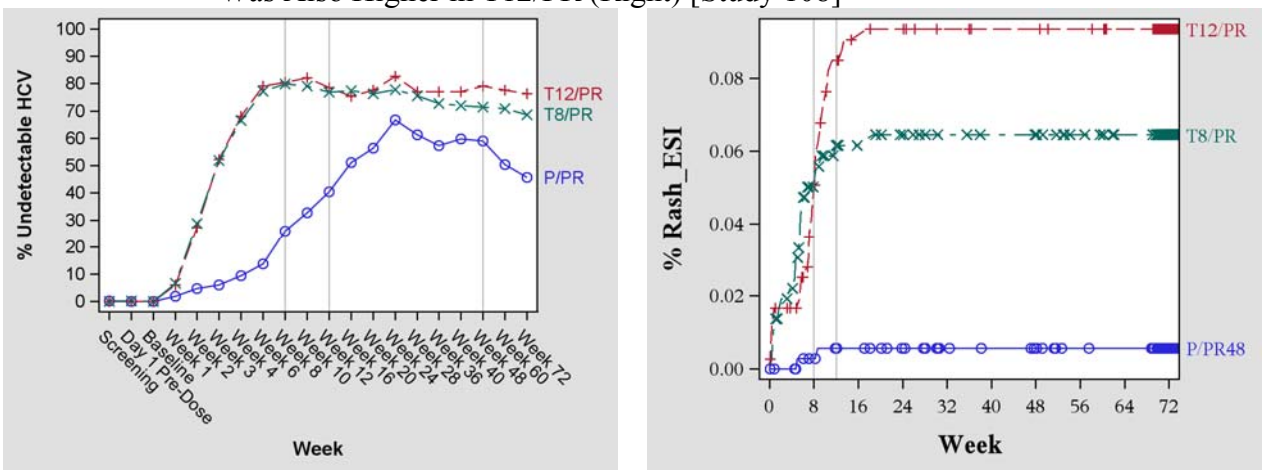
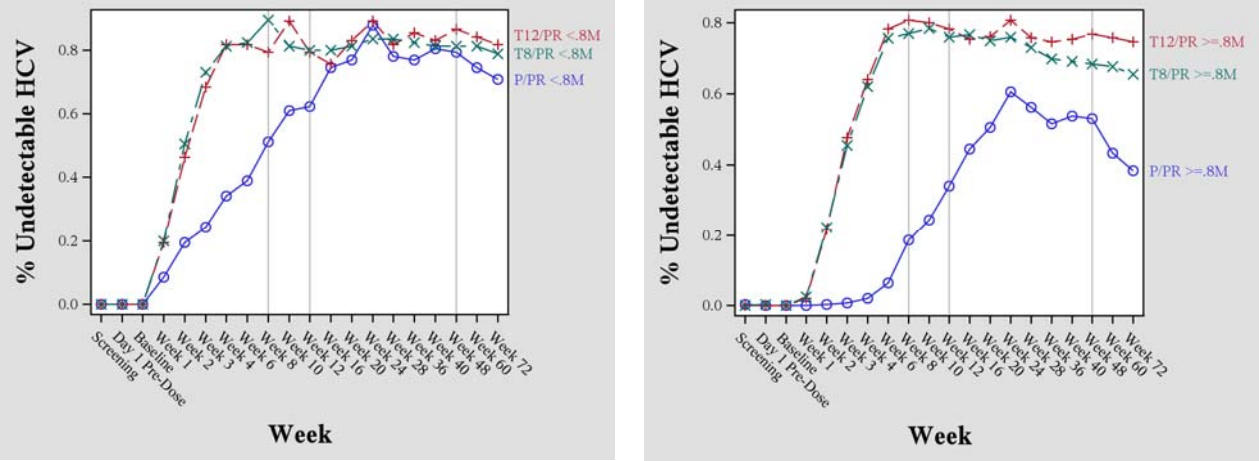


Figure 2.2.4.4-2 Proportion Achieving SVR in T8/PR Was Comparable to T12/PR Among Patients with Low Baseline HCV RNA Levels (Left: Baseline HCV RNA <800,000 IU/mL, Right: Baseline HCV RNA ≥800,000 IU/mL) [Study 108]




An additional unresolved dosing issue involves the directions for administration with food. The Applicant is proposing that telaprevir be administered "with food." In the phase 3 studies, patients were instructed to take telaprevir with a meal that is part of a regular diet (not low-fat). The label should reflect similar instructions to patients, particularly in light of the significantly lower telaprevir exposures following a low-fat meal as compared with a standard fat meal or high-fat meal. (See Sect. 2.5.3 for further details.)

## 2.2.5 What are the PK characteristics of telaprevir and VRT-127394?

### 2.2.5.1 What are the single dose and multiple dose PK parameters?

Telaprevir exhibits both non-linear and time-dependent PK. At single doses, the half-life increases and clearance decreases with increasing telaprevir dose (Table 2.2.5.1-1). The half-life of single-dose telaprevir at the therapeutic dose (750 mg) is approximately 4 hours while the half-life following multiple doses is ~11 hours. After multiple doses in healthy subjects, telaprevir trough concentrations increase during the first 2-3 days, followed by a steady decrease in concentrations until steady-state is reached around day 7 of dosing, indicating that telaprevir causes mixed effects on its own metabolism (both inhibiting and inducing CYP3A). However, the net result is higher concentrations at steady-state than after a single dose. From study VX04-950-101, in healthy subjects, the accumulation ratio for $AUC_\tau$ at the therapeutic dose is approximately 3.1 between day 1 and steady-state (day 5) and in HCV-infected patients, the accumulation ratio for $AUC_\tau$ is

approximately 1.8 between day 1 and steady-state (day 14) (see section 2.2.5.9 for further discussion). Mean telaprevir and VRT-127394 PK parameters from representative single-dose studies in healthy volunteers at the telaprevir therapeutic dose of 750 mg are presented in the tables below.

Table 2.2.5-1 Mean Single-Dose Telaprevir PK Parameters in Healthy Subjects from Study VX07-950-017 in the Fed State (SD)

| PK Parameter | 375 mg (N=19) | 750 mg (N=19) | 1125 mg (N=18) | 1500 mg (N=9) | 1875 mg (N=9) |
|---|---|---|---|---|---|
| $C_{max}$ (ng/mL) | 539.79 | 1740.84 | 2346.67 | 3232.22 | 3259.44 |
| | (217.75) | (785.28) | (917.21) | (1496.90) | (1661.71) |
| $AUC_{0\text{-last}}$ (hr*ng/mL) | 3084.24 | 11102.16 | 18297.72 | 25991.47 | 30393.76 |
| | (1513.28) | (6692.22) | (8941.90) | (14006.59) | (17129.77) |
| $AUC_{0\text{-}\infty}$ (hr*ng/mL) | 3146.52 | 11749.10[b] | 19362.18[c] | 24250.23[d] | 34944.13[e] |
| | (1579.56) | (7484.56) | (11199.97) | (10194.68) | (22574.69) |
| $t_{max}$ (hr)[a] | 5 (3.55,6) | 5 (3.5,12) | 5 (3.5,12) | 5 (3,8) | 5 (2.5,8) |
| $t_{1/2}$ (hr) | 3.23 | 3.96[b] | 5.44[c] | 6.49 | 8.31 |
| | (0.70) | (1.10) | (1.79) | (2.20) | (3.30) |
| Cl/F (L/hr) | 157.43 | 100.61 | 77.96 | 68.88 | 92.83 |
| | (98.82) | (85.44) | (55.60) | (40.39) | (115.75) |
| Vz/F (L) | 692.80 | 522.53 | 560.09 | 574.30 | 1102.52 |
| | (367.89) | (342.80) | (293.69) | (281.23) | (1634.82) |

Table 2.2.5-2 Mean Single-Dose Telaprevir PK Parameters Across Studies VX06-950-010, VX-950-TiDP24-C121, and VX07-950-017 Following a 750-mg Dose (2 X 375 mg tablets) and Standard Fat Breakfast in Healthy Volunteers

| **Mean ± SD or (range)** | **Cmax** (ng/mL) | **Tmax** (hr) | **$AUC_{0\text{-}24h}$** (ng*hr/mL) | **$AUC_{inf}$** (ng*hr/mL) | **$T_{1/2}$** (hr) | **Cl/F** (L/hr) |
|---|---|---|---|---|---|---|
| Study VX06-950-010 (N=24) | 2144 ± 901 | 4 (2.5-6) | 13522 ± 7572 | 14039 ± 8454 | 3.96 ± 1.1 | ND |
| Study VX-950-TiDP24-C121 (N=28) | 2217 ± 836 | 4 (1.5-6) | 14350 ± 6547 | 14930 ± 7297 | 4.04 ± 1.1 | ND |
| Study VX07-950-017 (N=19) | 1741 ± 785 | 5 (3.5-12) | 11102 ± 6692 | 11749 ± 7484 | 3.96 ± 1.1 | 100.6 ±85 |

ND = Not determined

Table 2.2.5-3 Mean Single-Dose VRT-127394 PK Parameters Across Studies VX07-950-017 and VX-950-TiDP24-C121 Following a 750-mg Dose (2 X 375 mg tablets) and Standard Fat Breakfast in Healthy Volunteers

| **Mean ± SD or (range)** | **Cmax** (ng/mL) | **Tmax** (hr) | **$AUC_{0\text{-}24h}$** (ng*hr/mL) | **$AUC_{inf}$** (ng*hr/mL) | **$T_{1/2}$** (hr) | **Cl/F** (L/hr) |
|---|---|---|---|---|---|---|
| Study VX07-950-017 (N=19) | 511 ± 255 | 5 (4-12) | 4712 ± 3261 | 5203 ± 3959 | 4.77 ± 1.3 | ND |
| Study VX-950-TiDP24-C121 (N=28) | 731 ± 279 | 5 (2.5-8) | 6520 ± 3204 | 7019 ± 3900 | 4.42 ± 1.4 | ND |

ND = Not determined

Figure 2.2.5-1 Mean Telaprevir Plasma-Concentration vs. Time Profiles Following a Single Dose at Various Doses (Study VX07-950-017)

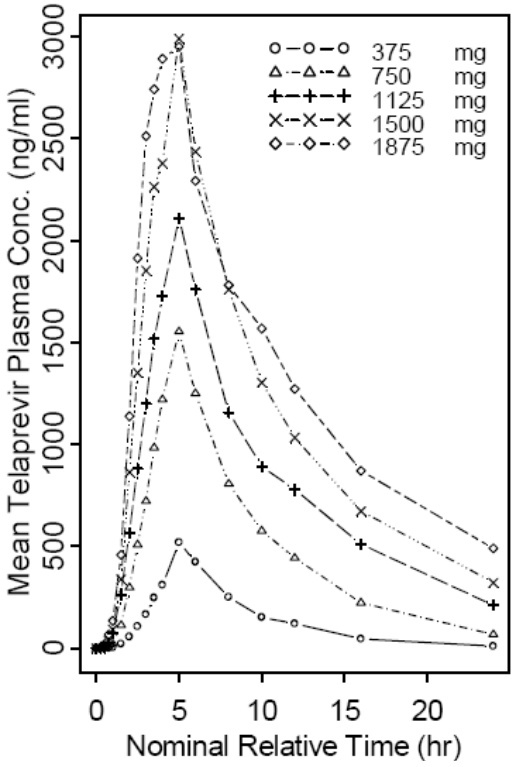



Figure 2.2.5-2 Mean VRT-127394 Plasma-Concentration vs. Time Profiles Following a Single Dose at Various Doses (Study VX07-950-017)

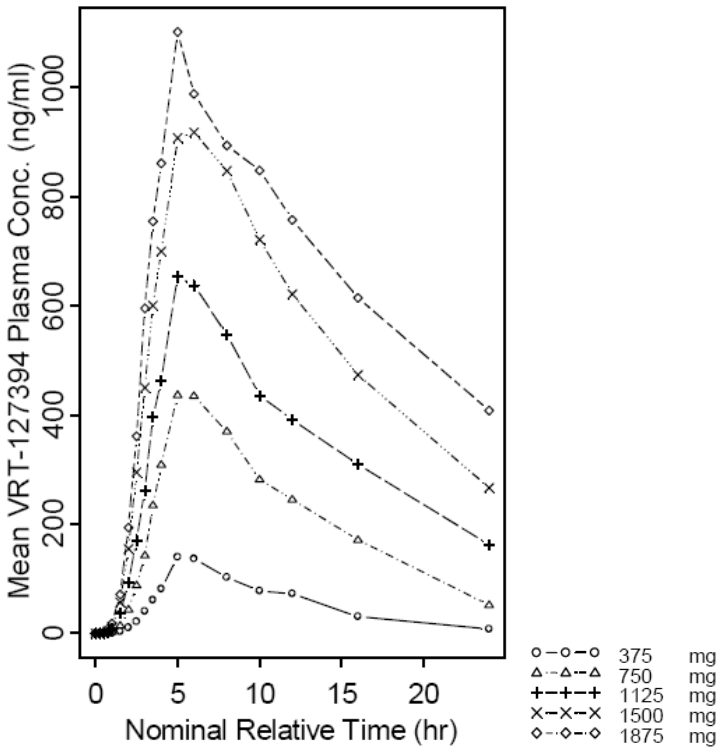


Table 2.2.5-4 Mean Multiple-Dose Telaprevir PK Parameters Across Studies VX07-950-018, VX-950-TiDP24-C123, and VX-950-TiDP24-C124 Following a 750-mg Dose (2 X 375 mg tablets) and Standard Fat Breakfast in Healthy Volunteers

| **Mean ± SD or (range)** | **Cmax** (ng/mL) | **Tmax** (hr) | **$AUC_{0-8h}$** (ng*hr/mL) | **Cmin** (ng/mL) |
|---|---|---|---|---|
| StudyVX07-950-018 (N=19) | 3167 ± 778 | 2.7 (1-4) | 20470 ± 5317 | 1981 ± 660 |
| Study VX-950-TiDP24-C123 (N=16) | 3338 ± 766 | 3 (1.5-5) | 20810 ± 5230 | 1903 ± 618 |
| Study VX-950-TiDP24-C124 (N=20) | 3104 ± 752 | 3.5 (2-5) | 18850 ± 4091 | ND |

ND = Not determined

Table 2.2.5-5 Mean Multiple-Dose VRT-127394 PK Parameters Across Studies VX07-950-018, VX-950-TiDP24-C123, and VX-950-TiDP24-C124 Following a 750-mg Dose (2 X 375 mg tablets) and Standard Fat Breakfast in Healthy Volunteers

| **Mean ± SD or (range)** | **Cmax** (ng/mL) | **Tmax** (hr) | **$AUC_{0-8h}$** (ng*hr/mL) | **Cmin** (ng/mL) |
|---|---|---|---|---|
| StudyVX07-950-018 (N=19) | 2076 ± 643 | 2.7 (0.75-3) | 14143 ± 4342 | 1461 ± 459 |
| Study VX-950-TiDP24-C123 (N=16) | 1804 ± 432 | 3.75 (0-6) | 12320 ± 3145 | 1303 ± 424 |
| Study VX-950-TiDP24-C124 (N=20) | 2033 ± 420 | 4.0 (2-6) | 13660 ± 2598 | ND |

ND = Not determined

Mean exposure parameters for both Telaprevir and VRT-127394 were generally in good agreement across studies when comparing within the single-dose or multiple-dose regimens in healthy volunteers.

### 2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

In study VX04-950-101, multiple ascending doses of telaprevir were administered to both healthy and HCV-infected subjects. Three doses of telaprevir were used in this study: 450 mg q8h, 750 mg q8h, and 1250 mg BID. Intensive PK sampling took place on days 1 and 5 in the healthy subject cohort and on days 1 and 14 in the HCV-infected subject group.

The results show that following a single dose, AUCτ in HCV-infected subjects were approximately 51% higher at the therapeutic dose of telaprevir (750 mg q8h) than in healthy subjects (Tables 2.2.5.2-1 and 2.2.5.2-2). However, following multiple doses, exposures were not significantly different between the two populations. The increase in AUC was more proportional with dose in healthy subjects than in HCV-infected subjects following both single and multiple doses, with exposure increasing less than dose proportional in HCV patients. The accumulation at

steady-state at the 750 mg dose was higher for healthy subjects than in infected subjects (accumulation ratios were 3.1 vs. 1.8, respectively).

Table 2.2.5.2-1 Telaprevir and VRT-127394 $AUC_{0-8h}$ Values (ng*hr/mL) for Healthy Subjects (Part A)

| Analyte, Time Point | VX-950 Dose | n | Median | Mean | CV |
|---|---|---|---|---|---|
| **VX-950, Day 1** | 450 | 6 | 1996 | 2039 | 64% |
| | 750 | 6 | 3478 | 3766 | 45% |
| | 1250 | 6 | 6626 | 6619 | 51% |
| **VX-950, Day 5** | 450 | 6 | 6991 | 7854 | 37% |
| | 750 | 6 | 10520 | 11554 | 33% |
| | 1250 | 6 | 15923 | 15045 | 26% |
| **VRT-127394, Day 1** | 450 | 6 | 468 | 645 | 80% |
| | 750 | 6 | 1062 | 1024 | 41% |
| | 1250 | 6 | 2471 | 2435 | 54% |
| **VRT-127394, Day 5** | 450 | 6 | 3574 | 3937 | 35% |
| | 750 | 6 | 5201 | 5630 | 40% |
| | 1250 | 6 | 10580 | 10117 | 33% |

Table 2.2.5.2-2 Telaprevir and VRT-127394 $AUC_{0-8h}$ Values (ng*hr/mL) for HCV-Infected Subjects (Part B)

| Analyte, Time Point | VX-950 Dose | N | $t_{last}$ | Median | Mean | CV |
|---|---|---|---|---|---|---|
| **VX-950, Day 1** | 450 | 10 | 8 | 5512 | 5593 | 51% |
| | 750 | 8 | 8 | 5612 | 5699 | 39% |
| | 1250[a] | 10 | 8 | 7135 | 7194 | 30% |
| | | | 12 | 9224 | 9426 | 29% |
| **VX-950, Day 14** | 450 | 10 | 8 | 9276 | 9626 | 37% |
| | 750 | 8 | 8 | 9476 | 10078 | 36% |
| | 1250[a] | 10 | 8 | 11231 | 11021 | 29% |
| | | | 12 | 13923 | 13867 | 26% |
| **VRT-127394, Day 1** | 450 | 10 | 8 | 2501 | 2360 | 43% |
| | 750 | 8 | 8 | 2039 | 2254 | 43% |
| | 1250[a] | 10 | 8 | 2194 | 2372 | 29% |
| | | | 12 | 3489 | 3557 | 28% |
| **VRT-127394, Day 14** | 450 | 10 | 8 | 5088 | 5705 | 50% |
| | 750 | 8 | 8 | 6129 | 6174 | 34% |
| | 1250[a] | 10 | 8 | 5606 | 5469 | 27% |
| | | | 12 | 7196 | 7291 | 23% |

[a] AUC data for the 1250 mg group are shown for a $t_{last}$ of 8 hours to facilitate comparison with the other dose groups and for a $t_{last}$ of 12 hours because that was the dosing interval for the 1250 mg group. $t_{last} = 8$ then $AUC_{last} = AUC_{0-8}$ ; $t_{last} = 12$ then AUClast = $AUC_{0-12}$

### 2.2.5.3 What are the characteristics of drug absorption?

Telaprevir is most likely absorbed in the small intestine, with no evidence for absorption in the colon. To evaluate absorption in the colon, healthy subjects received a single oral dose of 200 mg telaprevir in the fasted state, using the Enterion™ capsule, which targeted delivery of drug to the ascending colon. Nine out of 10 subjects received capsules that were successfully activated in the targeted colonic release site, and 8 of these subjects had telaprevir concentrations below the limit of quantification (2 ng/mL). These results suggest that telaprevir is most likely absorbed in the small intestine.

Telaprevir's absorption is also influenced by P-gp transporter efflux. *In vitro* studies performed with human Caco-2 cells indicated that telaprevir is a

substrate of P-gp. (Caco-2 study results suggested that telaprevir is highly subject to efflux.) *In vitro* studies did not demonstrate that telaprevir is an inhibitor of P-gp; however a subsequent clinical study showed a drug interaction with digoxin, suggesting that telaprevir may inhibit/saturate P-gp in the gut. Thus, the *in vitro* study for assessing P-gp inhibition was not predictive of the *in vivo* situation.

The absolute bioavailability of telaprevir has not been determined in humans. However, several formulations of telaprevir have been developed and studied. Based on cross-study comparisons, the early suspension formulation studied in VX03-950-001 had substantially lower bioavailability (~2-3 fold lower) than subsequent tablet formulations (both the 250-mg and the 375-mg tablets). The two tablet strengths also differed in bioavailability. The 375-mg tablet demonstrated ~40% higher bioavailability than the 250-mg tablet when administered in the fed state (study VX06-950-010).

Food also affects the bioavailability of telaprevir. A 3- to 4-fold increase in the AUC and $C_{max}$ of telaprevir was observed when the 375-mg tablet formulation that was used in the phase 3 studies was administered to healthy subjects as a single 750-mg dose in the fed state (standard breakfast: approximately 533 Kcal, 189 Kcal from fat) compared to the fasted state.

### 2.2.5.4 What are the characteristics of drug distribution?

Telaprevir is approximately 59% to 76% bound to human plasma proteins, mainly to α-1-acid glycoprotein (AAG) and human serum albumin (HSA) at concentrations ranging from 0.1 µM to 20 µM. The protein binding is concentration-dependent and decreases with increasing telaprevir concentrations at all concentrations of HSA and AAG. In addition, protein binding of telaprevir is affected by the concentration of HSA and AAG. Binding to telaprevir decreased as concentrations of HSA and AAG decreased. Telaprevir was displaced from its binding sites in human plasma in the presence of ritonavir or warfarin *in vitro*. The free fraction of $^{14}$C-telaprevir increased approximately 30% in the presence of either ritonavir or warfarin. However, the binding of warfarin or ritonavir was not affected by telaprevir over the concentration range of 0.1 through 20 µM.

The mean V/F of telaprevir in healthy subjects in phase 1 studies is approximately 377 L, suggesting a large volume of distribution, with extensive penetration of telaprevir into tissues beyond systemic circulation. V/F of telaprevir was estimated from population PK analyses of phase 2 and phase 3 studies in HCV-infected patients to be between 212 and 673 L.

### 2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

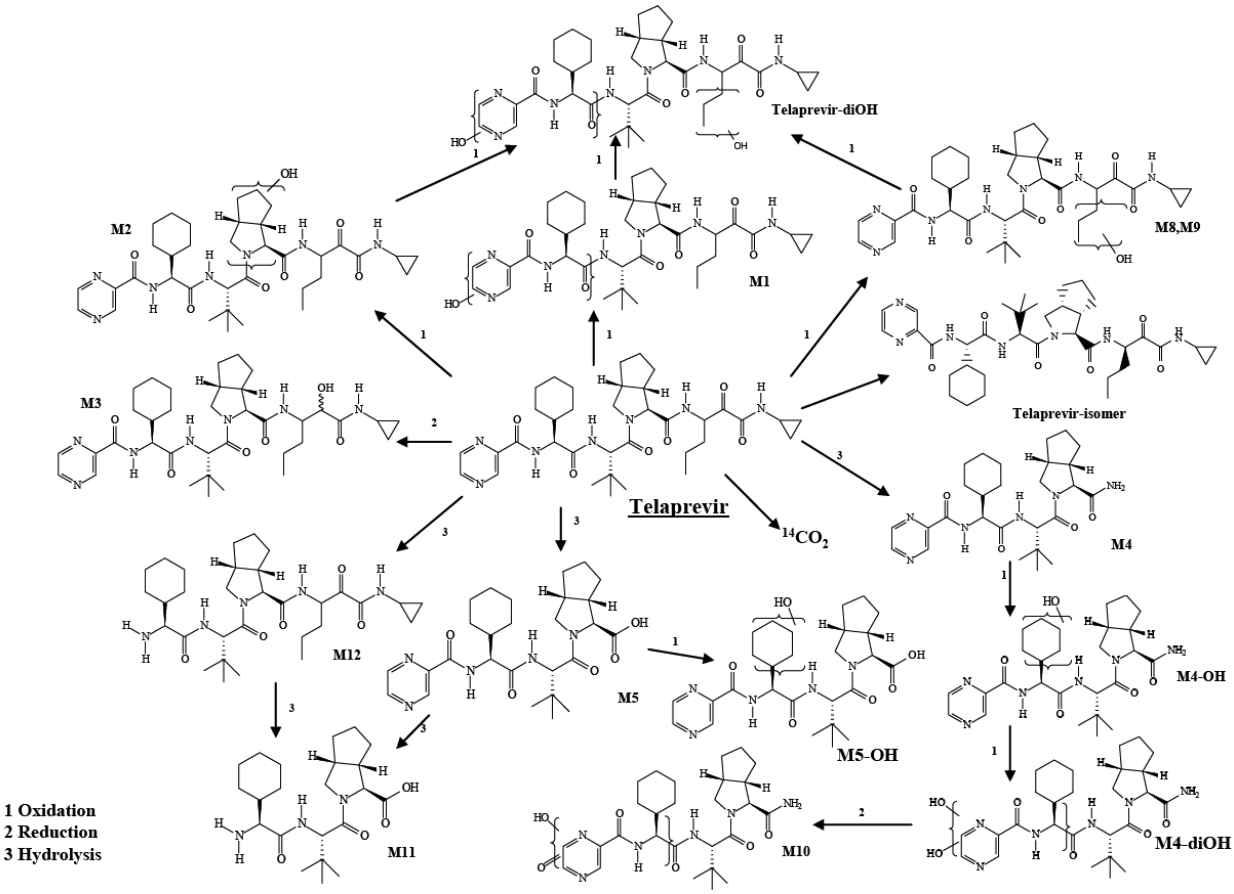
The mass balance study suggests that hepatic elimination is the major route of drug excretion. Only 1.00% of the administered dose of telaprevir was excreted in urine. See question 2.2.5.7 below for additional details on drug excretion.

### 2.2.5.6 What are the characteristics of drug metabolism?

Telaprevir is mainly metabolized via phase 1 metabolism pathways, namely oxidation, hydrolysis, and reduction of the parent drug. The primary CYP isoform responsible for telaprevir metabolism is CYP3A4.

A different metabolite profile exists following a single dose of telaprevir compared to following multiple doses to steady-state. Following a single dose of telaprevir, VRT-127394 (the *R*-diastereomer of telaprevir) was the only metabolite present at greater than 10% of total drug-related material. However, following administration of multiple doses of telaprevir (in combination with Peg-IFN and RBV) in HCV-infected patients, pyrazinoic acid (PZA), VRT-127394, and VRT-0922061 were all predominant metabolites that were present at >10% of total drug-related material at steady-state. The percent analyte to total drug-related material of PZA, VRT-127394, and VRT-0922061 were ~23%, ~22%, and ~10%, respectively. (A similar profile was obtained in healthy subjects administered multiple doses of telaprevir without Peg-IFN/RBV.) In addition to CYP-mediated biotransformations, the observed hydrolytic pathways suggest proteolytic enzymes are likely also involved in the metabolism of telaprevir. The figure below depicts major in vivo metabolic pathways and structures of main metabolites identified across all species evaluated (rat, dog, and human).

Figure 2.2.5.6-1 Metabolism Pathway for Telaprevir and Structures of All Main Metabolites Identified in Rat, Dog, and Human



### 2.2.5.7 What are the characteristics of drug excretion?

Telaprevir and its metabolites are primarily excreted in feces, with minimal renal elimination. In the single-dose human ADME study, 6 healthy male subjects were administered a single oral 750 mg dose of $^{14}$C-TVR (study VX06-950-005). Whole blood, plasma, urine, expired air, and feces were collected up to at least 168 hours post-dose. After oral administration of $^{14}$C-TVR, more than 81.6% of the administered dose was excreted in feces, with unchanged telaprevir and VRT-127394 accounting for 31.8% and 18.7% of excreted drug-related material in feces, respectively. Only 1.00% of the administered dose was excreted in urine, of which only 0.11% of the administered dose of unchanged telaprevir could be detected. Approximately 8.15% of the administered dose was recovered in expired air.

### 2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The relationship between dose and concentration is non-linear both following single-dose administration of telaprevir and following multiple-dose administration of telaprevir. In single-dose studies in healthy volunteers, telaprevir AUC and $C_{max}$ generally increased slightly greater than proportional to dose. The half-life also increased with increasing doses ranging from 375 to 1875 mg. In study VX07-950-017, single doses of 375 to 1875 mg telaprevir were administered to healthy subjects and dose-proportionality was assessed using a power model and analysis of variance (ANOVA). In general, Cmax increased proportional to dose within the 750- to 1500-mg dose range and $AUCt_{last}$ and $AUC_{inf}$ increased greater than proportional to dose at all doses greater than the 750-mg reference dose.

In a 5-day multiple-dose study (study C136), an increase in dose from 750 mg q8h to 1875 mg q8h resulted in a less than proportional increase in exposure (i.e., Cmin, Cmax, and $AUC_{8h}$ all increased by approximately 40%, whereas dose increased by 2.5-fold). Additionally, in study VX04-950-101, mean day 5 telaprevir $AUC_{8h}$ exposure increased by 47% and 30% while the dose increased (by 67%) from 450 mg to 750 mg and from 750 mg to 1250 mg, respectively, in healthy subjects. In HCV-infected subjects, mean day 14 telaprevir $AUC_{8h}$ exposure was unchanged while the dose increased (by 67%) from 450 mg to 750 mg Q8h and from 750 mg to 1250 mg Q8h, respectively.

### 2.2.5.9 How do the PK parameters change with time following chronic dosing?

Telaprevir exhibits both non-linear and time-dependent PK. At single doses, the half-life increases and clearance decreases with increasing telaprevir dose. Half-life also increases between a single dose (4 hours) and multiple doses (9-11 hours). In addition, the time to reach steady-state for telaprevir is greater than what its half-life would indicate following a single dose.

Data from study VX04-950-101 show that in HCV-infected patients, the accumulation ratio for $AUC_{last}$ at the therapeutic dose (750 mg) is approximately 1.8 between day 1 and day 14. Accumulation for the diastereomer, VRT-127394 is slightly higher than telaprevir (ratio is ~2.7).

#### 2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The inter-individual variability across phase 1 studies in healthy volunteers ranged from 19% to 48% for telaprevir $AUC_{8h}$, Cmax, and Cmin at steady-state. From a pooled population PK analysis of phase 2 studies 104, 104EU, 106, C208, 111 and phase 3 studies 108 and C216, the inter-subject variability estimates for CL/F and V/F of telaprevir were 27.2% and 72.2%, respectively. Although weight was found to be a significant covariate in the popPK analysis, differences in weight did not appear to be the major cause of variability. (The inter-individual variability in telaprevir clearance explained by weight was minimal compared to the overall inter-individual variability in clearance estimated for the population.) Some potential sources of variability may be from inter-individual differences in the expression of P-gp and CYP3A4 as well as body weight and hepatic function.

## 2.3 Intrinsic Factors

### 2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

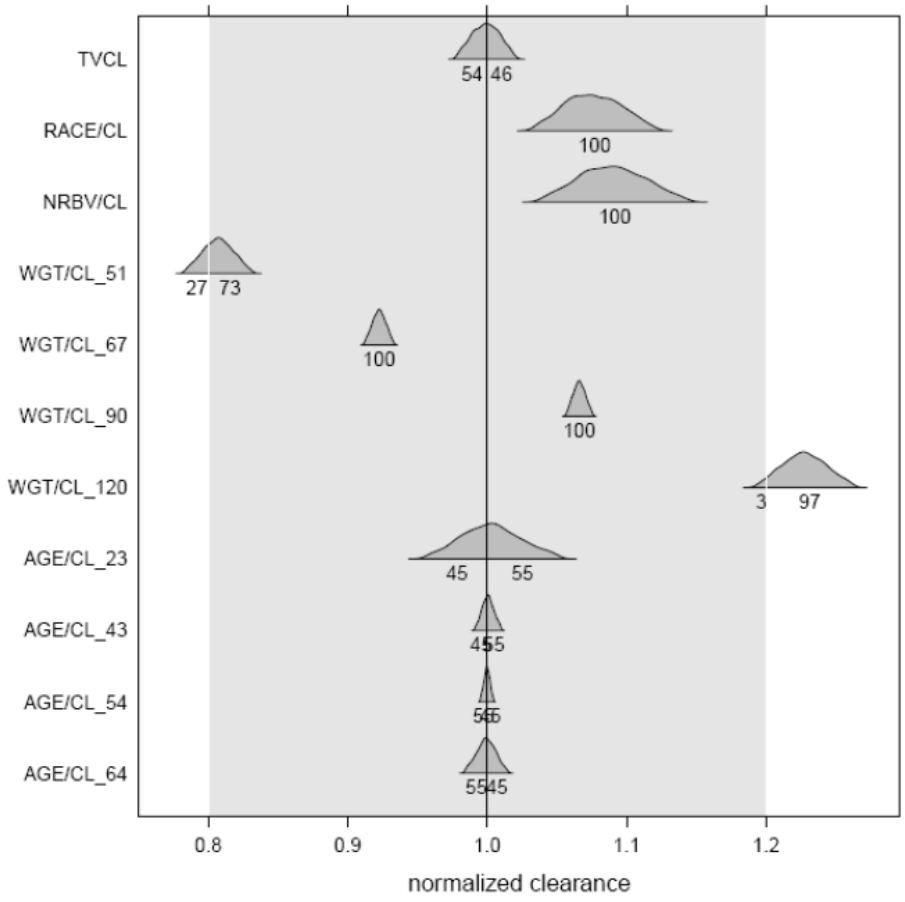
The effect of severe renal impairment on telaprevir exposure was studied in study C132. When taking into account the PK data for all subjects with severe renal impairment from that study, the LS means for telaprevir Cmax and $AUC_{inf}$ were approximately 3% and 21% higher, respectively, when compared with healthy volunteer controls. Due to telaprevir's non-linear PK, a multiple-dose study would have more accurately characterized the effect of renal impairment on telaprevir steady-state exposure. However, an additional study is not needed at this time. Based on the limited amount of telaprevir that is eliminated renally, the relatively small magnitude of change from the single-dose study in severely renally impaired subjects, and telaprevir's accumulation ratio, it is unlikely that the magnitude of increase in telaprevir exposure following multiple doses would be great enough to warrant a dose adjustment in patients with renal impairment. Furthermore, because anemia (the only toxicity that is associated with telaprevir exposure) is more strongly associated with RBV exposure than TVR exposure, anemia would most likely be managed by lowering the RBV dose. (see section 2.3.2.5 for further discussion).

The impact of hepatic impairment on telaprevir exposure was studied in two separate studies: study VX06-950-006 (mild hepatic impairment) and VX06-950-012 (moderate hepatic impairment). The presence of mild hepatic impairment in a subject did not substantially alter the PK of telaprevir. Thus, no dose adjustments were recommended

for this population. However, subjects with moderate hepatic impairment had significantly *lower* exposure to telaprevir. The reason for this observation is unclear but may partially be attributed to alterations in unbound protein concentrations, which were not measured in that study (see section 2.3.2.6 for further discussion).

The effect of race, gender, age, weight, and genetic polymorphism on the PK of telaprevir has not been specifically studied; however, analysis from pooled phase 2 and phase 3 data have been performed by the Applicant to evaluate the effect of these factors on clearance using a popPK model (see figure 2.3.1-1 and section 2.3.2 below for further discussion). The results indicate that the effects of age, gender, race, and RBV on telaprevir clearance were not significant. The effect of weight was significant; however, the relationship between telaprevir exposure and efficacy was shallow and the relationship between RBV exposure and Hgb toxicity is steep. Therefore, using dose reduction of RBV to manage Hgb toxicity and anemia, especially for very light patients, is likely to be a more effective approach. The effect of pregnancy on telaprevir PK has not been studied. The effect of concomitant disease is currently being studied in an ongoing phase 2a study in patients with HCV/HIV co-infection (study VX08-950-110).

Figure 2.3.1-1 Covariate Effects on Normalized Clearance (CL/F)



Distributions of the normalized CL/F values from the non-parametric bootstrap of the full covariate model. The reference CL/F used was the point estimate from the full covariate model of a typical male, Caucasian subject of median age and weight, who received concomitant administration of Peg-IFN and ribavirin. Normalized distributions of CL/F are shown for subjects of race other than Caucasian (RACE/CL), subjects who did not receive RBV (NRBV), subjects at the 2.5% quantile of weight (51kg, WGT/CL_51), subjects at the 25% quantile of weight (67kg, WGT/CL_67), subjects at the 75% quantile of weight (90kg, WGT/CL_90), subjects at the 97.5% quantile of weight (WGT/CL_120), subjects at the 2.5% quantile of age (23yrs, AGE/CL_23), subjects at the 25% quantile of age (43yrs, AGE/CL_43), subjects at the 75% quantile of age (54yrs, AGE/CL_54), and subjects at the 97.5% quantile of age (64yrs, AGE/CL_64).

A genetic polymorphism, rs12979860, near the *IL28B* gene (encoding interferon-lambda 3; hereafter referred to as "*IL28B* genotype") has been shown to be a strong predictor of SVR in patients receiving therapy with standard of care PR. Studies have demonstrated that patients who carry the variant alleles (C/T and T/T genotypes) have lower SVR rates than individuals with the C/C genotype. Genotyping for rs12979860 was performed in subsets of two Phase 2 trials (60% of 104 [naïve], 52% of 106 [failure]) and two Phase 3 trials (42% of 108 [naïve], 80% of C216 [failure]). The total number of subjects included in the analysis was 1374: 610 treatment naïve and 764 treatment experienced subjects.

Response rates and treatment effects were similar between the pharmacogenomic substudy and the overall trial populations for Studies 108 and C216. The Applicant's *IL28B* genetic substudy confirms previous reports of *IL28B* genotype effects on PR responses in that C/T and T/T subjects had significantly lower SVR rates in the Pbo/PR48 control arms. A similar genetic effect was apparent in the telaprevir-containing arms, although less pronounced than in Pbo/PR48. In both trials, subjects with the C/T and T/T genotypes had higher SVR rates with telaprevir-containing regimens than PR alone. Treatment naïve C/C subjects responded favorably to PR alone, although SVR rates were higher for all of the telaprevir-containing regimens in this subgroup. Table 2.3.1-1 summarizes the response rates by *IL28B* genotype in Studies 108 and C216. Telaprevir treatment effects did not appear to differ with regard to *IL28B* genotype (genotype x treatment interaction P>0.15). These results should be interpreted with caution because the sample size of some subgroups was small and the cohort may not fully represent the study population, however, the results are consistent with other studies evaluating the role of *IL28B* in treatment response.

Table 2.3.1-1 SVR Rates by *IL28B* Genotype, Treatment Arm, and Trial

| **Trial** | **Treatment** | **SVR, % (n/N)** | | | | |
|---|---|---|---|---|---|---|
| | | **Overall** | **Substudy** | **IL28B C/C** | **IL28B C/T** | **IL28B T/T** |
| **Treatment-naïve** | | | | | | |
| 108 | Pbo/PR48 | 44% (158/361) | 38% (61/161) | 64% (35/55) | 25% (20/80) | 23% (6/26) |
| | T8/PR24-48 RGT | 69% (250/364) | 67% (102/153) | 84% (38/45) | 57% (43/76) | 59% (19/32) |
| | T12/PR24-48 RGT | 75% (271/363) | 78% (109/140) | 90% (45/50) | 71% (48/68) | 73% (16/22) |
| **Treatment-experienced** | | | | | | |
| C216 | Pbo/PR48 | 17% (22/132) | 17% (18/105) | 29% (5/17) | 16% (9/58) | 13% (4/30) |

| Trial | Treatment | SVR, % (n/N) | | | | |
|---|---|---|---|---|---|---|
| | | Overall | Substudy | IL28B C/C | IL28B C/T | IL28B T/T |
| | T12/PR48 | 64% (250/364) | 62% (120/192) | 76% (31/41) | 63% (84/134) | 57% (21/37) |
| | T12 (DS)/PR48 | 66% (175/264) | 51% (114/225) | 83% (29/35) | 58% (76/132) | 65% (28/43) |

Severe cases of rash, including SJS and DRESS, have been observed with telaprevir. The Applicant tested associations of 143 HLA alleles (HLA-A, HLA-B, HLA-CW, HLA-DRB1, and HLADQB1) with rash in 114 cases (59 severe cases) and 73 controls. For rash of any severity, seven alleles were nominally significant at $P<0.05$, although none were significant after correcting for multiple comparisons. HLA-DQB1*0202 was the top-ranking allele, with an odds ratio of 3.42 (95% confidence interval 1.53-7.61, unadjusted P=0.0026). The positive predictive value of DQB1*0202 was 0.07 and the NPV was 1.00; sensitivity and specificity were 33.9% and 79.7%, respectively. This allele was also nominally significantly associated with severe rash. Replication of these results would be necessary. Alternative genotyping strategies such as a genome-wide association study would be useful to characterize the pathogenesis of rash in telaprevir-treated subjects and to identify markers that are potentially useful in minimizing the risk of this adverse event.

Refer to Appendix 3.4 for additional details the genetic substudies for telaprevir.

**2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative bases for the recommendation.**

**2.3.2.1 Elderly**

No dedicated studies of the elderly population were conducted with telaprevir. However, the Applicant conducted a pooled popPK analysis across studies 104, 104EU, 106, C208, 108, 111, and C216 to investigate the influence of various covariates on telaprevir exposure. A total of 35 patients who were either 65 or older were included in all 7 studies. Individual model-predicted exposures were derived from the empirical Bayes estimates of the pooled popPK analysis. Table 2.3.2.1-1 below shows the values for model-predicted telaprevir exposures in all age groups. The model predicted that patients in the oldest age group (≥65 years) would likely have the highest exposures. However, the reduced clearance in this age group follows a similar trend as reduced weight and also reduced renal function. Furthermore, there was no relationship between inter-individual variability in CL/F estimates and age (see Figure 2.3.2.1-1).

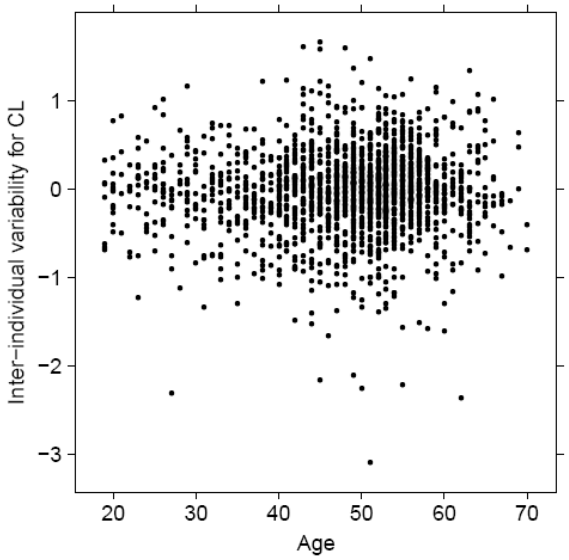
Subgroup analyses for efficacy indicate that elderly patients appear to respond to telaprevir/Peg-IFN/RBV treatment less well. In addition, old age may be associated with a higher risk of rash and Hgb toxicity. However, the exposure-safety

relationship seems to be independent of age. Therefore, no dose adjustment is necessary based on age. Nonetheless, caution should be exercised in the administration and monitoring of telaprevir in geriatric patients.

Table 2.3.2.1-1 Subgroup Analyses of Model-Predicted Telaprevir Exposures (Applicant's Analysis)

| | | $C_{avg}$ (ng/mL) | | $AUC_{\tau}$ (ng.h/mL) | |
|---|---|---|---|---|---|
| **Subgroup** | **N** | **Median (min, max)** | **Mean (SD)** | **Median (min, max)** | **Mean (SD)** |
| **Age Category** | | | | | |
| <45 years | 534 | 3070 (1210, 7180) | 3170 (871) | 24500 (9700, 57400) | 25400 (6970) |
| ≥45 to <65 years | 1267 | 2900 (1220, 7470) | 3040 (883) | 23200 (9780, 59800) | 24300 (7060) |
| ≥65 years | 35 | 3890 (1970, 7380) | 4010 (1300) | 31100 (15800, 59100) | 32100 (10400) |

Figure 2.3.2.1-2 Relationship between Inter-individual Variability in CL/F and Age (PM Reviewer's Analysis)




### 2.3.2.2 Pediatric patients

No studies in pediatric patients have been conducted to date. However, the Applicant has submitted a pediatric plan for future studies to be conducted. The study design and protocol have yet to be finalized.

### 2.3.2.3 Gender

No dedicated studies on the influence of gender were conducted with telaprevir. However, the Applicant evaluated the potential influence of gender in studies 104 and 104EU using popPK modeling. Gender was not found to be a significant covariate on the clearance of telaprevir in either study. Based on the empirical Bayes estimates generated from the pooled popPK analysis, the mean steady-state AUC of telaprevir in male and female subjects in phase 2/3 studies were

not clinically significant. Furthermore, any inter-individual differences in clearance were accounted for by weight. Thus, no dose-adjustments are necessary based on gender.

Table 2.3.2.4-1 Subgroup Analyses of Model-Predicted Telaprevir Exposures (Applicant's Analysis)

| | | $C_{avg}$ (ng/mL) | | $AUC_{\tau}$ (ng.h/mL) | |
|---|---|---|---|---|---|
| **Subgroup** | **N** | **Median (min, max)** | **Mean (SD)** | **Median (min, max)** | **Mean (SD)** |
| **Gender** | | | | | |
| Male | 1146 | 2810 (1210, 7180 ) | 2920 (796) | 22400 (9700, 57400) | 23400 (6370) |
| Female | 690 | 3250 (1310, 7470) | 3390 (985) | 26000 (10500, 59800) | 27100 (7880) |

### 2.3.2.4 Race

No dedicated studies on the influence of race on telaprevir were conducted. However, the Applicant conducted a pooled popPK analysis across studies 104, 104EU, 106, C208, 108, 111, and C216 to investigate the influence of various covariates on telaprevir exposure. The distributions of the normalized CL/F estimates for subjects of race other than Caucasian lie entirely within 20% of the typical reference value. Race had no apparent effect on the exposure to telaprevir (see Table 2.3.2.4-1 below).

Table 2.3.2.4-1 Subgroup Analyses of Model-Predicted Telaprevir Exposures

| | | $C_{avg}$ (ng/mL) | | $AUC_{\tau}$ (ng.h/mL) | |
|---|---|---|---|---|---|
| **Subgroup** | **N** | **Median (min, max)** | **Mean (SD)** | **Median (min, max)** | **Mean (SD)** |
| **Race** | | | | | |
| White | 1614 | 3020 (1220, 7470) | 3140 (909) | 24200 (9780, 59800) | 25100 (7280) |
| Black | 149 | 2620 (1450, 5800) | 2730 (763) | 20900 (11600,46400) | 21900 (6110) |
| Asian | 27 | 3070 (2120, 5850) | 3230 (876) | 24500 (16900, 46800) | 25800 (7010) |
| Other | 46 | 2780 (1210, 4600) | 2810 (632) | 22200 (9700, 36800) | 22500 (5060) |

### 2.3.2.5 Renal impairment

The Applicant conducted a renal impairment study using the reduced study design (subjects with severe renal impairment only). The study included a total of 12 subjects with severe renal impairment (defined as having creatinine clearance <30 mL/min as calculated by the Cockcroft-Gault equation) and 12 subjects with normal renal function (≥80 mL/min). All subjects were given a single dose of 750 mg telaprevir. Since telaprevir is not appreciably eliminated by the renal route, with ~1% of telaprevir eliminated unchanged in urine, a significant increase in telaprevir exposures in subjects with renal impairment was not anticipated. Study C132 demonstrated that subjects with severe renal impairment experienced a mean 3% increase in Cmax and mean 21% increase in $AUC_{inf}$ (based on LS means). There are two major issues associated with this study:

- One subject in the study with severe renal impairment (subject 132-0025) exhibited vastly different PK characteristics from the rest of the group. This

subject's Tmax was considerably delayed at 12 hours while the mean for the group was 5 hours. In addition, this subject's AUC value was considerably higher than the group mean (62,350 vs. 18,300 ng*h/mL). Neither this subject's demographics nor renal function were substantially different from the rest of the group. The Applicant has proposed to exclude this subject's PK data from the analysis (see table below for mean PK parameters). In the absence of this subject's data, the arithmetic mean Cmax and $AUC_{inf}$ values for renally impaired subjects are 9% and 34%, higher respectively, than control subjects (this subject's elimination rate constant could not be computed, thus the $AUC_{inf}$ remains the same whether this subject is removed from the dataset or not). Using LS means comparisons, the increase in Cmax and $AUC_{inf}$ were 3% and 21%, respectively. This approach to exclude subject 132-0025 is acceptable since the difference in his PK profile lies mainly within the absorption phase (Figure 2.3.2.5-1). Based on visual inspection of his profile, it does not appear that elimination was significantly affected, indicating that renal dysfunction was not the cause of the higher exposure to telaprevir.

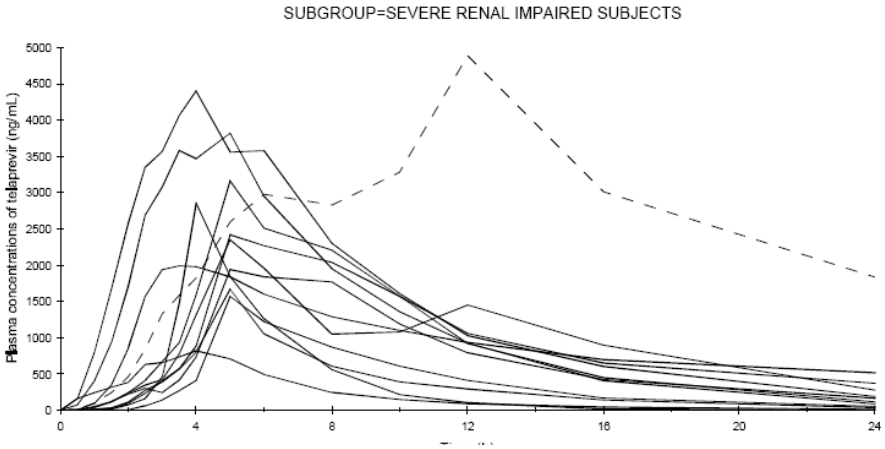
- A single dose of telaprevir was given in this study rather than multiple doses. For a drug with non-linear and time-dependent kinetics like telaprevir, multiple doses should be administered in order to evaluate the effect of renal impairment on steady-state concentrations of telaprevir. However, because the magnitude of change in this single-dose study was relatively small and telaprevir is not appreciably renally eliminated, it is unlikely that severe renal impairment would significantly affect telaprevir PK at steady-state. In addition, the only toxicity associated with telaprevir exposure (anemia) is more correlated with RBV and would be better managed with adjustment of the RBV dose. Thus, a multiple-dose study with telaprevir in subjects with renal impairment is not needed.

Table 2.3.2.5-1 Mean Total TVR PK Parameters Following a Single 750-mg Dose in Subjects with Severe Renal Impairment and in Healthy Subjects

| ***Pharmacokinetics of telaprevir (total)*** (mean ± SD, $t_{max}$: median [range]) | **Healthy subjects (reference)** | **Subjects with severe renal impairment (test 1)** | **Subjects with severe renal impairment, excluding Subject 132-0025[b] (test 2)** |
|---|---|---|---|
| n | 12 | 12[a] | 11 |
| $C_{max}$, ng/mL | 2256 ± 635.7 | 2658 ± 1218 | 2455 ± 1043 |
| $t_{max}$, h | 5.0 (3.92-6.0) | 5.0 (3.5-12.0) | 5.0 (3.5-5.0) |
| $AUC_{last}$, ng.h/mL | 14440 ± 5960 | 21980 ± 15650 | 18300 ± 9562 |
| $AUC_{\infty}$, ng.h/mL | 15140 ± 6736 | 20260 ± 11000 | 20260 ± 11000[c] |
| $\lambda_z$, 1/h | 0.1592 ± 0.02549 | 0.1528 ± 0.05882 | 0.1528 ± 0.05882[c] |
| $t_{1/2term}$, h | 4.470 ± 0.8012 | 5.511 ± 3.288 | 5.511 ± 3.288[c] |

[a] n=11 for $AUC_{\infty}$, $\lambda_z$ and $t_{1/2term}$
[b] Subject 132-0025 had a pharmacokinetic profile that differed greatly from that of the other subjects, although a root cause could not be identified.
[c] $\lambda_z$ could not be estimated for Subject 132-0025, consequently descriptive statistics for associated PK parameters are unchanged.

Figure 2.3.2.5-1 Individual Subject PK Profiles for the Renal Impairment Study (C132)




uded subjects with mild renal impairment (CrCl ≥50 mL/min) with no dose adjustments. In addition, based on the results of this study, the Applicant's proposal that no dose adjustments are needed for patients with mild, moderate, or severe renal impairment is acceptable.

### 2.3.2.6 Hepatic impairment

The effect of hepatic impairment on telaprevir exposure was studied in two separate studies: study VX06-950-006 (mild hepatic impairment) and VX06-950-012 (moderate hepatic impairment). In study VX06-950-006, subjects with mild hepatic impairment (C-P class A) and matched healthy controls received multiple doses of telaprevir 750 mg q8h for 5 days plus a final dose on the morning of day 6. Following multiple dosing, C-P A subjects had slightly *lower* exposure to telaprevir than healthy subjects. Mean Cmax was lower by ~12% and $AUC_{0\text{-}8h}$ was lower by ~16% in subjects with mild hepatic impairment (see Table 2.3.2.6-1 below). Based on geometric least squares analysis, the 90% confidence intervals were outside the routine no-effect limits of 80-125%. However, it is unlikely that the differences between the two populations following multiple dosing are clinically relevant. In addition, HCV-infected patients with cirrhosis were included in phase 3 studies. Based on popPK analysis of sparse samples, there was no difference in telaprevir exposure between patients with cirrhosis and patients without cirrhosis.

Table 2.3.2.6-1 Mean Telaprevir PK Parameters Following Multiple Doses (~5 days) in Subjects with Mild Hepatic Impairment and Matched Controls

| **Mean ± SD** | **Cmax** (ng/mL) | **Tmax** (hr) | **$AUC_{0\text{-}8h}$** (ng*hr/mL) | **$AUC_{inf}$** (ng*hr/mL) | **$T_{1/2}$** (hr) | **Cl/F** (L/hr) |
|---|---|---|---|---|---|---|
| Healthy (n=8) | 3425 ± 907 | 1.75 ± 0.93 | 20170 ± 5036 | ND | 6.2 ± 1.26 | 22 ± 6 |
| C-P A (n=8) | 3009 ± 505 | 1.50 ± 0.54 | 16879 ± 2944 | ND | 8.3 ± 2.21 | 23 ± 7 |

In study VX06-950-012, subjects with moderate hepatic impairment (C-P class B) and matched healthy controls received multiple doses of telaprevir 750 mg q8h for 5 days plus a final dose on the morning of day 6. Following multiple dosing, C-P B subjects had *lower* exposure to telaprevir than healthy subjects. Mean Cmax and $AUC_{0\text{-}8h}$ were both lower by ~50% in subjects with moderate hepatic impairment compared with healthy volunteers (see Table 2.3.2.6-2 below). Based on these results, the originally planned cohort for subjects with severe hepatic impairment was not initiated.

Table 2.3.2.6-2 Mean Telaprevir PK Parameters Following Multiple Doses (~5 days) in Subjects with Moderate Hepatic Impairment and Matched Controls

| **Mean ± SD** | **Cmax** (ng/mL) | **Cmin** (ng/mL) | **Tmax** (hr) | **$AUC_{0\text{-}8h}$** (ng*hr/mL) | **$T_{1/2}$** (hr) | **CL/F** (L/hr) | **V/F** (L) |
|---|---|---|---|---|---|---|---|
| Healthy (n=4) | 3272 ± 951 | 1505 ± 445 | 1.88 ± 1.18 | 18410 ± 4120 | 6.2 ± 1.5 | 25 ± 5 | 227 ± 100 |
| C-P B (n=6) | 1865 ± 587 | 1068 ± 167 | 4.33 ± 1.36 | 11706 ± 3685 | 8.3 ± 2.4 | 33 ± 16 | 371 ± 138 |

Based on the results of these two hepatic impairment studies, the Applicant has proposed that the dose does not need to be adjusted in subjects with mild hepatic impairment, while use in patients with moderate and severe hepatic impairment is not recommended. In addition, RBV and Peg-IFN are contraindicated in patients with moderate or severe hepatic impairment and decompensated liver disease.

### 2.3.2.7 Pregnancy and Lactation Use

There is no pregnancy and lactation use information in the application. The use of ribavirin has been shown to be teratogenic and have embryocidal effects in all animal species exposed to ribavirin. Thus, ribavirin is contraindicated in women who are pregnant and in the male partners of women who are pregnant.

### 2.3.2.8 Body Weight

Based on the popPK analysis, body weight has a significant influence on telaprevir exposure. The popPK analysis found that clearance for a patient weighing 51 kg (2.5% quantile of weight) was 81% of the value in a 79 kg patient (median weight). Clearance for a patient weighing 120 kg (97.5% of weight) was 123% of the value for the median patient.

In the pooled data from phase 2 and 3 trials, patients in the lowest quartile of weight (42-68 kg) had approximately 28% higher telaprevir, 51% higher Peg-IFN, and 24% higher RBV mean exposures than patients in the highest quartile (91-153 kg). The relationship between telaprevir exposure and efficacy were shallow. However, the relationship between RBV exposure and Hgb toxicity is steep. Therefore, using dose reduction of RBV to manage Hgb toxicity and anemia, especially for very light patients, would be reasonable.

## 2.4 Extrinsic Factors

### 2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

The effect of various drugs on the exposure of telaprevir (and vice versa) are discussed in section 2.4.2. The effect of different types of meals on the bioavailability of telaprevir is discussed in section 2.5.3. The effect of smoking, herbal products, and alcohol use were not evaluated by the Applicant.

### 2.4.2 Drug-drug interactions

#### 2.4.2.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

Yes, *in vitro* experiments investigating telaprevir metabolism identified CYP3A4 as the major CYP enzyme involved in the metabolism of telaprevir. Incubations were conducted at 2 concentrations of telaprevir (2 and 20 μM) and included the evaluation of the potential for five additional isoforms to metabolize telaprevir: CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP2E1. No other isoform appeared to contribute substantially to telaprevir metabolism.

Telaprevir is an inhibitor of CYP3A4 *in vitro* and *in vivo*. Incubations with select CYP probe substrates and expressed CYP1A2, CYP2C9, CYP2C19, or CYP3A4 were performed in the presence of telaprevir or a 55:45 mixture of telaprevir:VRT-127394 at concentrations ranging between 0.05 and 10 μM. In addition, telaprevir and VRT-127394 (0.1-100 μM) were tested in a subsequent study for inhibitory effects on the metabolism of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. These studies demonstrated that CYP2A6, CYP2B1, and CYP2E1 were not inhibited by telaprevir or VRT-127394. CYP1A2, CYP2C9, and CYP2D6 were not or were weakly inhibited by telaprevir, VRT-127394, and the 55:45 mixture of telaprevir:VRT-127394. CYP2C8 and CYP2C19 were weakly inhibited by telaprevir and VRT-127394 ($IC_{50}$>100μM). Telaprevir, VRT-127394, and the 55:45 mixture of telaprevir:VRT-127394 inhibited CYP3A4 with $IC_{50}$ values <18.9 μM.

Additional studies were performed to further characterize the potential for telaprevir and VRT-127394 to inhibit CYP3A4/5. Those studies revealed that telaprevir and VRT-127394 were competitive *in vitro* inhibitors of CYP3A4/5 when using midazolam and testosterone as the substrates. Corresponding Ki values of telaprevir and VRT-127394 were 1.43 μM and 0.94 μM, respectively, using midazolam as substrate and 18.6 and 5.18 μM, respectively, using testosterone as substrate. The inhibition of CYP3A4/5 by telaprevir is both time- and concentration-dependent with a maximum inactivation rate of 0.065 $min^{-1}$ and a dissociation constant of 1.5 μM.

The potential for telaprevir to induce CYP1A, CYP2C, and CYP3A activities was determined in primary cultures of human hepatocytes. Cells were incubated with telaprevir at 0.1, 1, and 100 μM. Induction of CYP activity was

assessed at the end of the 48-h treatment period using the corresponding probe substrate (7-ethoxyresorufin (CYP1A), S-mephenytoin (CYP2C), and testosterone (CYP3A). The data were compared to the data obtained with the concurrent positive controls omeprazole and rifampicin. At the highest concentration tested (100 μM), incubations with telaprevir resulted in average induction values of 1.4-, 0.4-, and 0.1-fold for CYP1A, CYP2, and CYP3A, respectively. Even though 1.4-fold induction value was observed for CYP1A, the increase in activity was only 2% to 3% of the positive control. Based on the results of this study, telaprevir was concluded to have a low potential to induce CYP2C, CYP3A, or CYP1A. However, it is important to note that these experiments did not include an mRNA assessment of CYP expression. According to literature evidence, a false negative could result without confirmatory mRNA assessment of CYP induction.

#### 2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Yes, telaprevir is a substrate for CYP3A4. Polymorphisms in the gene encoding CYP3A4 have not been shown to have a significant effect on enzyme function; however, genetic variation in CYP3A5 has been shown to be relevant to enzyme activity of some drugs. There are no data available on the effect of CYP3A4/5 polymorphisms on telaprevir exposure. Thus, it is unclear whether a specific polymorphism in the gene encoding CYP3A5 would have an effect on telaprevir metabolism. However, since there was not an extremely high inter-subject variability in telaprevir exposure that was not explained by other covariates (weight, race, concomitant medications), it is unlikely that genetic variations in the genes encoding CYP3A4/5 would have a significant impact on telaprevir exposure.

#### 2.4.2.3 Is the drug an inhibitor and/or inducer of CYP enzymes?

Yes, telaprevir is a demonstrated *in vitro* and *in vivo* inhibitor of CYP3A4. Telaprevir also exhibits mixed induction effects on CYP3A4 as evidenced by its pharmacokinetic profile and results of drug interaction studies. In several drug interaction studies with known CYP3A4 substrates (ethinyl estradiol, escitalopram, methadone, several HIV protease inhibitors), telaprevir lowered exposure of the concomitant drug, indicating that telaprevir may have some inductive effects on CYP3A4 and possibly other CYP enzymes. Of note, telaprevir did not have the same effect on all CYP3A4 substrates; midazolam, CsA, and tacrolimus are all CYP3A4 substrates and concentrations of these agents were increased several-fold in the presence of telaprevir. Telaprevir was not specifically tested *in vivo* for its potential to induce other CYP enzymes.

#### 2.4.2.4 Is the drug a substrate and/or inhibitor of P-glycoprotein transport processes?

Telaprevir is a substrate for P-gp efflux. Study 5VERTP1R1 assessed the permeability of telaprevir in Caco-2 cells in the absence and presence of cyclosporine

A (CSA) and ritonavir (RTV), two inhibitors of P-gp. The bidirectional permeability of telaprevir (5 μM) was assessed in the absence and presence of CSA (10 μM) or RTV (200 μM). Cell monolayers were pre-incubated with CSA or RTV containing buffer for 10 min. As a control, digoxin (5 μM) was also assayed. Mean $P_{app}$ ratios were 20.5 for telaprevir alone (no CSA or RTV), versus >27 for digoxin. In the presence of CSA and RTV, the $P_{app}$ ratio for telaprevir decreased to 0.9 and 1.0, respectively. These results indicate that since significant inhibition of telaprevir efflux via inhibition of P-gp was observed, telaprevir is likely a substrate for P-gp transport.

Telaprevir was not shown to be a P-gp inhibitor *in vitro.* Study 6VERTP2 evaluated the bidirectional permeability of digoxin (p-gp substrate) in the presence and absence of telaprevir using Caco-2 cells. Digoxin was effluxed with a $P_{app}$ ratio of 11.6 in the control plate, indicating significant efflux. In the presence of 10 μM telaprevir the ratio decreased to 9.1, indicating no significant inhibition of digoxin efflux. Thus, it was concluded that telaprevir is not a P-gp inhibitor, as assessed in Caco-2 cells.

#### 2.4.2.5 Are there other metabolic/transporter pathways that may be important?

Telaprevir was also tested for its potential to inhibit uridine diphosphate glucuronyltransferase 1A1 (UGT1A1). UGT1A1 is primarily responsible for the glucuronidation of bilirubin in the liver. Human liver microsomes and bilirubin (as a probe substrate) were incubated in the presence of telaprevir at concentrations ranging between 0.045 to 100 μM. In this preliminary assessment, telaprevir did not inhibit UGT1A1-catalyzed bilirubin glucuronidation ($IC_{50}$ > 100 μM).

The potential for telaprevir to be a substrate for or inhibit major hepatic transporters such as OATP1B1, OATP1B3, and BCRP has not been evaluated *in vitro*. However, in a drug interaction study with atorvastatin (a known substrate for OATP1B1 and OATP1B3), co-administration with telaprevir resulted in an approximately 8-fold increase in atorvastatin exposure along with a commensurate decrease in the main metabolite for atorvastatin, ortho-hydroxy atorvastatin. Since ortho-hydroxy atorvastatin is also a substrate for OATP transporter, these results indicate that telaprevir is not likely to be an inhibitor of OATP. If telaprevir was an OATP inhibitor, concentrations of both atorvastatin *and* its metabolite would have increased.

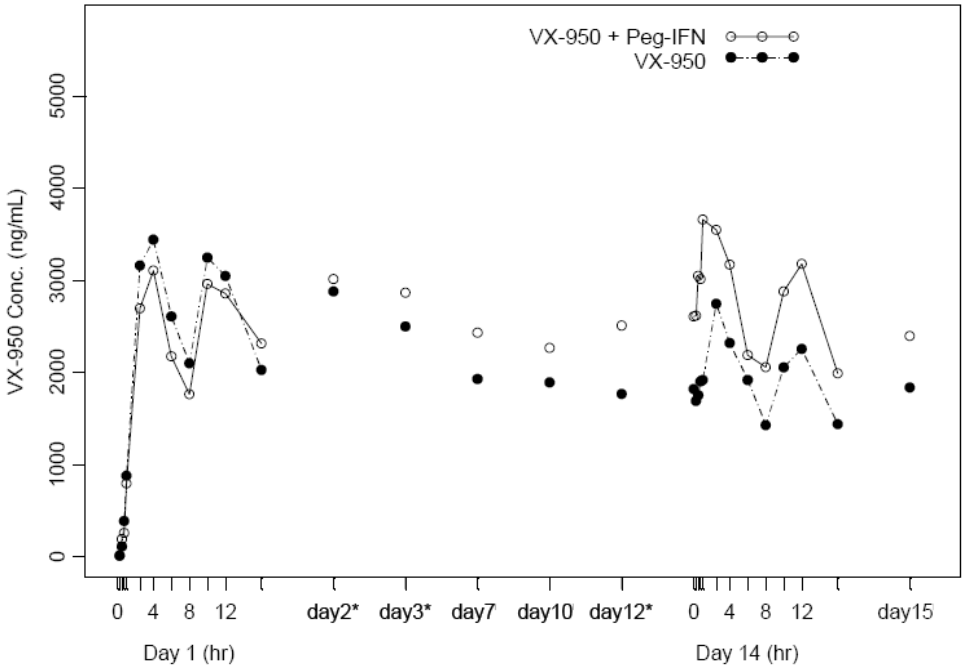
#### 2.4.2.6 Does the label specify co-administration of another drug, and if so, has the interaction potential between these drugs been evaluated?

Telaprevir is indicated for the treatment of chronic HCV in combination with Peg-IFN and RBV. The interaction potential between Peg-IFN/RBV and telaprevir has been investigated in study 103. The results of that study show that Peg-IFN co-administration appears to increase telaprevir exposure while RBV co-administration does not affect telaprevir exposure. Telaprevir co-administration does not appear to affect Peg-IFN or RBV concentrations at steady-state.

In study 103, the effect of dosing telaprevir with and without co-administration of Peg-IFN for 14 days was compared between 2 groups (n=8 HCV-infected, treatment-naïve subjects in each group): telaprevir 750 mg q8h or telaprevir 750 mg q8h + Peg-IFN-alfa-2a (180 µg/week). Peg-IFN-alfa-2a was administered the day before the first dose of telaprevir on days 1 and 8. Both telaprevir regimens included a single loading dose of 1250 mg as the first telaprevir dose on day 2, and telaprevir was administered as the 250-mg tablet, in the fed state. While the sample size was small in this study, there was a trend for higher telaprevir exposure on day 14 when given with Peg-IFN. Cmax, AUC, and Cmin at steady-state were approximately 43%, 38%, and 22% higher, respectively compared with telaprevir administration alone (see Figure 2.4.2.6-1 below). Similar results were obtained when telaprevir exposure was compared after monotherapy or after co-administration with Peg-IFN/RBV for 14 days in subjects with HCV genotype 2 or 3 in study C209 and genotype 4 in study C210.

Telaprevir co-administration does not appear to affect Peg-IFN or RBV concentrations at steady-state. In study 106, Peg-IFN and RBV concentrations remained relatively constant during both telaprevir co-administration and Peg-IFN/RBV phases of treatment, and between Peg-IFN/RBV and TVR/Peg-IFN/RBV groups. However, in the phase 3 study C216, average Peg-IFN concentrations were approximately 26% to 33 % higher and average RBV concentrations were 13% to 22% higher in telaprevir than in placebo treatment. The reason(s) for these interactions are unknown.

Figure 2.4.2.6-1 Median Concentration Time Profiles for Telaprevir Regimen and Telaprevir + Peg-IFN Regimen in Study 103




* Values for Days 2, 3, 7,10, 12, and 15 are pre-dose concentrations.

### 2.4.2.7 What other co-medications are likely to be administered to the target patient population?

Other medications that are likely to be co-administered in this target population of HCV-infected patients include antiretroviral agents for the treatment of HIV, methadone therapy and buprenorphine therapy for the treatment of opioid addiction, antidepressants and other mood-stability medications, and combined oral contraceptives in women to prevent pregnancy. Drug interaction studies have been conducted with telaprevir in combination with representative antiretrovirals, methadone, and ethinyl estradiol/norethindrone (see question 2.4.2.8 for further discussion). An *in vivo* drug interaction study investigating the interaction between telaprevir and buprenorphine is currently ongoing. In addition, as one of the major adverse events associated with telaprevir is rash, the co-administration of oral and topical steroids may be used widely to treat the rash. In the phase 3 study C216, approximately 28% of all subjects in the combined telaprevir arms received an oral or topical steroid. Since many corticosteroids are CYP3A4 substrates and telaprevir is a CYP3A4 inhibitor, there is the potential for a significant drug reaction leading to elevated plasma concentrations of the steroid(s). However, in consultation with the medical reviewer, the majority of steroids was administered topically and would only be applied extensively to the body if the rash was severe. In the case of severe rash, subjects were withdrawn from the phase 3 studies and the Applicant has proposed the same recommendation for the label (patients should discontinue use of telaprevir if severe rash occurs).

### 2.4.2.8 Are there any *in vivo* drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

A total of 15 *in vivo* drug interaction studies have been conducted with telaprevir. Representative studies that include commonly co-administered drugs, studies with probe substrates, or model inhibitors are summarized below. These studies include:

- Ketoconazole (KETO)
- Ritonavir (RTV)
- Ethinyl estradiol/norethindrone (EE/NE)
- Midazolam (MDZ)
- Digoxin (DIG)
- Rifampin (RFP)
- Lopinavir/Ritonavir (LPV/RTV)
- Tenofovir (TDF)
- Methadone (METH)

A table detailing the results of all drug interaction studies completed by the Applicant is provided at the end of this section (Tables 2.4.2.8-5 and 2.4.2.8-6).

**Ketoconazole** (Study VX06-950-003)

Telaprevir is a CYP3A substrate while ketoconazole (KETO) is as potent CYP3A inhibitor. Thus, this study evaluated the effect of a single dose 400-mg of KETO on the PK of telaprevir following administration of a single 750-mg dose.

The results of this study show that mean telaprevir $AUC_{inf}$ and mean $AUC_{0-24h}$ values were approximately 67% higher and mean telaprevir Cmax values were approximately 29% higher in subjects receiving telaprevir+KETO as compared with subjects receiving telaprevir alone. KETO concentrations were not assessed in this study.

The Applicant has proposed limiting the dose of KETO to not more than 200 mg/day in the label. Since telaprevir exhibits non-linear PK and is not dose proportional in the therapeutic dose range, a multiple-dose study with telaprevir should have been performed to more accurately characterize the effect of KETO on telaprevir exposures. However, the tQT study included multiple doses of telaprevir (1250 mg q8h x 4 days) in combination with 200 mg and 400 mg single doses of KETO. The results from that study showed that KETO increased telaprevir exposure by approximately 20%, irrespective of the KETO dose. In contrast, telaprevir increased KETO exposure by approximately 118% at the 200 mg KETO dose and by approximately 50% at the 400-mg KETO dose. Thus, the Applicant's proposed wording on limiting the dose of KETO to not more than 200 mg/day in the label is reasonable. Ritonavir-boosted HIV PI labels include the same recommendation when KETO exposures were increased by up to 2- to 3-fold (Prezista, Kaletra, Invirase) and when the concomitant PI exposure increased by up to 50%.

**Ritonavir** (Study VX06-950-009)

Telaprevir is a CYP3A and P-gp substrate. Ritonavir (RTV) is an inhibitor and an inducer of CYP3A and P-gp. Thus, this study evaluated the single-dose and steady-state PK of telaprevir 250 mg every 12 hours (q12h) or 750 mg q12h in combination with ritonavir (RTV) 100 mg q12h. A previous clinical study indicated that a single 100-mg dose of RTV increased telaprevir exposures and increased the median half-life of telaprevir. These results suggest that dosing twice daily with telaprevir in combination with low-dose RTV (100 mg) may produce trough levels of telaprevir that are similar to or greater than those produced by dosing every 8 hours with telaprevir alone.

The results of this study show that following 14 days of dosing, exposure to telaprevir (mean Cmax, Ctrough, and Cavg) was lower after administration of either telaprevir 250 mg q12h+RTV or telaprevir 750 mg q12h+RTV than with telaprevir 750 mg q8h alone in the fed state (see Table 2.4.2.8-1 below). RTV mean Cmax, Ctrough and Cavg values were higher following multiple-doses of telaprevir 750 mg q12h+RTV compared to that in the group that received telaprevir 250 mg q12h+RTV, indicating that telaprevir is a concentration-dependent CYP3A inhibitor (see Table 2.4.2.8-2).

Table 2.4.2.8-1 Mean (SD) Telaprevir PK Parameters after Multiple Doses (Day 14) of Telaprevir With and Without RTV in the Fed and Fasted States

| Treatment | Stat | $AUC_{0\text{-last}}$ (hr*ng/mL) | $C_{ave}$ (ng/mL) | $C_{trough}$ (ng/mL) | $C_{max}$ (ng/mL) | $t_{1/2}$ (hr) | $t_{max}$[a] (hr) | $t_{1/2,eff}$ (hr) | CLss/F (L/hr) |
|---|---|---|---|---|---|---|---|---|---|
| 250 mg telaprevir q12h + ritonavir, fed (Group A) | N | 6 | 6 | 6 | 6 | 5 | 6 | ND[b] | 6 |
| | Mean (SD) | 8535.01 (2728.04) | 711.25 (227.34) | 362.83 (70.99) | 1202.83 (479.98) | 5.00 (0.65) | 3.26 (1.5,5) | | 31.60 (8.87) |
| 750 mg telaprevir q12h + ritonavir, fed (Group B) | N | 5 | 5 | 5 | 5 | | 5 | | 5 |
| | Mean (SD) | 19059.13 (2878.05) | 1588.26 (239.84) | 948.6 (156.15) | 2368.4 (340.29) | ND | 2.02 (2,4) | ND | 40.0 (26.6) |
| 750 mg telaprevir q12h + ritonavir, fasted (Group C) | N | 6 | 6 | 6 | 6 | 3 | 6 | | 6 |
| | Mean (SD) | 14218.31 (3768.22) | 1184.86 (314.02) | 536.83 (117.85) | 1925 (600.27) | 4.60 (1.09) | 2.25 (1.5,4) | ND | 56.1 (6.29) |
| 750 mg telaprevir q8h, fed (Group D) | N | 6 | 6 | 6 | 6 | | 6 | 6 | 6 |
| | Mean (SD) | 16602.38 (2069.76) | 2075.3 (258.72) | 1386.17 (202.27) | 2808.17 (436.08) | ND | 2.5 (1.5,4) | 10.97 (3.45) | 45.82 (15.62) |

Table 2.4.2.8-2 Mean (SD) RTV PK Parameters after Multiple Doses of Telaprevir Co-administered with RTV in the Fed and Fasted States

| Treatment | $AUC_{0\text{-last}}$ (hr*ng/mL) | $C_{ave}$ (ng/mL) | $C_{trough}$ (ng/mL) | $C_{max}$ (ng/mL) | $t_{1/2}$ (hr) | $t_{max}$[a] (hr) |
|---|---|---|---|---|---|---|
| 250 mg telaprevir q12h + ritonavir, fed (Group A) | 3113.88 (1311.44) | 259.49 (109.29) | 139.05 (43.37) | 591.83 (284.59) | N=4 3.55 (0.47) | 4 (2,6) |
| 750 mg telaprevir q12h + ritonavir, fed (Group B) | 5064.76 (2513.2) | 422.06 (209.43) | 263.87 (285.28) | 979.67 (344.9) | N=4 3.46 (0.45) | 4 (1,5) |
| 750 mg telaprevir q12h + ritonavir, fasted (Group C) | 4183.44 (1558.45) | 348.62 (129.87) | 138.27 (84.73) | 882.33 (331.97) | N=5 3.39 (0.95) | 3.75 (2.5,4) |

The main conclusion from this study is that a combination of telaprevir 750 mg q12h and RTV 100 mg q12h appears to be inadequate to compensate for the effect of the lower daily doses of telaprevir (1500 mg per day in the 750 mg q12h regimen versus 2250 mg per day in the 750 mg q8h regimen) and may result in suboptimal exposure to telaprevir. However, because RTV administration alone is not used clinically for the treatment of HIV, combination studies with RTV-boosted protease inhibitors would be more clinically relevant.

**Ethinyl estradiol/norethindrone** (Study VX06-950-007)

Because telaprevir is a CYP3A inhibitor and ethinyl estradiol (EE) is a CYP3A substrate and widely used as a component of hormonal contraceptives, this study was conducted to evaluate plasma steady-state PK of EE and norethindrone (NE) in healthy adult female subjects (following administration of Modicon®) before and after co-administration of telaprevir 750 mg q8h for 28 days and to evaluate the steady-state PK of telaprevir as a result of co-administration with EE/NE.

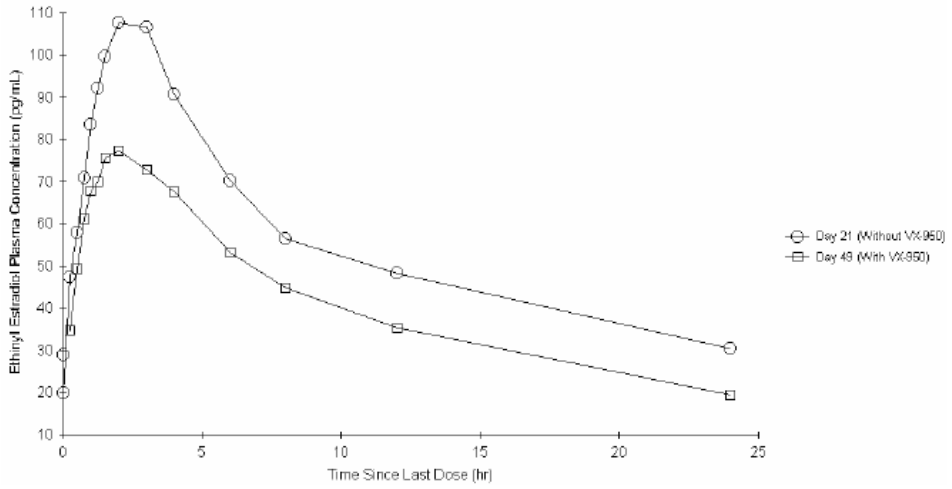
The results of this study show that 21 days of dosing with Modicon (0.5 mg NE + 0.035 mg EE) and telaprevir resulted in a decrease in EE plasma concentrations as compared with Modicon administration for 21 days alone (see

Figure 2.4.2.8-1). Mean EE Cmax, Cmin, and AUCss were decreased by 26%, 32%, and 27%, respectively. Telaprevir also decreased NE exposure: mean NE Cmax, Cmin, and $AUC_{ss}$ were decreased by 16%, 7%, and 10%, respectively. On the contrary, mean telaprevir plasma concentrations were not significantly affected by the co-administration of Modicon.

Plasma samples were analyzed for LH, FSH, and progesterone concentrations at screening, days 7 and 21 in cycle 1 (Modicon alone), and days 35 and 49 in cycle 2 (Modicon plus telaprevir). As expected with oral contraceptives, mean values of both LH and FSH declined from day 7 to day 21 in both cycles. However, the magnitude of decrease in LH and FSH levels were not as great when telaprevir was co-administered, resulting in higher LH and FSH levels on day 49 in cycle 2 (Modicon+telaprevir) compared to day 21 in cycle 1 (Modicon alone). Likewise, the magnitude of the decrease in progesterone levels observed from day 35 to day 49 (Modicon+telaprevir) was not as great as when Modicon was administered alone. Based on a consult with the reproductive/urologic team within the Office of Clinical Pharmacology, when considering the clinical relevance to pregnancy prevention, the plasma concentrations of EE/NE are of primary significance while the pharmacodynamic measures are secondary.

The main conclusion from this study is that the effect of ~30% lower EE concentrations resulting from co-administration of telaprevir on the efficacy of oral contraceptives is unknown. Considering the teratogenic and embryocidal effects of RBV, the Applicant should include a statement in the label recommending that two alternative (non-hormonal) methods of contraception should be used during telaprevir therapy. Alternative contraption may include barrier methods or IUDs.

Figure 2.4.2.8-1 Mean EE Plasma Concentration Vs. Time Profiles After Administration of Modicon Alone (Day 21) and With Telaprevir (Day 49)




**Midazolam** (Study VX06-950-011)

Because telaprevir is a demonstrated CYP3A inhibitor *in vitro*, this study with sensitive CYP3A substrate midazolam (MDZ) was conducted to assess the effect

of telaprevir on the single-dose pharmacokinetics of MDZ administered both orally and intravenously.

A single dose of IV MDZ (0.5 mg) was administered on day 1 and telaprevir 750 mg q8h was administered from days 8 through 23. On day 17, another single dose of IV MDZ was administered following the morning dose of telaprevir. Similarly, in a separate group of subjects, a single dose of oral MDZ was administered on day 3 and again on day 19. The results of this study show that the exposure to MDZ ($AUC_{0-\infty}$) increased by more than 5-fold and the mean elimination half-life increased 4-fold in the presence of telaprevir when MDZ is administered IV. When MDZ was administered as an oral dose, MDZ $C_{max}$ increased approximately 3-fold, the mean elimination half-life increased 4-fold, and the overall exposure to MDZ ($AUC_{0-tlast}$) increased by more than 9-fold. Due to the significant inhibitory effect of telaprevir on the metabolism of midazolam, no subjects had measurable concentrations of 1-hydroxymidazolam at all time points on day 17.

The main conclusion from this study is that telaprevir is a potent inhibitor of CYP3A, which could lead to prolonged or increased sedation or respiratory distress in patients following oral MDZ. The Applicant has proposed that co-administration of oral MDZ with telaprevir be contraindicated and co-administration with IV MDZ should be done in a setting which ensures clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. The Applicant has also recommended that dose reduction for MDZ should be considered, especially if more than a single dose of MDZ is administered. In addition to these recommendations, all sensitive CYP3A substrates with narrow therapeutic indices should be contraindicated in the label.

**Digoxin** (Study VX06-950-011)

Telaprevir is a substrate for P-gp, but it is not known whether telaprevir is an inducer or an inhibitor of P-gp *in vivo*. Inhibition or induction of P-gp can affect the disposition of other drugs that are also substrates of P-gp, such as digoxin. Therefore, this trial was designed to characterize the effects of telaprevir on the PK of digoxin (a sensitive substrate of P-gp).

A single oral dose of 0.5 mg digoxin was administered on day 3 and 19 of the study while telaprevir was administered daily (750 mg q8h) from day 8 through day 23. The results of this study show that telaprevir caused a nearly 2-fold increase in exposure (Cmax, $AUC_{last}$) to digoxin (see Table 2.4.2.8-3). Clearance of digoxin was decreased by 46% in the presence of telaprevir. Given the narrow therapeutic index of digoxin, the extent of the interaction is clinically significant. Co-administration with a single dose of digoxin did not significantly alter the PK of telaprevir.

The main conclusion from this study is that telaprevir appears to have an inhibitory effect on P-gp, as evidenced by a statistically significant increase in the exposure of digoxin, a model P-gp substrate. The Applicant proposed (in the label) that the lowest dose of digoxin should be initially prescribed. Serum digoxin concentrations should be monitored and used for titration of digoxin dose to obtain the desired clinical effect.

Table 2.4.2.8-3 Summary of PK Parameters of Digoxin Following Oral Administration Without (Day 3) and With (Day 19) Telaprevir

| Day | Parameter | $t_{½}$ (hr) | $t_{max}$ (hr) | $C_{max}$ (ng/mL) | $AUC_{0\text{-tlast}}$ (ng*hr/mL) | $AUC_{0\text{-}\infty}$ (ng*hr/mL) | Vz/ F (L) | CL/ F (L/hr) |
|---|---|---|---|---|---|---|---|---|
| 3 | N | 23 | 23 | 23 | 23 | 23 | 23 | 23 |
| | Mean | 38.33 | 1.32 | 2.43 | 24.63 | 31.66 | 914.89 | 17.15 |
| | SD | 8.16 | 0.45 | 0.90 | 9.16 | 10.24 | 212.58 | 4.61 |
| | Min | 21.85 | 0.50 | 1.36 | 12.34 | 18.59 | 619.18 | 8.89 |
| | Median | 39.66 | 1.50 | 2.14 | 22.37 | 29.01 | 886.09 | 17.24 |
| | Max | 62.17 | 2.00 | 5.17 | 45.39 | 56.26 | 1391.84 | 26.89 |
| | % CV | 21.30 | 34.00 | 37.10 | 37.20 | 32.30 | 23.20 | 26.90 |
| 19 | N | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | Mean | 49.64 | 1.22 | 3.58 | 46.68 | 57.47 | 662.69 | 9.30 |
| | SD | 6.14 | 0.45 | 1.03 | 13.91 | 15.84 | 181.08 | 2.39 |
| | Min | 40.36 | 0.50 | 2.02 | 22.73 | 33.41 | 387.83 | 5.15 |
| | Median | 48.05 | 1.25 | 3.30 | 45.60 | 54.95 | 643.82 | 9.10 |
| | Max | 60.61 | 2.03 | 6.20 | 81.02 | 97.05 | 1031.04 | 4.96 |
| | % CV | 12.40 | 36.90 | 28.80 | 29.80 | 27.60 | 27.30 | 25.70 |

**Rifampin** (Study VX06-950-016)

Since telaprevir is a substrate for CYP3A, this interaction study with model CYP3A4 inducer, rifampin was conducted to evaluate the effect of steady-state rifampin on the single-dose PK of telaprevir.

A single oral dose of 750 mg telaprevir was administered to subjects on day 1. Daily doses of 600 mg rifampin were administered from days 2 through 9 along with a second single oral dose of telaprevir 750 mg on day 9. The results of the study confirm that rifampin causes a significant increase in CYP3A4 metabolism resulting in a greater than 10-fold decrease in telaprevir $AUC_{last}$ exposure and 7-fold decrease in Cmax (see Table 2.4.2.8-4). Tmax and half-life were not significantly affected; however, clearance was increased between by ~10-fold.

Table 2.4.2.8-4 Summary of Pharmacokinetic Parameters of Telaprevir Following Oral Administration Without (Day 1) and With (Day 9) Rifampin

| Day | Parameter | $t_{max}$ (hr) | Half Life (hr) | $C_{max}$ (ng/ml) | $AUC_{0\text{-last}}$ (hr*ng/ml) | $AUC_{0\text{-}\infty}$ (hr*ng/ml) | Vz/F (L) | CL/F (L/hr) |
|---|---|---|---|---|---|---|---|---|
| **1** | **N** | 16 | 16 | 16 | 16 | 16 | 16 | 16 |
| | **Mean** | 3.28 | 3.81 | 1899.06 | 10363.89 | 10586.30 | 537.41 | 97.90 |
| | **SD** | 1.05 | 0.82 | 940.12 | 5308.92 | 5512.16 | 429.76 | 70.41 |
| | **Min** | 2.00 | 2.68 | 324.00 | 2680.60 | 2756.62 | 199.96 | 30.47 |
| | **Median** | 3.25 | 3.65 | 2005.00 | 10317.06 | 10545.39 | 383.28 | 71.46 |
| | **Max** | 6.00 | 5.68 | 3760.00 | 23894.87 | 24617.64 | 1752.76 | 272.07 |
| | **CV%** | 31.86 | 21.48 | 49.50 | 51.23 | 52.07 | 79.97 | 71.92 |
| **9** | **N** | 16 | 16 | 16 | 16 | 16 | 16 | 16 |
| | **Mean** | 3.50 | 2.11 | 248.63 | 817.13 | 837.56 | 3415.58 | 1054.81 |
| | **SD** | 0.86 | 0.74 | 106.03 | 338.39 | 335.11 | 2446.59 | 498.65 |
| | **Min** | 1.00 | 1.28 | 117.00 | 287.19 | 298.92 | 957.39 | 495.81 |
| | **Median** | 4.00 | 1.90 | 246.00 | 812.86 | 837.88 | 2536.27 | 896.14 |
| | **Max** | 4.02 | 4.06 | 462.00 | 1500.02 | 1512.69 | 10815.02 | 2509.05 |
| | **CV%** | 24.59 | 34.84 | 42.65 | 41.4 | 40.01 | 71.63 | 47.27 |

The main conclusion from this study is that rifampin causes a sharp increase in CYP3A4-mediated metabolism resulting in potentially subtherapeutic telaprevir concentrations. Use of rifampin and other potent CYP3A inducers during telaprevir treatment is contraindicated.

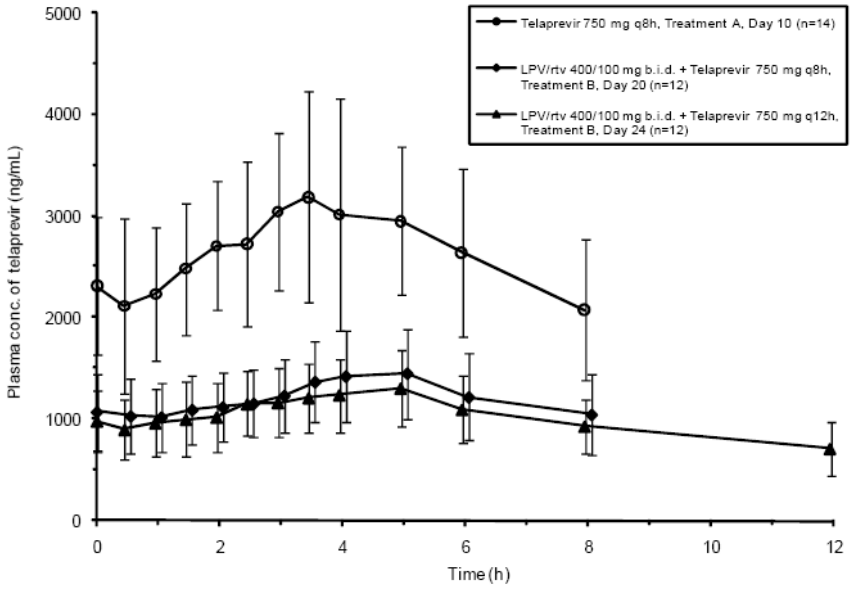
**Lopinavir/Ritonavir** (Study VX-950-TiDP24-C122)

The combination of lopinavir/ritonavir (LPV/RTV) inhibits CYP3A4 and P-gp. Telaprevir is a substrate of both CYP3A4 and P-gp, and its pharmacokinetics are likely to be altered during co-administration of these HIV protease inhibitors (PIs). Furthermore, inhibition of CYP3A4 by telaprevir could also affect the pharmacokinetics of the LPV, which is a CYP3A4 substrate. Thus, this study aimed to assess the 2-way PK interaction between telaprevir and LPV to provide guidance on dose recommendations for future combined administration of these drugs in the treatment of HCV/HIV co-infected patients.

Telaprevir 750 mg q8h was administered from days 1-9 with a morning dose on day 10. In a separate group, LPV/RTV 400/100 mg BID was administered on days 1 to 23 with a morning dose on day 24, while telaprevir was administered as 750 mg q8h from days 11 to 20 and then 750 mg q12h from days 21 to 23 with a morning dose on day 24. The results of the study show that the co-administration of LPV/RTV with telaprevir caused an unexpected and significant decrease in telaprevir plasma concentrations as compared with telaprevir administration alone (see Figure 2.4.2.8-2). The co-administration of telaprevir with LPV/RTV did not cause a significant change in LPV exposure.

The main conclusion from this study is that LPV/RTV significantly lowers telaprevir exposure (54% decrease in $AUC_\tau$ and 55% decrease in Cmax) and could result in subtherapeutic concentrations of telaprevir. Therefore, the co-administration of LPV/RTV with telaprevir is not recommended.

Figure 2.4.2.8-2 Mean Plasma Concentration-Time Curves of Telaprevir



**Tenofovir Disoproxil Fumarate** (Study VX-950-TiDP24-C123)

As telaprevir is primarily metabolized in the liver and excreted in feces, renal elimination would not be anticipated to play a significant role in the elimination of telaprevir. Likewise, telaprevir would not be expected to inhibit or compete for renal elimination when given in combination with a drug that is primarily renally excreted. Tenofovir disoproxil fumarate (TDF), the prodrug of the active ingredient tenofovir, is a widely used nucleotide reverse transcriptase inhibitor (NRTI) for the treatment of HIV infection, in combination with other antiretroviral agents. Tenofovir is largely excreted into the urine unchanged and is a substrate for the renal transporters hOAT1 and hOAT3 and possibly P-gp in the gut. However, previous trials have shown the potential for drug interactions with CYP3A4 substrates/inhibitors such as HIV protease inhibitors that did not involve CYP-related interactions. Thus, this study assessed the 2-way PK interaction between telaprevir and TDF in order to provide guidance on dose recommendations for future combined administration of these drugs in the treatment of HCV/HIV co-infected patients.

Telaprevir (750 mg q8h) and TDF (300 mg QD) were administered separately for 7 days and then co-administered for a total of 7 days in a 3-treatment, 3-period, 6-sequence design. The results of the study show that tenofovir does not affect telaprevir exposure; however, telaprevir increases exposure to tenofovir (30% increase in $AUC_{24h}$ and 28% increase in Cmax). Although tenofovir is mainly renally eliminated, it is not uncommon for this effect to be observed with protease inhibitors. Co-administration with ATZ/RTV, LPV/RTV, DRV/RTV, and SQV/RTV all resulted in similar increases in tenofovir Cmin, Cmax, and AUC. The hypothesis for this observation is inhibition of P-gp in the gut. The total amount of tenofovir excreted in urine (0-24 hours) was not affected by telaprevir; however, renal clearance was decreased by approximately 32%.

The main conclusion from this study is that although telaprevir increased exposures to tenofovir, the magnitude of the increase is likely not great enough to warrant a dose adjustment of TDF in the case of co-administration with telaprevir (no dose adjustment is recommended for TDF when given in combination with Kaletra®, which resulted in a ~32-51% increase in tenofovir exposures). However, increased monitoring is warranted.

**Methadone** (Study VX-950-TiDP24-C135)

Because telaprevir is a CYP3A4 inhibitor and methadone is primarily metabolized by CYP3A4 and is a commonly co-administered drug in this patient population (HCV-infected), a study was performed to assess the effect of steady-state telaprevir on the PK of methadone and vice versa.

Subjects on stable methadone maintenance therapy participated in this study to investigate the potential interaction between telaprevir and methadone at steady-state. Seven days of telaprevir therapy (750 mg q8h) was added to subjects' current methadone therapy. The results of the study show that based on historical comparisons of steady-state telaprevir exposure, methadone did not affect telaprevir PK. However, telaprevir lowered subjects' exposure to R-methadone by approximately 30% (the component that confers the opioid effect) (see Figure 2.4.2.8-

3). Telaprevir also lowered S-methadone (the component that poses a safety concern due to QTc prolongation) exposure to approximately the same extent. This observation of lower methadone exposure has also been reported for some HIV PIs. The cause of the finding is unknown.

Since R-methadone is primarily responsible for the opioid effect, lower exposure to this component could have clinical consequences on patients maintained on methadone treatment. However, because methadone dosing is extremely individualized and co-administration of telaprevir with methadone in this study did not result in increased signs of withdrawal, the starting dose may not need adjustment. Dose adjustment based on clinical monitoring for signs of withdrawal would be warranted.

Figure 2.4.2.8-3 Mean Plasma Concentration-Time Curves of R-Methadone

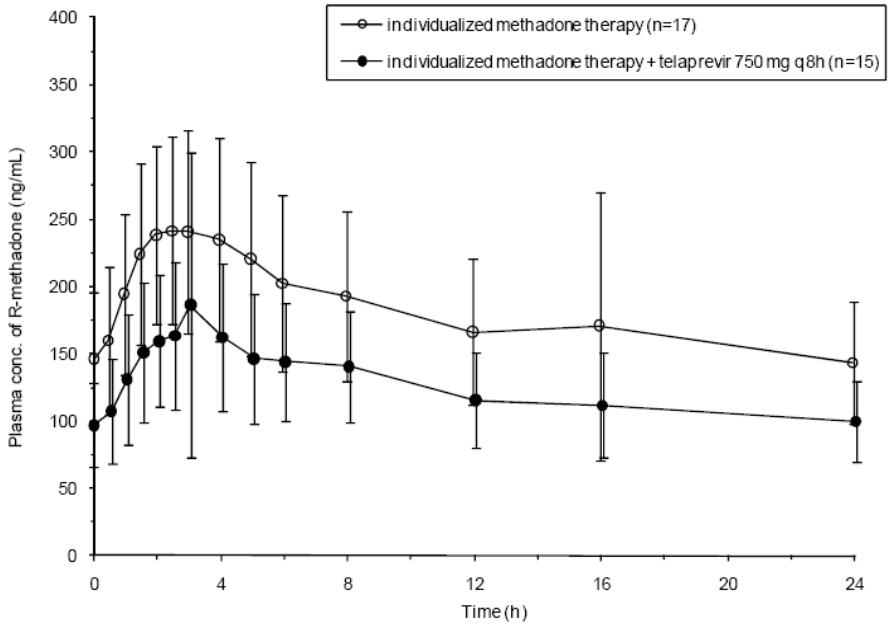



**Table 2.4.2.8-5 Drug Interactions: Summary of Pharmacokinetic Parameters for Telaprevir in the Presence of Co-administered Drugs***

| Drug | Dose and Schedule | | N | Effect on Telaprevir PK[a] | LS Mean Ratio (90% CI) of Telaprevir PK With/Without Coadministered Drug | | | Clinical Comment/Outomce |
|---|---|---|---|---|---|---|---|---|
| | Drug | Telaprevir | | | $C_{max}$ | AUC or $C_{avg,ss}$[b] | $C_{min}$ | |
| Escitalopram | 10 mg qd for 7 days | 750 mg q8h for 14 days | 13 | ↔ | 1.00 (0.95; 1.05) | 0.93 (0.89; 0.97) | 0.91 (0.86; 0.97) | Doses of escitalopram may need to be adjusted. |
| Esomeprazole | 40 mg qd for 6 days | 750 mg single dose | 24 | ↔ | 0.95 (0.86; 1.06) | 0.98 (0.91; 1.05) | NA | None |
| Ketoconazole | Ketoconazole 400 mg single dose | 750 mg single dose | 17 | ↑ | 1.24 (1.10; 1.41) | 1.62 (1.45; 1.81) | NA | Limit KETO dose to 200 mg/day |

**Table 2.4.2.8-5 Drug Interactions: Summary of Pharmacokinetic Parameters for Telaprevir in the Presence of Co-administered Drugs***

| Drug | Dose and Schedule | | N | Effect on Telaprevir PK[a] | LS Mean Ratio (90% CI) of Telaprevir PK With/Without Coadministered Drug | | | Clinical Comment/Outomce |
|---|---|---|---|---|---|---|---|---|
| | Drug | Telaprevir | | | $C_{max}$ | AUC or $C_{avg,ss}$[b] | $C_{min}$ | |
| Oral Contraceptive | Norethindrone/ ethinyl estradiol 0.5 mg/0.035 mg qd for 21 days | 750 mg q8h for 21 days | 23 | ↔ | 1.00 (0.93; 1.07) | 0.99 (0.93; 1.05) | 1.00 (0.93; 1.08) | Use 2 alternative (barrier) forms of contraception |
| Rifampin | 600 mg qd for 8 days | 750 mg single dose | 16 | ↓ | 0.14 (0.11; 0.18) | 0.08 (0.07; 0.11) | NA | CONTRAINDICATED |
| **Anti-HIV Drugs** | | | | | | | | |
| Atazanavir (ATV)/ritonavir (rtv) | 300 mg ATV/ 100 mg rtv qd for 20 days | 750 mg q8h for 10 days | 14 | ↓ | 0.79 (0.74; 0.84) | 0.80 (0.76; 0.85) | 0.85 (0.75; 0.98) | None |
| Darunavir (DRV)/ritonavir (rtv) | 600 mg DRV/ 100 mg rtv bid for 20 days | 750 mg q8h for 10 days | 11 (N=14 for $C_{max}$) | ↓ | 0.64 (0.61; 0.67) | 0.65 (0.61; 0.69) | 0.68 (0.63; 0.74) | Not recommended for use with telaprevir |
| Efavirenz | 600 mg qd for 20 days | 750 mg q8h for 10 days | 21 | ↓ | 0.91 (0.82; 1.02) | 0.74 (0.65; 0.84) | 0.53 (0.44; 0.65) | None |
| Fosamprenavir (fAPV)/ ritonavir (rtv) | 700 mg fAPV/ 100 mg rtv bid for 20 days | 750 mg q8h for 10 days | 18 | ↓ | 0.67 (0.63; 0.71) | 0.68 (0.63; 0.72) | 0.70 (0.64; 0.77) | Not recommended for use with telaprevir |
| Lopinavir (LPV)/ritonavir (rtv) | 400 mg LPV/ 100 mg rtv bid for 20 days | 750 mg q8h for 10 days | 12 | ↓ | 0.47 (0.41; 0.52) | 0.46 (0.41; 0.52) | 0.48 (0.40; 0.56) | Not recommended for use with telaprevir |
| Ritonavir | 100 mg single dose | 750 mg single dose | 14 | ↑ | 1.30 (1.15; 1.47) | 2.00 (1.72; 2.33) | NA | None |
| Ritonavir | 100 mg q12h for 14 days | 750 mg q12h for 14 days | 5 | ↓ | 0.85 (0.63; 1.13) | 0.76[b,c] (0.60; 0.97) | 0.68 (0.57; 0.82) | None |
| Tenofovir disoproxil fumarate (TDF) | 300 mg qd TDF for 7days | 750 mg q8h for 7 days | 16 | ↔ | 1.01 (0.96; 1.05) | 1.00 (0.94; 1.07) | 1.03 (0.93; 1.14) | Increase clinical and laboratory monitoring for tenofovir-associated AEs (due to effect on TDF PK) |
| Tenofovir disoproxil fumarate (TDF) and efavirenz (EFV) | 600 mg EFV /300 mg TDF qd for 7 days | 1125 mg q8h for 7 days | 15 | ↓ | 0.86[c] (0.76; 0.97) | 0.82[c] (0.73; 0.92) | 0.75[c] (0.66; 0.86) | None |
| | 600 mg EFV /300 mg TDF qd for 7 days | 1500mg q12h for 7 days | 16 | ↓ | 0.97[c] (0.88; 1.06) | 0.80[b,c] (0.73; 0.88) | 0.52[c] (0.42; 0.64) | None |

**Table 2.4.2.8-5 Drug Interactions: Summary of Pharmacokinetic Parameters for Telaprevir in the Presence of Co-administered Drugs***

| Drug | Dose and Schedule | | N | Effect on Telaprevir PK[a] | LS Mean Ratio (90% CI) of Telaprevir PK With/Without Coadministered Drug | | | Clinical Comment/Outomce |
|---|---|---|---|---|---|---|---|---|
| | Drug | Telaprevir | | | $C_{max}$ | AUC or $C_{avg,ss}$[b] | $C_{min}$ | |
| NA: not available/ not applicable; N = Number of subjects with data; qd = once daily; bid = twice daily; q8h = every 8 hours; q12h = every 12 hours | | | | | | | | |

[a] The direction of the arrow (↑ = *increase,* ↓ = *decrease,* ↔ = *no change*) indicates the direction of the change in PK

[b] $C_{avg,ss}$ = Average concentrations at steady state ($AUC_\tau/\tau$).

[c] Value with co-administered drug and telaprevir / value with telaprevir 750 mg q8h alone

*Data provided are under fed conditions unless otherwise noted.

**Table 2.4.2.8-6 Drug Interactions: Summary of Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Telaprevir**

| Drug | Dose and Schedule | | N | Effect on Drug PK[a] | LS Mean Ratio (90% CI) of Drug PK With/Without Telaprevir [b] | | | Clinical Comment/Outomce |
|---|---|---|---|---|---|---|---|---|
| | Drug | Telaprevir | | | $C_{max}$ | AUC | $C_{min}$ | |
| Alprazolam | 0.5 mg single dose | 750 mg q8h for 10 days | 17 | ↑ | 0.97 (0.92; 1.03) | 1.35 (1.23; 1.49) | NA | Clinical monitoring for alprazolam |
| Amlodipine | 5 mg single dose | 750 mg q8h for 7 days | 19 | ↑ | 1.27 (1.21; 1.33) | 2.79 (2.58; 3.01) | NA | Use with caution. Dose reduction for amlodidpine should be considered. Clinical monitoring is recommended. |
| Atorvastatin | 20 mg single dose | 750 mg q8h for 7 days | 19 | ↑ | 10.60 (8.74;12.85) | 7.88 (6.84; 9.07) | NA | CONTRAINDICATED |
| Cyclosporine A (CsA) | 100 mg single dose when administered alone; 10 mg single dose when coadministered with telaprevir (D8) | 750 mg q8h for 11 days | 9 | ↑ | 0.13 (0.11;0.16) **Dose norm.:** 1.32 (1.08;1.60) | 0.46 (0.39; 0.55) **Dose norm.:** 4.66 (3.90;5.51) | NA | Use of telaprevir is not recommended in patients with organ transplants |
| Digoxin | 2 mg single dose | 750 mg q8h for 11 days | 20 | ↑ | 1.50 (1.36; 1.65) | 1.85 (1.70; 2.00) | NA | Start with lowest dose of digoxin. Serum digoxin concentrations should be monitored and titrated for clinical effect |
| Escitalopram | 10 mg qd, for 7 days | 750 mg q8h for 14 days | 13 | ↓ | 0.70 (0.65; 0.76) | 0.65 (0.60; 0.70) | 0.58 (0.52; 0.64) | Doses of escitalopram may need to be adjusted. |
| Ethinyl estradiol (EE), coadministered with norethindrone (NE) | 0.035 mg qd EE/ 0.5 mg qd NE for 21 days | 750 mg q8h for 21 days | 24 | ↓ | 0.74 (0.68; 0.80) | 0.72 (0.69; 0.75) | 0.67 (0.63; 0.71) | Use 2 alternative forms of contraception |

**Table 2.4.2.8-6 Drug Interactions: Summary of Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Telaprevir**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Ketoconazole | 400 mg single dose | 1250 mg q8h for 4 doses | 81 | ↑ | 1.23 (1.14; 1.33) | 1.46 (1.35; 1.58) | NA | Limit KETO dose to 200 mg/day |
| | 200 mg single dose | 1250 mg q8h for 4 doses | 28 | ↑ | 1.75 (1.51; 2.03) | 2.25 (1.93; 2.61) | NA | |
| *R*-Methadone | Methadone maintenance therapy (40 to 120 mg/daily) | 750 mg q8h for 7 days | 15 | ↓ | 0.71 (0.66; 0.76) | 0.71 (0.66; 0.76) | 0.69 (0.64; 0.75) | No initial dose adjustment. Clinical monitoring is recommended as maintenance dose of methadone may need to be adjusted. |
| *S*-Methadone | Methadone maintenance therapy (40 to 120 mg/daily) | 750 mg q8h for 7 days | 15 | ↓ | 0.65 (0.60; 0.71) | 0.64 (0.58; 0.70) | 0.60 (0.54; 0.67) | |
| Midazolam (iv) | 0.5 mg iv single dose | 750 mg q8h for 9 days | 22 | ↑ | 1.02 (0.8; 1.31) | 3.40 (3.04; 3.79) | NA | Co-administration should be done in controlled setting with proposer clinical monitoring and management. Dose reduction of midazolam should be considered especially if more than a single dose is administered. |
| Midazolam (oral) | 2 mg oral single dose | 750 mg q8h for 11 days | 21 | ↑ | 2.86 (2.52; 3.25) | 8.96 (7.75; 10.35) | NA | CONTRAINDICATED |
| Norethindrone (NE), coadministered with EE | 0.035 mg qd EE/ 0.5 mg qd NE for 21 days | 750 mg q8h for 7 days | 24 | ↔ | 0.85 (0.81; 0.89) | 0.89 (0.86; 0.93) | 0.94 (0.87; 1.0) | Use 2 alternative (barrier) forms of contraception (due to effect on EE component) |
| Tacrolimus | 2 mg single dose when administered alone; 0.5 mg single dose when coadministered with telaprevir (D8) | 750 mg q8h for 13 days | 9 | ↑ | 2.34 (1.68;3.25) **Dose norm.:** 9.35 (6.73;13.0) | 17.6 (13.2; 23.3) **Dose norm.:** 70.3 (52.9;93.4) | NA | Use of telaprevir is not recommended in patients with organ transplants |
| Zolpidem | 5 mg single dose | 750 mg q8h for 10 days | 19 | ↓ | 0.58 (0.52;0.66) | 0.53 (0.45; 0.64) | NA | Clinical monitoring and dose titration is recommended for zolpidem |
| **Anti-HIV Drugs** | | | | | | | | |
| Atazanavir (ATV), boosted with ritonavir (rtv) | 300 mg ATV/ 100 mg rtv qd for 20 days | 750 mg q8h for 10 days | 7 | ↔ | 0.85 (0.73; 0.98) | 1.17 (0.97; 1.43) | 1.85 (1.40; 2.44) | None |
| Darunavir (DRV), boosted with | 600 mg DRV/ 100 mg rtv bid for 20 days | 750 mg q8h for 10 days | 11 (N=14 for $C_{max}$) | ↓ | 0.60 (0.56; 0.64) | 0.60 (0.57; 0.63) | 0.58 (0.52; 0.64) | Not recommended for use with telaprevir |

**Table 2.4.2.8-6 Drug Interactions: Summary of Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Telaprevir**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| ritonavir (rtv) | | | | | | | | |
| | 600 mg DRV/ 100 mg rtv bid for 24 days | 1125 mg q12h for 4 days | 15 | ↓ | 0.53 (0.47; 0.59) | 0.49 (0.43; 0.55) | 0.42 (0.35; 0.51) | |
| Efavirenz | 600 mg qd for 20 days | 750 mg q8h for 10 days | 21 | ↔ | 0.84 (0.76; 0.93) | 0.93 (0.87; 0.98) | 0.98 (0.94; 1.02) | None |
| Efavirenz (EFV), coadministered with tenofovir disoproxil fumarate (TDF) | 600 mg EFV /300 mg TDF qd for 7 days | 1125 mg q8h for 7 days | 15 | ↓ | 0.76[b] (0.68; 0.85) | 0.82[b] (0.74; 0.90) | 0.90[b] (0.81; 1.01) | None |
| | 600 mg EFV /300 mg TDF qd for 7days | 1500 mg q12h for 7days | 16 | ↓ | 0.80[b] (0.74; 0.86) | 0.85[b] (0.79; 0.91) | 0.89[b] (0.82; 0.96) | |
| Fosamprenavir (fAPV), boosted with ritonavir (rtv) | 700 mg fAPV/ 100 mg bid rtv for 20 days | 750 mg q8h for 10 days | 18 | ↓ | 0.65 (0.59; 0.70) | 0.53 (0.49; 0.58) | 0.44 (0.40; 0.50) | Not recommended for use with telaprevir |
| | 700 mg fAPV/ 100 mg bid rtv for 24 days | 1125 mg q12h for 4 days | 17 (N=18 for $C_{min}$) | ↓ | 0.60[b] (0.55; 0.67) | 0.51[b] (0.47; 0.55) | 0.42[b] (0.37; 0.47) | |
| Lopinavir (LPV), boosted with ritonavir (rtv) | 400 mg LPV/ 100 mg rtv b.i.d for 20 days | 750 mg q8h for 10 days | 12 | ↔ | 0.96 (0.87; 1.05) | 1.06 (0.96; 1.17) | 1.14 (0.96; 1.36) | Not recommended for use with telaprevir |
| Tenofovir disoproxil fumarate | 300 mg qd for 7 days | 750 mg q8h for 7 days | 16 | ↑ | 1.30 (1.16; 1.45) | 1.30 (1.22; 1.39) | 1.41 (1.29;1.54) | Increase clinical and laboratory monitoring for tenofovir-associated AEs |
| Tenofovir, on coadministration of tenofovir disoproxil fumarate (TDF) and efavirenz (EFV) | 600 mg EFV /300 mg TDF qd for 7 days | 1125 mg q8h for 7 days | 15 | ↑ | 1.22[b] (1.12; 1.33) | 1.10[b] (1.03; 1.18) | 1.17[b] (1.06; 1.28) | None |
| | 600 mg EFV /300 mg TDF qd for 7 days | 1500 mg q12h for 7 days | 16 | ↑ | 1.24[b] (1.13; 1.37) | 1.10[b] (1.03; 1.17) | 1.06[b] (0.98; 1.15) | |

[a] The direction of the arrow (↑ = *increase,* ↓ = *decrease,* ↔ = *no change*) indicates the direction of the change in PK

[b] Value with co-administered drug and telaprevir / value with telaprevir 750 mg q8h alone

#### 2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

Although there are several pharmacokinetic drug-drug interactions, there are no known mechanistic bases for pharmacodynamic drug-drug interactions for telaprevir. However, since telaprevir's safety profile includes anemia as an adverse event and ribavirin similarly causes anemia, there is a potential for an additive effect on this AE.

#### 2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

There is one unresolved question pertaining to protein binding in the moderate hepatic impairment study. In study 012, mean telaprevir concentrations *decreased* in subjects with moderate hepatic impairment. The Applicant stated that the reason for this is unclear but may be related to decreased protein binding. However, the extent of protein binding was not assessed in that study. This issue will likely remain unresolved due to bioanalytical difficulties. Blood samples for the determination of telaprevir concentrations need to be stabilized with (b) (4) to prevent active inter-conversion between telaprevir and VRT-127394. This addition of (b) (4) would denature any proteins that are present in the sample, thus nullifying any attempt to quantify protein binding.

### 2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

There are no significant issues relating to dose, dosing regimens, or administration that remain unresolved at this time.

## 2.5 General Biopharmaceutics

### 2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

According to the Applicant, telaprevir is considered to be a Class II (low solubility/high permeability) drug. (b) (4) are of low solubility according to the BCS criteria. Because telaprevir is a P-gp substrate, *in vitro* assays of permeability are not conclusive; however, it is estimated that telaprevir will have high human intestinal permeability in the upper small intestine. Orally administered telaprevir shows dose proportionality for $C_{max}$ doses ranging from 750 to 1500 mg, suggesting that P-gp efflux

and metabolic pathways are not rate-limiting at these doses. The dissolution data for telaprevir show that telaprevir dissolves quickly in all pH's tested (see Figure 2.5.1-1).

(b) (4)

[redacted]

### 2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The relative bioavailability between the to-be-marketed formulation (film-coated 375-mg tablet) and the formulation used in the pivotal clinical trials (uncoated 375-mg tablet) was assessed in study VX07-950-017. The two tablets are identical in their formulations with the exception of (b) (4) [redacted] (see Table 2.5.2-1 below). The study was conducted under fed conditions (standard fat breakfast). The results showed that when dosed as a single 750-mg dose (2 X 375-mg tablets), the film-coated tablet had slightly higher bioavailability than the uncoated tablet. Mean telaprevir $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and Cmax were 15%, 14%, and 12% higher, respectively, following administration of the coated tablet compared with the uncoated tablet (Table 2.5.2-2). When the Applicant applied the standard BE limits to the results of their statistical test, the two formulations did not meet the criteria for bioequivalence (90% confidence intervals for all three telaprevir parameters' point estimate of least square means ratio within the 80-125% boundary). According to the Applicant's calculations, the 90% CI of all three parameters (Cmax, $AUC_t$, and $AUC_{inf}$) were outside the upper bound of the BE limits (see Table 2.5.2-3). When the reviewer re-calculated the BE statistics using a slightly revised data population (removal of one subject's data and addition of a subject that was dropped by the Applicant), the 90% CI for all three parameters were still not within the BE limits; however, the upper bound of the CI was slightly lower than the Applicant's results (Table 2.5.2-4). Based on the exposure-safety relationship with respect to hemoglobin toxicity, a 15% increase in mean AUC would likely result in a 3% increase in probability of acquiring anemia. Thus, there is not a clinically significant effect of a formulation that would result in a 15% increase in exposure.

Table 2.5.2-1 Components and Composition of 375-mg Uncoated Tablet vs. 375-mg Film-Coated Tablet


Table 2.5.2-2 Arithmetic Means (SD) of Telaprevir PK Parameters by Formulation

| PK Parameter | Uncoated (N=19) | Coated (N=20) |
|---|---|---|
| $C_{max}$ (ng/mL) | 1692.00 (750.9) | 1887.80 (830.5) |
| $AUC_{0\text{-}last}$ (hr*ng/mL) | 9871.12 (5780.11) | 11304.61 (6293.44) |
| $AUC_{0\text{-}\infty}$ (hr*ng/mL) | 10414.42 (6395.59) | 11920.95[b] (6840.44) |
| $t_{max}$ (hr)[a] | 5 (4,8) | 5 (2,8) |
| $t_{1/2}$ (hr) | 4.72 (1.37) | 4.78 (1.53) |
| Cl/F (L/hr) | 99.43 (57.91) | 94.72 (81.35) |
| Vz/F (L) | 652.05 (393.24) | 620.41 (516.08) |

Table 2.5.2-3 BE Statistical Analysis—Test vs. Reference (Applicant-calculated)

| Comparison | Parameter | Point Estimate (%) of geometric least squares mean ratio | 90% Confidence interval |
|---|---|---|---|
| Coated (test) versus. Uncoated (reference) | $C_{max}$ Ratio | 107.41 | [89.94, 128.26] |
| | $AUC_{0\text{-}last}$ Ratio | 110.70 | [94.52, 129.65] |
| | $AUC_{0\text{-}\infty}$ Ratio[a] | 111.93 | [94.99, 131.90] |

Table 2.5.2-4 BE Statistical Analysis—Test vs. Reference (reviewer-calculated)

| Parameter | Point estimate of LSM ratio (coated to uncoated) | 90% Confidence interval |
|---|---|---|
| **Cmax** | 1.06 | 89.04-127.36 |
| **$AUC_{0\text{-}last}$** | 1.08 | 91.51-127.61 |
| **$AUC_{0\text{-}inf}$** | 1.09 | 92.10-128.26 |

### 2.5.2.1 What data support or do not support a waiver of *in vivo* BE data?

Not applicable to this submission.

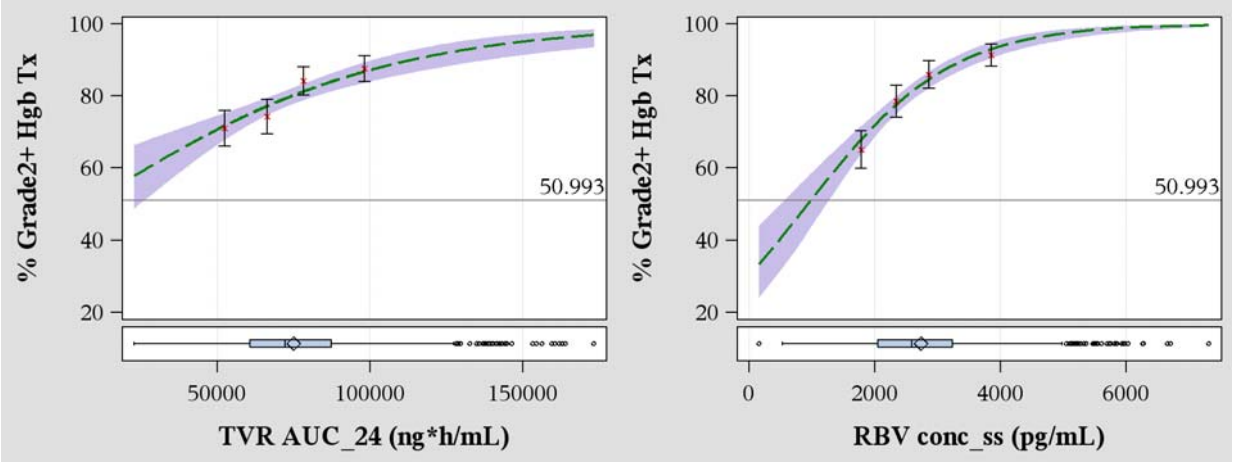
### 2.5.2.2 What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

From a strict statistical point of view, the results of the BA/BE study VX07-950-017 show that the to-be-marketed formulation is not bioequivalent to the formulation used in the pivotal phase 3 studies. However, that does not preclude the acceptability/approvability of the coated tablet. Since the coated tablet has higher exposures relative to the uncoated tablet, an issue of concern would be safety. A decrease in hemoglobin levels (risk of anemia) is the only safety issue that has been found to be associated with telaprevir exposure. See section 2.5.2.3 below for further discussion on data supporting the approval of the to-be-marketed product.

### 2.5.2.3 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

Because higher telaprevir exposure could potentially pose a safety issue with reference to anemia, an examination of the exposure-response relationship for safety between telaprevir $AUC_{\tau,ss}$ and % change in hemoglobin levels from baseline provides some rationale in support of the use of the coated tablet as the intended commercial formulation. When a univariate analysis on pooled data from the phase 2 and phase 3 trials is performed on the relationship between telaprevir exposure ($AUC_{\tau,ss}$) and % change in hemoglobin levels, the slope of the line is shallower than the relationship between ribavirin exposure and % change in hemoglobin levels (see Figure 2.5.2.3-1 below). This suggests that changes in ribavirin exposure would drive the probability of acquiring anemia more than changes in telaprevir exposure. With a 15% increase in AUC (observed difference between the coated and uncoated tablets), the probability of acquiring Hgb toxicity at the median telaprevir $AUC_{\tau,ss}$ would increase marginally from 75% to 78%.

Figure 2.5.2.3-1 Effect of Telaprevir Exposure on Hgb Toxicity (Left)
Effect of RBV Exposure on Hgb Toxicity (Right)




**2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?**

The effect of fasting and different types of food on the bioavailability of telaprevir was assessed in study VX-950-TiDP24-C121. A single oral dose of 750 mg telaprevir was administered in the following fasting and fed states:

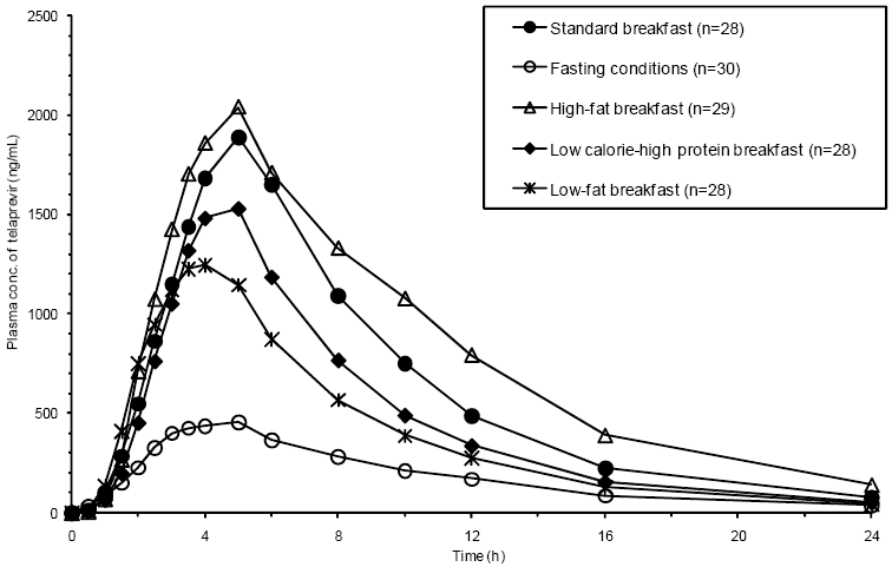
- Treatment A: Telaprevir intake after a standard breakfast (4 slices of bread, 1 slice of ham, 1 slice of cheese, butter, jelly and 2 cups of decaffeinated coffee or tea with milk and/or sugar, if desired)
- Treatment B: Telaprevir intake under fasting conditions
- Treatment C: Telaprevir intake after a high-calorie high-fat breakfast (2 eggs fried in butter, 2 strips of bacon, 2 slices of white bread with butter, 1 croissant with 1 slice of cheese and 240 mL of whole milk)
- Treatment D: Telaprevir intake after a low-calorie high-protein breakfast (115 g turkey without skin, 1 slice of bread and 1 teaspoon fat [mayo or butter])
- Treatment E: Telaprevir intake after a low-calorie low-fat breakfast (2 slices of white bread, jam [20 g] and low-calorie low-fat yogurt [100 g])

The results of this study show that fasting conditions resulted in the lowest exposure to TVP compared with any other type of meal (Figure 2.5.3-1). A high-fat breakfast resulted in the highest Cmax and AUC values; however, Tmax was also longer by an average of 1 hour as compared with the other types of meals. Relative to fasting, $AUC_{last}$ and Cmax increased 3.4-fold and 4.4-fold, respectively, with a standard meal (breakfast). Compared to a standard meal, a low-fat meal resulted in a 36% and 33% decrease in $AUC_{last}$ and Cmax. A high-fat meal resulted in a 28% and 4% increase in $AUC_{last}$ and Cmax compared with a standard meal; however, the difference between a high-fat meal and a low-fat meal was nearly 2-fold in $AUC_{last}$.

With the exception of fasting conditions, the inter-subject variability (%CV) of Cmax was comparable for all treatments, with values ranging from 38 to 45%. The inter-subject variability for TLP administered after a standard breakfast, after a high-calorie high-fat breakfast, after a low-calorie high-protein breakfast, or after a low-calorie low-fat breakfast was higher for $AUC_{last}$ and $AUC_{inf}$, ranging from 43 to 67%. A higher inter-subject variability was observed for Cmax, $AUC_{last}$, and $AUC_{inf}$ when telaprevir was administered under fasting conditions, 99%, 84%, and 85%, respectively.

Given the results of this study, telaprevir is recommended for use with food. In the phase 3 studies, patients were instructed to take telaprevir with a meal that is part of a regular diet (not low-fat). The label should reflect similar instructions to patients, particularly in light of the significantly lower telaprevir exposures following a low-fat meal as compared with a standard fat meal or high-fat meal.

Figure 2.5.3-1 Mean Plasma Concentration-Time Curves of Telaprevir Under Different Food Conditions




## 2.5.4 When would a fed BE study be appropriate and was one conducted?

A fed BA/BE study (using a standard fat breakfast) was performed comparing the to-be-marketed formulation (coated tablet) to the formulation used in the pivotal phase 3 studies (uncoated tablet). Since there is a substantial food effect on telaprevir exposure (see section 2.5.3) and the label will include instructions to take telaprevir with food, all studies should be conducted in the fed state.

## 2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

Please refer to the ONDQA review for a full discussion of dissolution conditions and specifications.

**2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?**

Not applicable to this submission. Only one strength is proposed for marketing.

**2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?**

Not applicable to this submission.

**2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?**

Not applicable to this submission.

**2.5.9 What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?**

There are no other significant, unresolved issues relating to dissolution or *in vivo* BA/BE for this submission.

## 2.6 Analytical Section

**2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?**

Telaprevir and its R-diastereomer, VRT-127394, were measured in plasma and urine using HPLC and tandem mass spec detection (LC-MS/MS). Initially, an HPLC method using a non-chiral column was developed for the detection of telaprevir and VRT-127394 in plasma and urine. In later years, a chiral method was validated and used (b) (4). The initial bioanalytical methods were developed by (b) (4); however, subsequently, the methods were cross-validated and split into a "high range" assay and "low range" assay by (b) (4).

**2.6.2 Which metabolites have been selected for analysis and why?**

A major metabolite that was selected for analysis (VRT-127394) is actually the R-diastereomer of telaprevir. It was selected for analysis because it was present at >10% of total drug-related material. Following a single dose, the proportion of VRT-127394 to telaprevir+VRT-127394 is ~29%, while following multiple doses, the proportion is

~37%. The two other metabolites present at greater than 10% of total drug-related material (PZA and VRT-0922061) were not identified as major metabolites until multiple-dose studies in HCV-infected patients (in combination with Peg-IFN/RBV) had been conducted. These metabolites demonstrate at least 30-fold lower protease activity than telaprevir according to *in vitro* study results.

### 2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

The total (bound+unbound) moiety of telaprevir and VRT-127394 were measured. This is acceptable since the addition of (b) (4) to stabilize the inter-conversion between the S- and R- diastereomers would have denatured the proteins in plasma, rendering measurement of unbound concentrations impracticable.

### 2.6.4 What bioanalytical methods are used to assess concentrations?

For the earlier clinical studies, the bioanalytical method developed at (b) (4) included normal phase HPLC with tandem mass spec detection for the entire calibration range for telaprevir and VRT-127394 in plasma and urine. For the later studies, (b) (4) developed two separate methods (one for the low range of the calibration curve and one for the high range of the calibration curve) for the detection of telaprevir and VRT-127394 in plasma. Additionally, (b) (4) also utilized a method with a chiral column to improve separation of the diastereomers. The new chiral method was cross-validated with the previous (b) (4) method, thus a full validation was not performed.

#### 2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The following are the ranges of the standard curves for both telaprevir and VRT-127394:

(b) (4) (plasma):
2.0, 4.0, 10.0., 50.0, 200, 500, 800, 1000 ng/mL

(b) (4) (urine):
2.0, 4.0, 10.0., 50.0, 200, 500, 800, 1000 ng/mL

(b) (4) (low range assay, plasma):
2.0, 4.0, 10.0., 50.0, 200, 500, 800, 1000 ng/mL

(b) (4) (high range assay, plasma):
20, 40, 100, 250, 650, 1600, 4000, 5000 ng/mL

The [redacted] methods incorporating both a low-range and high-range calibration curve were appropriate to cover the entire range of plasma concentrations (without necessitating dilution) observed in the multiple-dose studies with telaprevir. For all calibration curves, linear regression was used with a weighting factor of $1/x^2$ for curve fitting.

### 2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

The LLOQ for both telaprevir and VRT-127394 was 2.0 ng/mL for all methods used with the exception of [redacted] where the LLOQ was 20 ng/mL. The ULOQ was 1000 ng/mL for all methods used with the exception of [redacted] where the LLOQ was 5000 ng/mL.

### 2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

The precision, accuracy, and selectivity (for telaprevir) for each method are summarized below.

[redacted] (plasma):
Accuracy at LLOQ: 97.8%
Precision at LLOQ (between-run %CV): 10.7%
Accuracy at high QC (800 ng/mL): 96%
Precision at high QC (between-run %CV): 6%
Selectivity: The assay method is sufficiently selective towards endogenous plasma compounds. The responses of co-eluting peaks in none of the six blanks and in none of the six zeros exceeded 20% of the mean peak response of the analyte in the LLOQs and responses of co-eluting peaks in none of the six blanks exceeded 5% of the mean peak response of the internal standard in the zero samples.

[redacted] (urine):
Accuracy at LLOQ: 99.8%
Precision at LLOQ (between-run %CV): 2%
Accuracy at high QC (800 ng/mL): 96.6%
Precision at high QC (between-run %CV): 2.8%
Selectivity: The assay method is sufficiently selective towards endogenous urine compounds. The responses of co-eluting peaks in none of the six blanks and in none of the six zeros exceeded 20% of the mean peak response of the analyte in the LLOQs and responses of co-eluting peaks in none of the six blanks exceeded 5% of the mean peak response of the internal standard in the zero samples.

[redacted] (low range assay, plasma):
Accuracy at LLOQ: 101%

Precision at LLOQ (between-run %CV): 5.1%
Accuracy at ULOQ: 99.6%
Precision at ULOQ (between-run %CV): 2.7%
Selectivity: Testing was conducted to assess the potential for ribavirin, pegasys, ketoconazole, or ritonavir to interfere with the assay. For the pure solution and blank matrix samples, there was no significant interference in the chromatographic regions of interest for VX-950, VRT-127394 (<20.0% of the LLOQ) or VX-950 D-11 (<5.0% of internal standard response in the control zero sample). For the LQC, the mean concentration showed a RSD of ≤15.0% and mean accuracy within the range of 85.0 to 115.0%. It was therefore concluded that the method demonstrated acceptable selectivity in the presence of ribavirin, pegasys, ketoconazole, or ritonavir.

(b) (4) (high range assay, plasma):
Accuracy at LLOQ: 100.5%
Precision at LLOQ (between-run %CV): 7.3%
Accuracy at ULOQ: 99%
Precision at ULOQ (between-run %CV): 3.1%
Selectivity: Aliquots of blank human plasma were tested for endogenous interferences. The VX-950, VRT-127394, and d11-VX-950 regions were free from significant interference (<20.0% of the mean utilized LLOQ of method VX9HPP or <5.0% of internal standard response in the control zero sample).

**2.6.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?**

The long-term, freeze-thaw, sample handling, sample transport, and autosampler stabilities (for telaprevir) for each method are summarized below.

(b) (4)
(plasma):
Long-term: validated for 377 days at -20° C and 638 days at -70° C
Freeze-thaw: validated for 3 cycles
Sample handling (benchtop): validated for 26 hours
Sample transport: validated for 13 days at -20° C
Autosampler: validated for 24 hours

(b) (4) (urine):
Long-term: validated for 30 days at -20 C and 370 days at -70 C
Freeze-thaw: validated for 3 cycles
Sample handling (benchtop): validated for 26 hours
Sample transport: validated for 6 days at -20° C
Autosampler: validated for 72 hours

[redacted] (low range assay, plasma):
Long-term: validated for 6 months at -60° to -80° C
Freeze-thaw: validated for 3 cycles
Sample handling (benchtop): validated for at least 28 hours
Sample transport: validated for 6 months at -10° to -30° C
Autosampler: validated for at least 50 hours

[redacted] (high range assay, plasma):
Long-term: validated for 702 days at -70° C
Freeze-thaw: validated for 9 cycles
Sample handling (benchtop): validated for 12 hours
Sample transport: not reported
Autosampler: validated for 71 hours

**2.6.4.5 What is the QC sample plan?**

The QC sample plans for each method are summarized below.

[redacted] (plasma):
Low QC: 2.00 ng/mL
Medium QC: 6.00 ng/mL, 250 ng/mL
High QC: 800 ng/mL

[redacted] (urine):
Low QC: 2.00 ng/mL
Medium QC: 6.00 ng/mL, 250 ng/mL
High QC: 800 ng/mL

[redacted] (low range assay, plasma):
Low QC: 6.00 ng/mL
Medium QC: 250 ng/mL
High QC: 750 ng/mL

[redacted] (high range assay, plasma):
Low QC: 60.0 ng/mL
Medium QC: 500 ng/mL
High QC: 3750 ng/mL

## 3. Appendices

### 3.1 Changes to the Label Relevant to Clinical Pharmacology

(b) (4)

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

## 3.2 Individual Study Reviews

### 3.2.1 *In Vitro* Studies

**Caco-2 Cell Permeability Studies**
03-VERT.P09R1
6VERTP2
5VERTP1R1
7VERTP1R1

Early studies (03-VERT.P09R1, 6VERTP2, 5VERTP1R1) indicated that the permeability of telaprevir was high and that telaprevir is a substrate of efflux proteins, but did not inhibit P-gp up to a concentration of 10 μM. However, these studies did not include internal standards with known intestinal permeability. The study results for these 3 studies are summarized below. These studies were confirmed by repeating the study using internal standards in 7VERTP1R1. This study is described in further detail. Study methodology, including equations and quality controls, are identical for the 4 studies, except where otherwise noted.

**7VERTP1R1**

**Objective**: Determine the bidirectional permeability of telaprevir in Caco-2 cell monolayers for classification of permeability according to BCS Guidelines.

Per the validated Absorption Systems model for classification of permeability using Caco-2 cells, the criterion for classification as high permeability is an apparent permeability coefficient ($P_{app}$) value not less than that of positive controls minoxidil and pindolol, which are absorbed by 90% in humans.[1]

**Methods:**

(b) (4)

Calculations included the following:

(b) (4)

Permeability of the test compound through a blank (cell-free) membrane was evaluated. Recovery results were only 72.6%, indicating loss of telaprevir to the membrane due to non-specific binding. Therefore, a 15-min. pre-incubation period was added to the method.

**Results:**
All QC tests met their pre-defined acceptance criteria.

The $P_{app}$ (A→B) value of telaprevir was about 4.40 x $10^{-6}$ cm/s when it was dosed alone. When it was co-dosed with the reference compounds, the value decreased slightly to 3.63 x $10^{-6}$. This value was lower than the $P_{app}$ (A→B) values of both pindolol and minoxidil (4.91 and 4.69 x $10^{-6}$, respectively). Therefore, telaprevir cannot be classified as highly permeable. The recoveries of all compounds were acceptable (105% to 110%, st. dev. <2.2). Based on Absorption Systems' historical data of the Caco-2 permeability assay, $P_{app}$ ratios greater than 3 are considered biologically significant. The ratio for telaprevir was 5.29 when dosed alone; therefore, there was significant asymmetric flux for telaprevir. The reference P-gp substrate digoxin had a $P_{app}$ ratio of 5.74 in QC testing.

**Conclusion:**
Telaprevir cannot be classified as highly permeable. Significant efflux of telaprevir was observed. Efflux transporters, such as P-gp, might be involved in mediating telaprevir permeation.

**03-VERT.P09R1**
Study 03-VERT.P09R1 was a permeability study in Caco-2 cells similar in design to 7VERTP1R1, except internal controls were not used. The results from this study included a $P_{app}$ (A→B) value of 5.7 x $10^{-6}$ for telaprevir, similar to that reported for 7VERTP1R1. The $P_{app}$ ratio was 5.9, indicating significant efflux, again in agreement with 7VERTP1R1. **The conclusions from this study were that telaprevir has high absorption and significant efflux.**

**6VERTP2**

Study 6VERTP2 evaluated the bidirectional permeability of digoxin (p-gp substrate) in the presence and absence of telaprevir using Caco-2 cells. Study design and methodology was similar to that of 7VERTP1R1, except digoxin (10 μM) was evaluated alone (control) and in combination with telaprevir (10 μM). Telaprevir was not evaluated alone. The study was conducted in 2 replicates, and the timepoints for collection were at 1 and 2 hours.

Digoxin was effluxed with a $P_{app}$ ratio of 11.6 in the control plate, indicating significant efflux. In the presence of 10 μM telaprevir the ratio decreased to 9.1, indicating no significant inhibition of digoxin efflux. **Thus, it was concluded that telaprevir is not a P-gp inhibitor, as assessed in Caco-2 cells.**

**5VERTP1R1**

The objectives of this study included the determination of telaprevir permeability in Caco-2 cells in the absence and presence of cyclosporine A (CSA) and ritonavir (RTV), two inhibitors of P-gp. The study methodology was similar to that as outlined above for 7VERTP1R1. The permeability of telaprevir was assessed in the cell-free (blank) membrane. The recovery results for the blank membrane were 84%, versus 72.6% as observed in 7VERTP1R1. These results indicate less loss of test article to non-specific binding and appropriately free diffusion. Thus, there was no pre-incubation period added to the method. Results of all acceptance criteria were found acceptable. The bidirectional permeability of telaprevir (5 μM) was assessed in the absence and presence of CSA (10 μM) or RTV (200 μM). Cell monolayers were preincubated with CSA or RTV containing buffer for 10 min. As a control, digoxin (5 μM) was also assayed. All tests were done in 4 replicates. Mean $P_{app}$ ratios were 20.5 for telaprevir alone (no CSA or RTV), versus >27 for digoxin. In the presence of CSA and RTV, the ratio for telaprevir decreased to 0.9 and 1.0, respectively. **These results indicate significant inhibition of telaprevir efflux, likely via inhibition of P-gp.**

[1]Absorption Systems Report No. 6ASLPBCSval. Revalidation of the Caco-2 System for BCS *In Vitro* Permeability Studies.

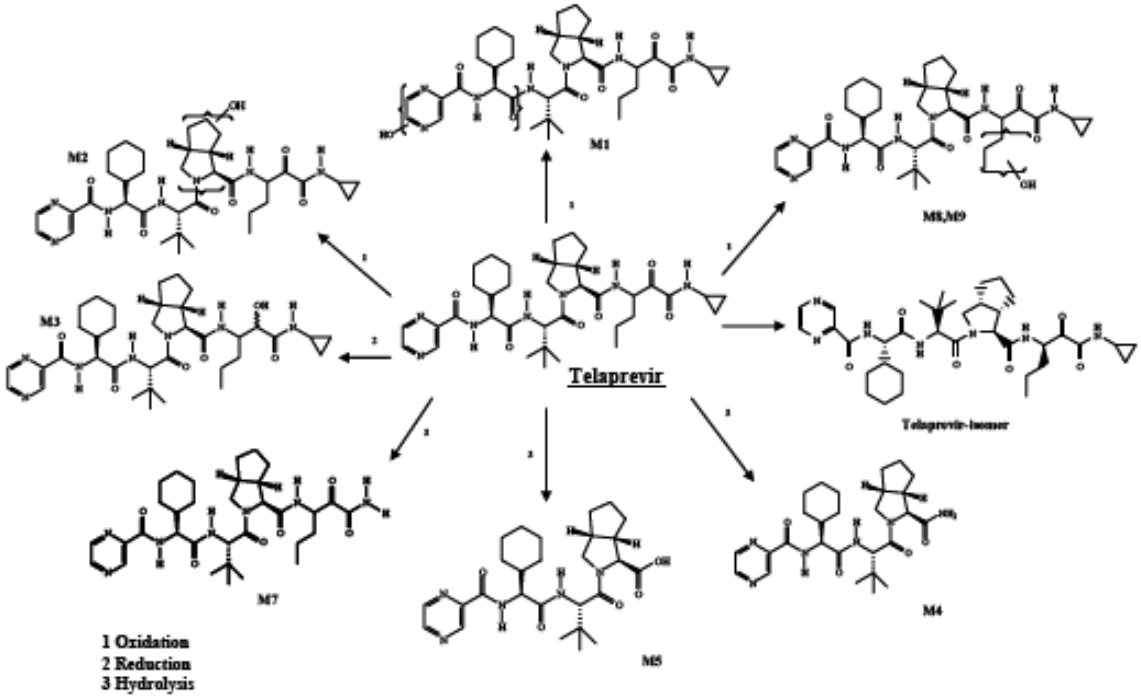
## In Vitro Metabolism Studies

| *Metabolic Profiling* | *Inhibition Studies* | *Induction Studies* |
|---|---|---|
| 6536-392 | 03-VERT-P09R1-Report 5 | 6536-307 |
| 013465 | B050860 | |
| 03-VERT.P09R1-Report 4 | 6VERTP3 | |
| VX-950-NCD-MET-001 | 6536-306 | |
| | A124 | |


**Summary**

In study 6536-392 the *in vitro* metabolism of $^{14}$C-telaprevir was studied in liver microsomal and S9 fractions of rats, dogs and humans. $^{14}$C-telaprevir was extensively metabolized in all species. In addition to the parent (telaprevir) and epimer (VRT-127394), a number of oxidative metabolites were identified, including M1 isomers, M2, M8/M9 (telaprevir-OH) and isomer, and diOH-telaprevir (Figure 1). Additional metabolites included M3 isomers (telaprevir reduction product), M4, M5, M7, and M12. M1 was the major metabolite observed in all species regardless of sub-cellular fraction (microsomal or S9) or sex. Comparison across species indicated that no metabolites were unique to humans. The results from this study are in general agreement with preliminary results from 3 preceding studies evaluating non-radiolabeled telaprevir in liver microsomal and S9 fractions from rats, dogs, monkeys and humans (studies 013465, 03-VERT.P09R1 and VX-950-NCD-MET-001).


**Figure 1 Metabolic Profile of Telaprevir from In Vitro Assessments (Liver Microsomal and S9 Fractions)**



The CYP enzymes involved in the metabolism of telaprevir were identified using human recombinant isoforms (Study 03-VERT-P09R1 – Report 5). The results of this study indicated CYP3A4 is the major isoform responsible for telaprevir metabolism. As the concentration of telaprevir increased, it was less susceptible to metabolic turnover, which correlates with the results from the CYP inhibition study. The potential for telaprevir and a 55:45 mixture of telaprevir:VRT-127394 to inhibit CYP probe substrates (CYP1A2, 2C9, 2C19 or 3A4) was assessed in 03-VERT.P09R1 – Report 1. Telaprevir and VRT-127394 were tested in a subsequent study for inhibitory effects on these same enzymes, in addition to CYP2A6, 2B6, 2C8, 2D6, and 2E1 (B050860). In a third study, VRT-127394 was tested for inhibitory effects on CYP1A2, 2C9, 2C19, 2D6 and 3A4 (6VERTP3). These studies demonstrated that CYP1A2, 2C9, and 2D6 were either weakly inhibited or not inhibited by telaprevir, VRT-127394, and the 55:45 mixture. CYP2C8 and 2C19 were weakly inhibited by telaprevir and VRT-127394 ($IC_{50}$>100μM). Telaprevir, VRT-127394, and the 55:45 mixture inhibited CYP3A4 with $IC_{50}$ values <18.9 μM. Additional studies were performed to explore the inhibitory potential of telaprevir and/or VRT-127394 towards CYP3A4/5, including potential metabolism-dependent inhibition using pooled human liver microsomes (6536-306 and A124). Studies 03-VERT-P09R1 – Report 5, B050860, and 6536-306 are reviewed in full detail below.

An additional study evaluating the *in vitro* metabolism of telaprevir in human skin microsomal and S9 fractions was conducted to determine the potential etiology of rash observed in clinical studies (Study F205). Both microsomal and S9 incubations were unable to produce formation of any oxidative or hydrolytic metabolites for telaprevir. Therefore, biotransformation of telaprevir in human skin is presumed unlikely to occur at a level relevant to the development of rash. This study is not reviewed further.

Telaprevir was also assessed for its potential inhibition of uridine diphosphate glucuronyltransferase 1A1 (UGT1A1) in a preliminary study. Incubation with human liver microsomes and bilirubin as a probe substrate were performed in the presence of telaprevir (0.045 to 100 μM). The results indicate telaprevir did not inhibit UGT1A1-catalyed glucuronidation of bilirubin ($IC_{50}$ > 100 μM). The study report for this assessment was not submitted.

The enzyme induction potential of telaprevir was assessed using isolated human hepatocytes (6536-307). At the highest concentration tested (100 μM), mean induction values were 1.4-, 0.4- and 0.1-fold for CYP1A, CYP2C and CYP3 probe substrates, respectively. The 1.4-fold increase in CYP1A was low relative to the 8- to 13-fold increase caused by the prototypical inducer omeprazole. Based on these results, it was concluded telaprevir has a low potential for inducing CYP enzymes *in vivo*, though potential mild induction of CYP1A2 may be observed. This study report is reviewed in full below.

**03-VERT-P09R1 – Report 5: CYP Reaction Phenotyping of Telaprevir Using Supersomes®**

**Objective:**

Assess CYP reaction phenotyping of telaprevir at two concentrations (2 and 20 μM)

**Methods:**

(b) (4)

[redacted]

**Results:**

Tests of the known substrates evaluated to confirm the activity of the supersomes all disappeared as expected, indicating activity of the CYP enzymes. Purity of the test article was confirmed with the Certificate of Analysis provided by the Applicant.

When assayed at 2 μM, telaprevir exposure substantially diminished in the CYP3A4 reaction (13.9% remaining), but remained constant in all other reactions. When assayed at 20 μM, telaprevir diminished again in CYP3A4, but to a lesser extent than at 2 μM (78.9%). Results were more variable for some of the reactions at the 20 μM concentration, possibly due to the test concentration approaching solubility limits.

**Conclusions:**

CYP3A4 appears to be the major CYP enzyme responsible for the metabolism of telaprevir. However, as the concentration increased from 2 to 20 μM, diminishment of telaprevir conversion by CYP3A4 was reduced, indicating saturation or inhibition of metabolism.

**B050860: Inhibitory Effects of Telaprevir and VRT-127394 on the Specific Activities of Human Cytochrome P450 Isoforms**

**Objective**:

To investigate the effects of telaprevir and its D-diastereomer VT-127394 on the metabolic activities of human CYP isoforms using human liver microsomes in vitro.

**Methods:**

(b) (4)

[redacted]

(b) (4). Stability of the test solutions was confirmed for the storage conditions.

The following metabolic activities were evaluated:

7-ethoxyresorufin O-deethylase (CYP1A2)
coumarin 7-hydroxylase (CYP2A6)
7-ethoxy-4trifluoromethylcoumarin O-deethylase (CYP2B6)
paclitaxel 6α-hydroxylase (CYP2C8)
diclofenac 4'-hydroxylase (CYP2C9)
(S)-mephenytoin 4'-hydroxylase (CYP2C19)
bufuralol 1'-hydroxylase (CYP2D6)
chlorzoxazone 6-hydroxylase (CYP2E1)
midazolam 1'-hydroxylase (CYP3A4)
testosterone 6β-hydroxylase (CYP3A4)

Each specific substrate for CYP isoforms was incubated with the microsomes in the presence or absence of telaprevir and VT-127394 and the metabolic activity of the CYP isoforms was determined by measurement of remaining enzyme activity, the inhibition ratio (%) and the concentration of test article corresponding to 50% inhibition ($IC_{50}$). The following equations were used to make calculation:

Metabolic activity (pmol/mg/min) = Concentration of metabolite (pmol/mL)/ Microsomal protein concentration (mg/mL)/ Reaction time (min)

Remaining activity (% of vehicle control) = activity in "test" or "positive control" / activity in "vehicle control" x 100%

Inhibition ratio (%) = 100 – Remaining activity

The relationship between metabolic activity value and telaprevir or VRT-127394 concentrations was analyzed using an inhibitory Emax model (WinNonlin v. 4.1) to determine $IC_{50}$ values.

A known positive inhibitor for each CYP isoform was used as a positive control. (b) (4) Final concentrations of telaprevir and VT-127394 in the reaction mixtures ranged from 0 to 100 μM. The lowest concentration was 0.1 μM.

*Reviewer Comment: The Cmax of telaprevir in plasma following a single 750 mg dose in healthy volunteers is ~2 μg/mL (~2.9 μM). The Cmax ratio of telaprevir:VRT-127394 in vivo is approximately 3:1 following a single dose. Thus, the concentration range of telaprevir and VRT-127394 evaluated in this study is appropriate for characterizing potential CYP inhibition.*

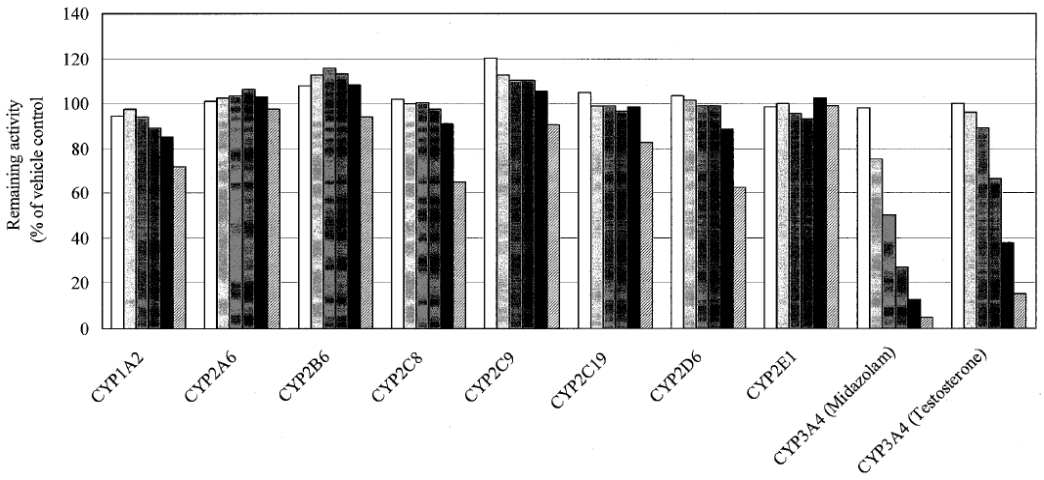
Analysis of substrates and metabolites was performed using LC/MS/MS. The influence of telaprevir, VRT-127394 and telaprevir metabolites on analysis of test substrates was assessed and determined to not influence the assay of marker metabolites in any of the CYP assays.

**Results**:

The effect of telaprevir and VRT-127394 on specific isoform activity with increasing concentration is shown below in Figures 1 and 2. Telaprevir had no inhibitory effect on CYP2A6, 2B1, 2C9 and 2E1 (inhibition ≤ 9.5%) up to a concentration of 100 µM. Telaprevir weakly inhibited CYP1A2 (28%), 2C8 (35%), 2C19 (17.1%) and 2D6 (37.5%); however, the effect was minor ($IC_{50}$ values >100 µM). The $IC_{50}$ values for telaprevir's inhibition of CYP3A4 were estimated to be 3.3 µM (midazolam) and 18.9 µM (testosterone).

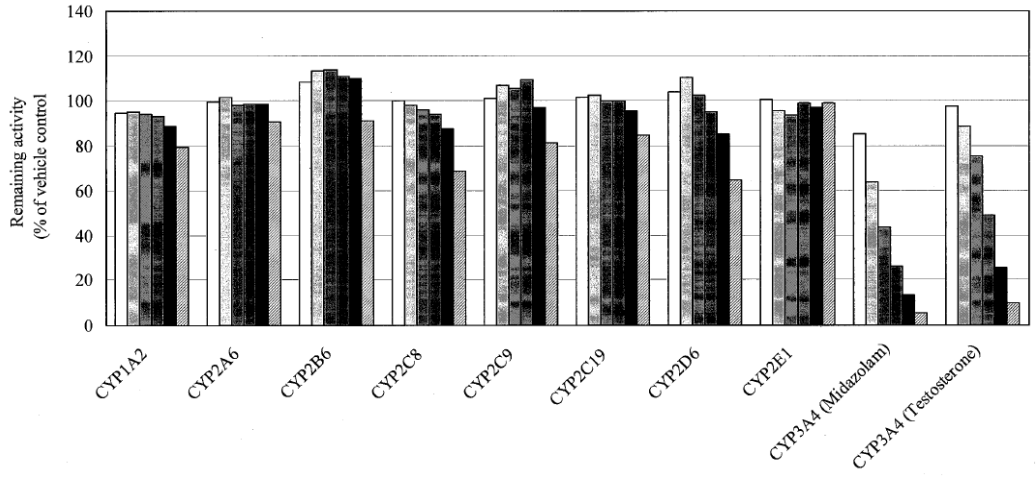
VRT-127394 had no inhibitory effect on CYP2A6, 2B1 and 2E1 (inhibition ≤ 9.5%) up to a concentration of 100 µM. At 100 µM, VRT-123794 very weakly inhibited CYP1A2 (21%), 2C8 (31%), 2C9 (19%), 2C19 (15%) and 2D6 (35%). The $IC_{50}$ values for VRT-127394 inhibition of CYP3A4 were estimated to be 2.8 µM (midazolam) and 9.9 µM (testosterone).

**Figure 1 Remaining Activities of CYP Isoforms in Human Liver Microsomes with Telaprevir**




0.1 (□), 1 (□), 3 (■), 10 (■), 30 (■), and 100 (▨) µmol/L
Remaining activity was calculated from the mean activity data of duplicate incubations.

**Figure 2 Remaining Activities of CYP Isoforms in Human Liver Microsomes with VRT-127394**




0.1 (□), 1 (□), 3 (■), 10 (■), 30 (■), and 100 (▨) µmol/L
Remaining activity was calculated from the mean activity data of duplicate incubations.

**Table 1 $IC_{50}$ values for telaprevir (MP-424) and VRT-127394 in human liver microsomes**

| CYP isoform | Metabolic reaction | $IC_{50}$ (μmol/L) | |
|---|---|---|---|
| | | MP-424 | VRT-127394 |
| CYP1A2 | 7-Ethoxyresorufin *O*-deethylation | > 100 | > 100 |
| CYP2A6 | Coumarin 7-hydroxylation | > 100 | > 100 |
| CYP2B6 | 7-Ethoxy-4-trifluoromethyl-coumarin *O*-deethylation | > 100 | > 100 |
| CYP2C8 | Paclitaxel 6α-hydroxylation | > 100 | > 100 |
| CYP2C9 | Diclofenac 4'-hydroxylation | > 100 | > 100 |
| CYP2C19 | *(S)*-Mephenytoin 4'-hydroxylation | > 100 | > 100 |
| CYP2D6 | Bufuralol 1'-hydroxylation | > 100 | > 100 |
| CYP2E1 | Chlorzoxazone 6-hydroxylation | > 100 | > 100 |
| CYP3A4 | Midazolam 1'-hydroxylation | 3.3 | 2.8 |
| CYP3A4 | Testosterone 6β-hydroxylation | 18.9 | 9.9 |

**Conclusions**:

Telaprevir and VRT-127394 had similar metabolic inhibitory profiles. Aside from very weak inhibition of a few isoenzymes ($IC_{50}$ >100 μM), telaprevir and VRT-127394 inhibited only CYP3A4, with $IC_{50}$ values of 2.8-19 μM. The Cmax of telaprevir in plasma following a single 750 mg dose in healthy volunteers is ~2 μg/mL (~2.9 μM). The Cmax ratio of telaprevir:VRT-127394 in plasma is approximately 3:1 following a single dose in humans. Based on the results of this study, telaprevir may be a potentially clinically relevant inhibitor of CYP3A4 metabolism at the clinical dose of 750 mg TID.

**6536-306: Inhibitory Potential of VX-950 (Telaprevir) Towards Human Hepatic Microsomal CYP3A4/5 Isoenzyme**

**Objective:**

To characterize the in vitro inhibitory potential of telaprevir towards specific isoenzymes of human CYPs.

**Methods**:

(b) (4)


**Results**:

*d*,*l*-VX-950 was a competitive inhibitor of both midazolam 1-hydroxylase ($IC_{50}$ = 3.82 μM, Ki = 0.77 μM) and testosterone 6β-hydroxylase ($IC_{50}$ = 7.0 μM, Ki = 6.4 μM). Likewise, both *d*-VX-950 (VRT-127394) and *l*-VX-950 (telaprevir) were competitive inhibitors, with $IC_{50}$ values of 1.7 and 3.5 μM for midazolam (Ki values 0.94 and 1.4 μM), respectively, and $IC_{50}$ values of 5.7 and 11.8 μM for testosterone (Ki values 5.2 and 18.6 μM), respectively. Telaprevir was approximately half as potent of an inhibitor as VRT-127394.

Metabolism-dependent inhibition of CYP3A4/5 was observed for all 3 test compounds. *d*-VX-950 (VRT-127394) exhibited weak inhibition (approximately 23-25% greater inhibition following the pre-incubation period vs. no pre-incubation), while *l*-VX-950 (telaprevir) exhibited stronger metabolism-dependent inhibition (approx. 59-66% greater inhibition following pre-incubation). For the mixture *d*,*l*-VX-950, there was 46-50% greater inhibition following pre-incubation.

**Table 1 In Vitro Inhibition of CYP3A4/5 in HLM by *d*-VX-950 (VRT-127394), *l*-VX-950 (telaprevir), and *d*,*l*-VX-950**

| Compound | Substrate | $IC_{50}$ (μM) | $K_i$ (μM) | Type of Inhibition |
|---|---|---|---|---|
| *d*,*l*-VX-950 | Midazolam | 3.82 | 0.77 | Competitive |
| | Testosterone | 7.04 | 6.40 | Competitive |
| *d*-VX-950 | Midazolam | 1.74 | 0.94 | Competitive |
| | Testosterone | 5.65 | 5.18 | Competitive |
| *l*-VX-950 | Midazolam | 3.53 | 1.43 | Competitive |
| | Testosterone | 11.8 | 18.6 | Competitive |

**Table 2 Mean Isoenzyme Activity as Measured in HLM Pre-Incubated for 0 and 15 min. with *d*-VX-950 (VRT-127394), *l*-VX-950 (telaprevir), and *d,l*-VX-950**

| | | Test Article Concentration | Pre-Incubation Time | | | |
|---|---|---|---|---|---|---|
| | | | 0 Minutes | | 15 Minutes | |
| Compound | Substrate | (μM) | Activity | %SC | Activity | %SC |
| *d,l*-VX-950 | Midazolam | 0 | 784 | 100 | 1130 | 100 |
| | | 1 | 507 | 64.6 | 377 | 33.4 |
| | Testosterone | 0 | 1510 | 100 | 1340 | 100 |
| | | 3 | 1170 | 77.3 | 556 | 41.5 |
| *d*-VX-950 | Midazolam | 0 | 784 | 100 | 1130 | 100 |
| | | 0.1 | 791 | 101 | 879 | 77.8 |
| | Testosterone | 0 | 1510 | 100 | 1340 | 100 |
| | | 1 | 1250 | 83.0 | 833 | 62.2 |
| *l*-VX-950 | Midazolam | 0 | 784 | 100 | 1130 | 100 |
| | | 1 | 631 | 80.4 | 369 | 32.7 |
| | Testosterone | 0 | 1510 | 100 | 1340 | 100 |
| | | 3 | 1310 | 86.6 | 390 | 29.1 |

Note Activity expressed as pmol/min/mg protein and as a percentage of the solvent control (%SC).

**Conclusions**:

In HLM, telaprevir and VRT-127394 were competitive inhibitor of CYP3A4/5 as assessed using midazolam and testosterone as substrates. Telaprevir was approximately half as potent an inhibitor as VRT-127394. There is evidence of metabolism-dependent inhibition of CYP3A4/5, particularly for telaprevir.

**6536-307: Evaluation of CYP450 Induction using Primary Cultures of Human Hepatocytes**

**Objective**:

Measure the extent of induction of CYP1A, CYP2C and CYP3A following exposure of hepatocytes to VX-950 (telaprevir) as compared to prototypical inducers.

**Methods**:

(b) (4)


**Results**:

Two of the 3 donors had a drug history; one each had a history of diazepam and simvastatin use. The investigators did not consider either of the drug histories to make the cells unsuitable for use in the study. Cell viability was determined to be >80% upon receipt from the supplier.

*Reviewer Comments: Details regarding the diazepam and simvastatin treatment histories were not provided. However, neither are documented inhibitors or inducers of CYP. There was no information regarding genetic polymorphisms of metabolizing enzymes for the donors, nor was a smoking history documented (potential 1A induction).*

*CYP1A*

Omeprazole induced CYP1A activity by 8- to 13.5-fold over the controls among the 3 donors, demonstrating responsiveness of induction in all donor hepatocytes. The 3 test article had a negligible effect on EROD activity in Donor 1. However, in Donor 2, *d*,*l*-VX-950 and *d* -VX-950 (VRT-127394) increased activity 1.9-fold at 100 μM, and *l*-VX-950 (telaprevir) increased activity 1.2-fold at all concentrations. Activity was further increased in Donor 3, with a 1.6-fold increase with 1 μM *d*,*l*-VX-950, a 1.9-fold increase with 1μM *l*-VX-950 (telaprevir) and a 1.6-fold increase with 1 μM *d*-VX-950 (VRT-127394). These data suggest telaprevir may be a mild inducer of CYP1A2 at clinically relevant concentrations. However, there is no evidence that the inductive effect of telaprevir is stereoselective.

*CYP2C*

Rifampin induced CYP2C19 activity, as assessed by hydroxylation of *S*-mephenytoin, by 2.4- and 5.1-fold in Donors 1 and 3, respectively. There was no quantifiable *S*-mephenytoin activity detected in the hepatocytes of Donor 2, suggesting this donor may be a CYP2C19 genotypic poor metabolizer. All 3 test articles, *d*,*l*-VX-950, *d*-VX-950 and *l*-VX-950, caused a reduction in CYP2C19 activity. Activity decreased to 0.3- to 0.6-fold that of the control across all concentrations in Donor 1, and it decreased to 0.2- to 0.9-fold in Donor 2. Although there was a very slight increase in inhibition with increasing concentration for all 3 test articles, inhibition was largely independent of concentration.

*Reviewer Comments: Previous in vitro studies assessing potential inhibition of CYP (reviewed above), indicated 2C19 was weakly inhibited by telaprevir and VRT-127394. However, $IC_{50}$ values were >100μM in these studies. The results of this study indicate more potent inhibition by telaprevir and VRT-127394. At 1 μM, telaprevir (l-VX-950) and VRT-127394 (d-VX-950) decreased CYP2C19 activity to 0.3- to 0.6-fold and 0.4- to 0.6-fold that of controls, respectively, in the two responsive donors. This compares to a plasma telaprevir Cmax ~2.9 μM at the therapeutic dose, and a Cmax ratio of ~3:1 with VRT-127394.*

*As the investigators discuss in the report, loss of enzyme activity in hepatocytes may be a sign of enzyme inhibition or cytotoxicity. As there was no apparent effect on CYP1A-mediated activity, it is unlikely the VRX-950 test articles were cytotoxic.*

*CYP3A*

Rifampin was demonstrated to effectively induce CYP3A-mediated activity in hepatocytes, with 3.8- to 4.1-fold increases in activity over control in the 3 donors. The 3 test articles of VX-950 produced concentration-dependent decreases in CYP3A-activity, up to 0.1-fold that of controls. There was no apparent stereoselective effect, with all 3 test articles effecting activity to a similar extent.

**Conclusion**:

The results of the study indicate telaprevir and VRT-127394 are unlikely to be inducers of CYP2C19 or CYP3A-mediated activity. However, they may be mild inducers of CYP1A activity, particularly at higher concentrations, although the clinical relevance of this observation is unclear given the ≥ 8-fold increase in enzyme activity caused by omepazole. Concentration-dependent inhibition of CYP2C19 and CYP3A was observed in vitro, including at concentrations consistent with those observed in the plasma of subjects receiving a therapeutic dose of telaprevir.

### 3.2.2 General Pharmacokinetics

**Individual Study Review—VX06-950-005**

Title (Study VX06-950-005)

"A Phase 1 Mass Balance Study to Investigate the Absorption, Metabolism, and Excretion of $^{14}$C-VX-950 Following Oral Administration to Healthy Male Subjects"

Objectives

- To characterize the pharmacokinetics, route(s) and rate of elimination, total recovery of $^{14}$C-VX-950, and total radioactivity after a single, oral dose of $^{14}$C-VX-950 in healthy male subjects.
- To isolate and identify, if possible, the major metabolites of VX-950 (telaprevir, TVR) in healthy male subjects following the administration of a single oral dose of $^{14}$C-VX-950.
- To assess the safety of the VX-950 administered dose in healthy male subjects.

Study Dates and Location(s):
Study initiation: June 13, 2006 (first screening)
Study completion: July 7, 2007 (last follow-up)
Clinical Site: PRA International, Stationsweg 163, 9471 GP Zuidlaren, The Netherlands

Study Design

This was an open label, non-randomized, mass balance study to investigate the PK, route(s) and rate of elimination, total recovery of $^{14}$C-VX-950 and total radioactivity after a single, oral dose of 14C-VX-950 in healthy male subjects. A total of 6 healthy male subjects received a single oral dose of $^{14}$C-VX-950, formulated as 750 mg/2.84 MBq blended powder mixture of $^{14}$C-VX-950 and unlabeled VX-950 in a 30 mL suspension. Each subject received their oral dose within 5 to 15 minutes of a standard breakfast. (The regular breakfast (non-high fat) consisted of 632 kcal and was comprised of 16.5% protein, 34.3% fat and 49.2% carbohydrates.)

Study Dose Used and Dose Rationale

A single 750-mg dose of TVR was used for this study. Previous studies using doses ranging from 25 to 1250 mg have indicated that 750 mg q8h resulted in the highest Ctrough of VX-950 and the greatest median decrease in HCV RNA levels. In addition, a single oral dose of 750 mg was expected to provide sufficient exposure to adequately characterize the pharmacokinetics of VX-950. A dose of 750 mg q8h was evaluated in the phase 3 studies.

Formulation(s) Used

An oral suspension was made from 750 mg of VX-950 powder along with 2.84 MBq $^{14}$C-labeled VX-950 and the following vehicle: 1% HPMC 60SH50, 0.35% vitamin E TPGS, and 0.01% simethicone in water. This suspension had a total volume of 30 mL.

*Key Inclusion Criteria:*
-Male subjects between 18 and 60 years of age (inclusive)

-Subjects who agreed to use 2 methods of contraception, including 1 barrier method (e.g.; a condom and spermicide), during and for 90 days following the last dose of study drug
-Subjects who had a body mass index (BMI) from 19.0 to 30.0 $kg/m^2$ (inclusive) at screening
-Subjects who had hematology and clinical chemistry values within normal range or showed no clinically significant deviations from normal range during the screening period (as judged by the investigator)
-Subjects who had physical examination results, including vital signs and screening electrocardiogram (ECG), that were without clinically relevant deviations (as judged by the investigator)

*Key Exclusion Criteria:*
-Subjects who had a history of any illness that, in the opinion of the investigator or the subject's general practitioner, might confound the results of the study or pose an additional risk in administering study drug(s) to the subject
-Regular treatment with prescription medications. Subjects were to have ended any short courses of prescription medications at least 14 days prior to the screening visit. Prescription medications were not to be administered during the study. (Potential subjects were not to stop any chronic, prescribed medication being taken at the direction of a physician, without obtaining agreement from that physician)
-Regular treatment with over-the-counter medications. Subjects were to end over-the-counter medication on the date of the screening visit but no less than 2 days prior to administration of study drug. Occasional use of acetaminophen or ibuprofen was allowed during the study for the treatment of pain (under supervision of the investigator)
-Subjects who consumed herbal medications or dietary medications, dietary supplements (e.g., St. John's Wort, ginkgo biloba, garlic supplements), vitamins, and grapefruit or grapefruit juice within 14 days before administration of study drug (Day 1). Subjects were not to consume these items until the last PK sample following the last dose of study drug
-Subjects who consumed more than 2 units of alcoholic beverages per day or more than 14 units per week. Subjects were not to consume any alcohol 72 hours before or after study drug administration through the follow-up visit
-Subjects who consumed an average of more than 8 cups of coffee or other caffeinated beverage, or 7 cans of cola per day. Additionally, subjects were not allowed any caffeinated beverages 72 hrs prior to dosing until the collection of the last PK samples at each dosing occasion
-Subjects who had a history of drug or alcohol abuse or addiction within 2 years prior to dosing, or who tested positive for alcohol or drugs of abuse such as cannabis, cocaine, amphetamines or opiates during the screening period
-Subjects who had participated in a clinical study involving administration of either an investigational or a marketed drug within 2 months or 5 half lives (whichever is longer) prior to the screening visit
-Subjects who tested positive for any of the following infectious disease tests: hepatitis B antigen (HBsAg), hepatitis C virus antibody (HCVAb), human immunodeficiency virus 1 antibody (HIV1Ab), or human immunodeficiency virus 2 antibody (HIV2Ab)
-Subjects who had a female partner who was pregnant, nursing, or planning to become pregnant during the study or within 90 days of the VX-950 dose

PK Analysis

Blood samples for VX-950 PK and radiokinetic analyses were collected on day 1 at the following times: pre-dose, 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours post-dose, and every 24 hours thereafter until discharge. PK assessments on VRT-127394 were conducted with the blood samples collected at: pre-dose, 5, 12, 24, and 48 hours post-dose. Urine samples for radiokinetic and TVR and VRT-127394 PK assessments were collected at: pre-dose, and 0-4, 4-8, 8-12, 12-24 hours post-dose, and every 24-hr interval thereafter until discharge. Feces samples for radiokinetic and VRT-127394 PK assessments were collected at: pre-dose and in 24-hr intervals following dosing thereafter until discharge. Expired air samples for radiokinetics were collected at: 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours post-dose, and every 24 hours thereafter until at least 2 consecutive breath samples were below the limit of quantitation of radioactivity. The average of 2 measurements was used at each timepoint.

Bioanalytical Results

Metabolite profiling for this study was conducted at (b) (4) . Plasma, urine, and feces samples were analyzed by HPLC, LC/MS, and LC/MS/MS. The bioanalytical assays for assessment of radioactivity and plasma, urine, and fecal concentrations of VX-950 and VRT-127394 were performed at (b) (4) .

*Unchanged VX-950 and VRT-127394 in Plasma*

All samples were received between June 26, 2006 and July 4, 2006 and were analyzed between July 19, 2006 and July 20, 2006. The samples were stored at -70°C. The maximum sample storage time until analysis did not exceed the maximum time during which long-term frozen stability was validated (6 months).

The calibration standard concentrations for both TVR and VRT-127394 were 2.0, 4.0, 10.0, 50.0, 200.0, 500, 800, and 1000 ng/mL. The mean accuracy and precision estimates at each standard concentration are presented in Tables 1 and 2 below. All mean accuracy and precision (%CV) values were within the acceptable range (≤20% from nominal at the LLOQ concentration and ≤15% from nominal at all other concentrations). Quality control concentrations were 6.0, 250, and 800 ng/mL. The mean accuracy ranged from 91.2 to 108.2% for TVR and 100.0 to 104.1% for VRT-127394. The mean precision ranged from 2.6 to 12.1% for TVR and 6.0 to 14.1% for VRT-127394.

**Table 1 Mean Calibration Standard Concentrations and Statistics for TVR**

| Nominal Concentrations (ng/mL) | 2.00 | 4.00 | 10.0 | 50.0 | 200 | 500 | 800 | 1000 |
|---|---|---|---|---|---|---|---|---|
| Run ID | Back-Calculated Concentrations (ng/mL) | | | | | | | |
| AQ08-001 | 2.11 | 4.39 | 9.44 | 46.2 | 217 | 538 | 770 | 1013 |
| | 1.80 | 4.24 | 9.26 | 45.5 | 198 | 475 | 1557 [1)] | 1109 |
| AQ08-002 | 2.09 | 4.15 | 9.13 | 47.8 | 200 | 531 | 837 | 1097 |
| | 1.93 | 4.11 | 8.97 | 46.4 | 195 | 509 | 788 | 1049 |
| Mean (ng/mL) | 1.98 | 4.22 | 9.20 | 46.5 | 202 | 513 | 798 | 1067 |
| SD (ng/mL) | 0.1 | 0.1 | 0.2 | 1.0 | 9.8 | 28.3 | 34.9 | 44.5 |
| CV (%) | 7.3 | 2.9 | 2.2 | 2.1 | 4.8 | 5.5 | 4.4 | 4.2 |
| Accuracy (%) | 99.0 | 105.6 | 92.0 | 93.0 | 101.2 | 102.7 | 99.8 | 106.7 |
| n | 4 | 4 | 4 | 4 | 4 | 4 | 3 | 4 |

[1)] Rejected calibration standard: result outside acceptance criteria [±15% from nominal concentration], not included in statistical calculations.

**Table 2 Mean Calibration Standard Concentrations and Statistics for VRT-127394**

| Nominal Concentrations (ng/mL) | 2.00 | 4.00 | 10.0 | 50.0 | 200 | 500 | 800 | 1000 |
|---|---|---|---|---|---|---|---|---|
| Run ID | Back-Calculated Concentrations (ng/mL) | | | | | | | |
| AQ08-001 | 2.02 | 4.78 [1)] | 10.0 | 44.8 | 221 | 558 | 733 | 1020 |
| | 1.94 | 4.17 | 10.2 | 49.2 | 188 | 489 | 1770 [1)] | 1169 [1)] |
| AQ08-002 | 1.96 | 4.38 | 10.2 | 49.5 | 188 | 492 | 970 [1)] | 1096 |
| | 1.93 | 4.10 | 9.63 | 46.8 | 192 | 501 | 822 | 1018 |
| Mean (ng/mL) | 1.96 | 4.22 | 10.0 | 47.6 | 197 | 510 | 778 | 1045 |
| SD (ng/mL) | 0.0 | 0.1 | 0.3 | 2.2 | 16.0 | 32.2 | 62.7 | 44.5 |
| CV (%) | 1.9 | 3.4 | 2.7 | 4.7 | 8.1 | 6.3 | 8.1 | 4.3 |
| Accuracy (%) | 98.1 | 105.4 | 100.1 | 95.2 | 98.5 | 102.0 | 97.2 | 104.5 |
| n | 4 | 3 | 4 | 4 | 4 | 4 | 2 | 3 |

[1)] Rejected calibration standard: result outside acceptance criteria [±15% from nominal concentration], not included in statistical calculations.

*Unchanged VX-950 and VRT-127394 in Urine*

All samples were received between June 27, 2006 and June 30, 2006 and were analyzed between July 14, 2006 and July 21, 2006. The samples were stored at -70°C. The maximum sample storage until analysis was 24 days, which is within the validated long-term frozen stability duration of 370 days.

The calibration standard concentrations for both TVR and VRT-127394 were 2.0, 4.0, 10.0, 50.0, 200.0, 500, 800, and 1000 ng/mL. The mean accuracy and precision estimates at each standard concentration are presented in Tables 3and 4 below. All mean accuracy and precision (%CV) values were within the acceptable range (≤20% from nominal at the LLOQ concentration and ≤15% from nominal at all other concentrations). Quality control concentrations were 6.0, 250, and 800 ng/mL. The mean accuracy ranged from 94.9to 99.9% for TVR and 99.6 to 107.9% for VRT-127394. The mean precision ranged from 2.0 to 2.8% for TVR and 1.6 to 3.3% for VRT-127394.

**Table 3 Mean Calibration Standard Concentrations and Statistics for TVR**

| Nominal Concentrations (ng/mL) | 2.00 | 4.00 | 10.0 | 50.0 | 200 | 500 | 800 | 1000 |
|---|---|---|---|---|---|---|---|---|
| Run ID | Back-Calculated Concentrations (ng/mL) | | | | | | | |
| AQ08-001 | 2.01 | 4.16 | 9.38 | 46.9 | 203 | 499 | 822 | 975 |
| | 1.95 | 4.16 | 9.66 | 49.5 | 191 | 514 | 841 | 1058 |
| AQ08-002 | 2.07 | 3.87 | 9.99 | 47.8 | 201 | 534 | 833 | 1095 |
| | 1.98 | 4.00 | 9.68 | 48.7 | 203 | 478 | 775 | 959 |
| Mean (ng/mL) | 2.00 | 4.05 | 9.68 | 48.2 | 200 | 506 | 818 | 1022 |
| SD (ng/mL) | 0.1 | 0.1 | 0.3 | 1.1 | 5.7 | 23.8 | 29.6 | 65.4 |
| CV (%) | 2.6 | 3.4 | 2.6 | 2.3 | 2.8 | 4.7 | 3.6 | 6.4 |
| Accuracy (%) | 100.2 | 101.2 | 96.8 | 96.4 | 99.8 | 101.3 | 102.2 | 102.2 |
| n | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

**Table 4 Mean Calibration Standard Concentrations and Statistics for VRT-127394**

| Nominal Concentrations (ng/mL) | 2.00 | 4.00 | 10.0 | 50.0 | 200 | 500 | 800 | 1000 |
|---|---|---|---|---|---|---|---|---|
| Run ID | Back-Calculated Concentrations (ng/mL) | | | | | | | |
| AQ08-001 | 2.06 | 3.62 | 8.80 | 47.1 | 193 | 474 | 778 | 998 |
| | 2.00 | 4.34 | 10.0 | 53.5 | 195 | 518 | 865 | 1109 |
| AQ08-004 | 1.99 | 4.13 | 9.13 | 46.4 | 196 | 534 | 865 | 1026 |
| | 2.04 | 3.94 | 10.0 | 48.3 | 190 | 505 | 834 | 1003 |
| Mean (ng/mL) | 2.02 | 4.01 | 9.50 | 48.8 | 194 | 508 | 836 | 1034 |
| SD (ng/mL) | 0.0 | 0.3 | 0.6 | 3.2 | 2.4 | 25.7 | 40.9 | 51.4 |
| CV (%) | 1.5 | 7.7 | 6.7 | 6.6 | 1.2 | 5.1 | 4.9 | 5.0 |
| Accuracy (%) | 101.0 | 100.2 | 95.0 | 97.7 | 96.8 | 101.5 | 104.4 | 103.4 |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

*$^{14}$C-Radioactivity in Plasma, Whole Blood, Urine, Expired Air, and Feces*

All samples were received between June 26, 2006 and July 13, 2006 and were analyzed between July 7, 2006 and July 24, 2006. All samples (with the exception of expired air, which was stored at 4$^{o}$ C) were stored at -70° C and radioactivity was analyzed using a validated liquid scintillation count method. All quick count samples were analyzed on the day of receipt of sample so there was no appreciable storage time. Following analysis, samples were stored at -70° C.

The following are the quality control mean accuracy and precision ranges for each matrix:

Plasma QC (concentrations: 75, 1000, 20000 dpm.mL$^{-1}$):
- Accuracy: 104.8 to 105.8%
- Precision: 0.8 to 7.1%

Whole blood QC (concentrations: 75, 750, 5000 dpm.mL$^{-1}$):
- Accuracy: 101.6 to 106%
- Precision: 0.3 to 7.4%

Urine QC (concentrations: 50, 5000, 40000 dpm.mL$^{-1}$):
- Accuracy: 103.7 to 118.5% (118.5% was at the LLOQ level)
- Precision: 0.2 to 6.7%

Expired air QC for dpm <1000 (concentrations: 75, 500, 900 dpm):
- Accuracy: 99.6 to 109.9%
- Precision: 1 to 4.8%

Expired air QC for dpm >1000 (concentrations: 500, 900, 5000 dpm):
- Accuracy: 99.6 to 104.5%
- Precision: 0 to 4.9%

Feces QC using LLCM-low level counting mode (concentrations: 100, 6400, 128000 dpm.g$^{-1}$):
- Accuracy: 91.6 to 98.8%
- Precision: 0.5 to 10.6%

Feces QC using NCM-normal counting mode (concentrations: 128000, 400000, 800000 dpm.g$^{-1}$):
- Accuracy: 97.4 to 98.2%
- Precision: 0.9 to 2.8%

*Reviewer's Comments:*
*-The bioanalytical results are acceptable.*

Results

A total of 9 subjects were approved for enrollment; however, only 6 subjects initiated dosing and completed the study. The demographics of these 6 subjects are listed below.

*Demographics*

| Parameter | | N = 6 |
|---|---|---|
| Age (yr) | mean (SD) | 32.5 (18.4) |
| | median | 22.5 |
| | range: min - max | 19 - 58 |
| Weight (kg) | mean (SD) | 74 (6.9) |
| | median | 74.7 |
| | range: min - max | 63.5 - 84.6 |
| Height (cm) | mean (SD) | 182 (6.6) |
| | median | 180.5 |
| | range: min - max | 175 - 191 |
| BMI ($kg/m^2$) | mean (SD) | 22.3 (1.9) |
| | median | 22.3 |
| | range: min - max | 20.3 - 24.5 |

*Safety*

Overall a total of 3 adverse events were reported by 2 subjects. The 3 treatment-emergent adverse events were diarrhea, headache and catheter site pain, all of which were mild in intensity, transient in nature and resolved without sequelae. None of the treatment-emergent AEs were considered by the Medical Investigator to be related to the study drug. There were no deaths or other SAEs during the study, and no subjects discontinued from the study because of an adverse event.

*Pharmacokinetics*

Following oral administration, $^{14}$C-VX-950 was metabolized extensively. The mean ratios of VX-950 and VRT-127394 to total radioactivity AUC were 0.035 and 0.014, respectively, indicating a small fraction of detectable plasma radioactivity can be attributed to VX-950 and VRT-127394. $^{14}$C-VX-950 and $^{14}$C-VRT-127394 were the main radioactive components detected in the 5-hour plasma sample. Major hydrolysis metabolites, M12 isomers, were detected in the 12- and 24-hour plasma samples but not in the 48 hour sample. Minor hydrolysis/oxidation metabolites M3, M4, and M8/M9 isomers were also detected in plasma at all time points. There was no quantitative determination for plasma metabolites due to the low levels of radioactivity in the samples. The mean ratio of whole blood to plasma radioactivity was 0.202 (%CV 114%), indicating limited partitioning to blood cells.

In urine, numerous metabolites were detected along with $^{14}$C-VX-950 and $^{14}$C-VRT-127394, which accounted for 0.11% and 0.06% of the administered dose, respectively. In feces, unchanged $^{14}$C-VX-950 accounted for 31.8% of the total administered dose, and $^{14}$C-VRT-127394 accounted for 18.7% of the total administered dose, indicating a high unabsorbed fraction of $^{14}$C-VX-950. The major fecal metabolites (isomers of M4, M6, M11, and M12) were products of hydrolysis of VX-950 at different sites of the molecule (see Table 5 below).

**Figure 1 Median Plasma Concentration-Time Profile of Radioactivity, VX-950 and VRT-127394**

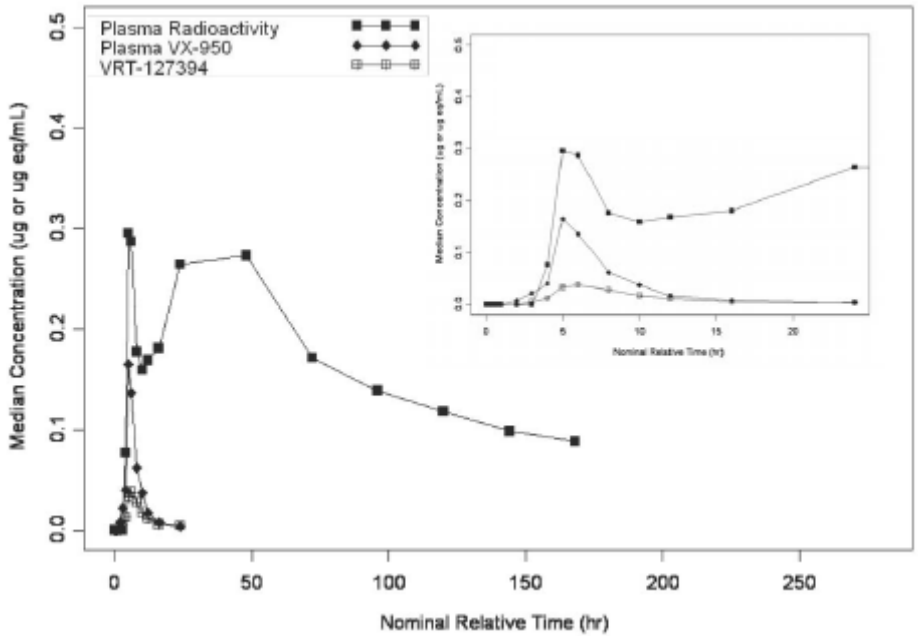



**Table 5 Unchanged $^{14}$C-VX-950 and Metabolites Detected in Human Plasma and Excreta Samples Expressed as Percent of Total Administered Radioactivity**

| | Percent of Administered Dose | | | |
|---|---|---|---|---|
| | Matrix | | | |
| Compound | Feces | Urine | Plasma[a] | Total |
| M4-diOH isomers | ND | 0.15 | ND | 0.15 |
| M4-OH | ND | 0.01 | ND | 0.01 |
| M5-OH | ND | 0.01 | ND | 0.01 |
| M11 isomers | 3.88 | ND | ND | 3.88 |
| VX-950-diOH isomers | 0.02 | 0.01 | ND | 0.03 |
| M12 isomers | 6.85 | 0.04 | b | 6.89 |
| M4 isomers | 3.36 | 0.10 | b | 3.46 |
| M8/M9 isomers | ND | 0.01 | b | 0.01 |
| M3 isomers | 1.13 | 0.01 | b | 1.14 |
| M6 isomers | 0.69 | ND | ND | 0.69 |
| VX-950 | 31.8 | 0.11 | b | 31.9 |
| VRT-127394 (VX-950 isomer) | 18.7 | 0.06 | b | 18.8 |
| Unknowns | 5.12 | 0.42 | ND | 5.54 |
| Total | 71.6 | 0.94 | NA | 72.5 |

NA Not applicable.
ND Not detected.
[a] The metabolite profile of pooled plasma is provided in the (b) (4) (Appendix to full study report)
[b] Detected but not quantified

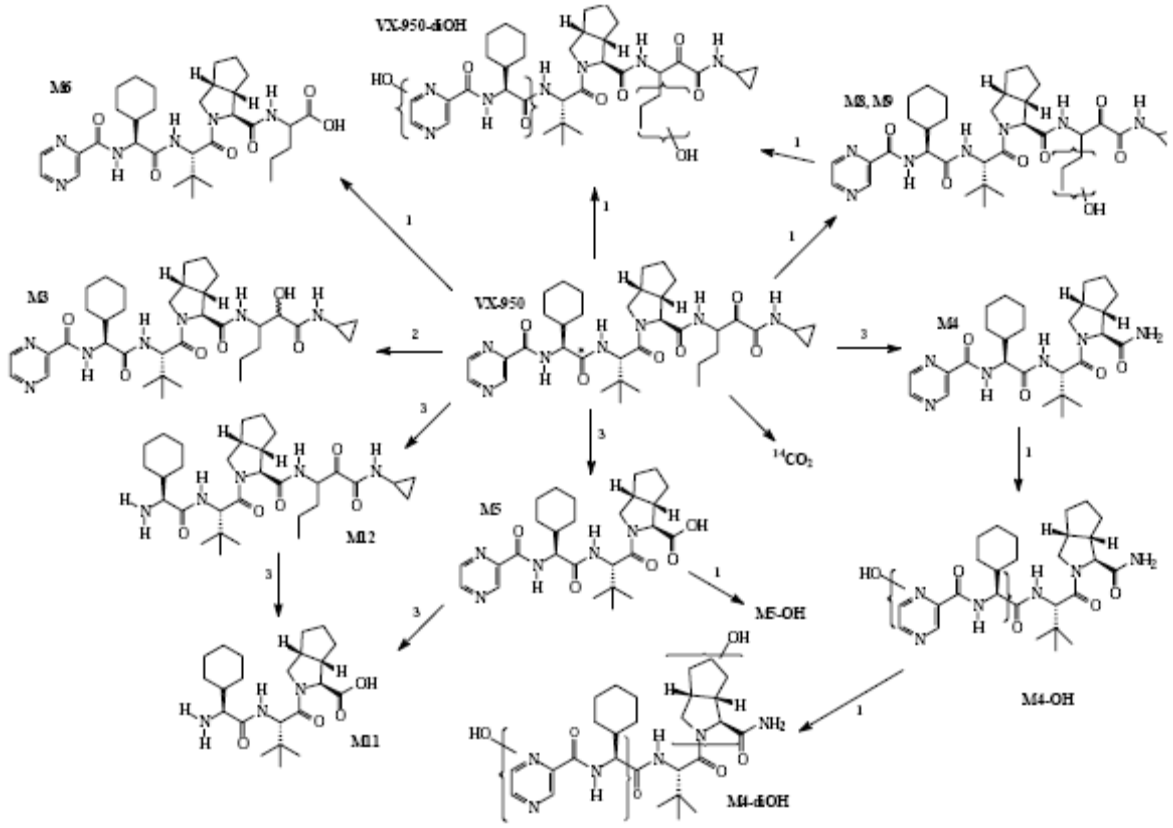
The $AUC_{inf}$ for VX-950 and VRT-127394 demonstrated high inter-subject variability, with a mean of 0.86 µg*hr/mL for VX-950 and 0.36 µg*hr/mL for VRT-127394. The apparent elimination half-lives for VX-950 and VRT-127394 were similar, with a mean of 4.65 hours for VX-950 and 5.07 hours for VRT-127394. The apparent elimination half-life of total radioactivity

was approximately 10-fold higher than that for VX-950. Approximately 0.13% of the administered VX-950 dose was recovered in urine as parent drug and 0.05% was recovered as VRT-127394.

Quantification of $^{14}C$-radioactivity in urine, feces, and expired air provided calculations of the cumulative amount of radioactivity excreted. Approximately 82% (mean) of the radioactive dose was excreted in feces, 8% was in expired air and 1% was in urine. Over 90% of the administered radioactivity was recovered within 96 hours post-dose. Ninety-one percent of the administered dose was recovered 264 hours after dosing; therefore, recovery was considered essentially complete.

*Reviewer's Comments:*
*-AUC exposure to VX-950 is considerably lower in this study (8-10-fold) than observed in previous studies. The Applicant attributed the difference to differences in bioavailability between the tablet formulation (used in previous studies) and the powder for suspension formulation used in this study.*

The following metabolic pathway for VX-950 is proposed based on the metabolic profiling of VX-950 in plasma, urine and feces:




Conclusions

Over 90% of the administered radioactivity was recovered in urine, feces, and expired air in this study, indicating that the mass balance of VX-950 was achieved. Approximately 82% of the administered radioactive dose was recovered in the feces, 8% in expired air and approximately 1% in urine. In addition, radiochromatographic profiling of plasma, feces and

urine samples showed the presence of 10 metabolites. Although $^{14}$C-VX-950 and $^{14}$C-VRT-127394 were the main radioactive components present in plasma samples, plasma metabolites included the M3, M4, M8/M9, and M12 isomers. However, these metabolite levels were too low to be quantified in plasma. Overall, VX-950 and VRT-127394 only contributed a small fraction to total detectable plasma radioactivity. A large portion of the radioactivity recovered in feces is likely attributable to unabsorbed drug, with unchanged $^{14}$C-VX-950 and $^{14}$C-VRT-127394 accounting for 31.8% and 18.7% of the total administered dose. In addition, VX-950 exposure was approximately 8-10-fold lower than that previously observed with a tablet formulation, further indicating poor bioavailability of the suspension in the current study.

**Individual Study Review—VX06-950-010**

Title (Study VX06-950-010)

"An Open-Label Phase 1 Study to Evaluate the Bioequivalence of 2 Oral Formulations of Telaprevir When Administered as a Single 750-mg Dose to Healthy Subjects"

Objectives

- To evaluate the bioequivalence of 2 oral formulations of telaprevir when administered as a single 750-mg dose to healthy subjects in the fed state
- To evaluate the bioequivalence of 2 oral formulations of telaprevir when administered as a single 750-mg dose to healthy subjects in the fasted state
- To assess the safety and tolerability of a single dose of telaprevir when administered to healthy subjects in the fed state
- To assess the safety and tolerability of a single dose of telaprevir when administered to healthy subjects in the fasted state

Study Dates and Location(s):
Study initiation: April 18, 2007 (first subject enrolled)
Study completion: July 10, 2007 (last subject completed)
Clinical Site: Charles River Clinical Services Northwest, Inc., Tacoma, Washington

Study Design

This study was a Phase 1, randomized, open-label, single-dose, crossover study of 2 oral tablet formulations of TVR: Formulation A (250-mg tablet) and Formulation B (375-mg tablet). A 750-mg dose of TVR was used for each dosing occasion. This study consisted of 2 arms: arm 1, administration of TVR in the fed state, and arm 2, administration of TVR in the fasted state. Each arm had 2 dosing sequences, with 2 or 4 dosing occasions (see Table 1 below). A total of 118 subjects was planned: 26 for arm 1 and 92 for arm 2. A total of 115 subjects (26 subjects for arm 1 and 89 subjects for arm 2) was enrolled and randomized. The Applicant states that the standard 2 x 2 crossover design was used for arm 1 because the intra-subject variability of TVR exposure in the fed state was less than 30% in previous studies. A 2-sequence, 4-period replicate crossover design was used for arm 2, due to the high variability of TVR exposure observed in the fasted state in previous studies.

**Table 1 Study Design**

| **Arm 1 (Fed State)** | | | | | |
|---|---|---|---|---|---|
| **Sequence** | **N** | **Day 1** | **Day 8** | | |
| 1-1 | 13 | Formulation A | Formulation B | | |
| 1-2 | 13 | Formulation B | Formulation A | | |
| **Arm 2 (Fasted State)** | | | | | |
| **Sequence** | **N** | **Day 1** | **Day 8** | **Day 15** | **Day 22** |
| 2-1 | 44 | Formulation A | Formulation B | Formulation A | Formulation B |
| 2-2 | 48 | Formulation B | Formulation A | Formulation B | Formulation A |

N = number of subjects

Study Dose Used and Dose Rationale

The dose of TVR in this study was 750 mg. This dose was selected (at the time) because

it was the dose being used in phase 2 efficacy/safety studies in HCV-infected patients (studies VX05-950-104, VX05-950-104EU, and VX06-950-106).

Formulation(s) Used

Two formulations of TVR were tested in this study. The 250-mg tablet (formulation A) and the 375-mg tablet (formulation B). The 250-mg tablet was used in early phase 1 and phase 2 studies while the 375-mg tablet was used in phase 3. The components and composition for both tablets is listed in the table below.

**Table 2 Components and Composition of 250-mg and 375-mg Tablets**

| | 250-mg Tablet | | 375-mg Tablet | |
|---|---|---|---|---|
| | Target Quantity (mg/unit of tablet) | Content (%) | Target Quantity (mg/unit of tablet) | Content (%) |
| [redacted] | | | | |

(b) (4)

*Key Inclusion Criteria:*

-Subjects between 18 and 55 years of age (inclusive)

-Female subjects of documented non-child-bearing potential. Non-childbearing potential for female subjects was defined as postmenopausal (12 months of spontaneous amenorrhea at screening) or surgically sterile (bilateral oophorectomy with or without hysterectomy at screening) or hysterectomy without oophorectomy

-Male subjects agreed to use 2 methods of contraception that are highly effective, including at least 1 barrier method, during the dosing period and for 24 weeks after the last dosing of study drug (unless the subject is a male with documented surgical sterilization). Female partners of male subjects agreed to use the same precautions.

-Body mass index (BMI) from 18 to 32 kg/m2 (inclusive) at screening

-Judged to be in good health on the basis of medical history, physical examination, and laboratory evaluations. Medical history, physical examination, and ECG were without major or clinically significant findings

*Key Exclusion Criteria:*

-History of any illness that, in the opinion of the investigator, might have confounded the results of the study or posed an additional risk in administering study drug to the subject

-Regular treatment with prescription medications. Subjects had to stop any short-duration courses of prescription medications at least 14 days before the first dosing of study drug
-Prescription medications were not administered during the study. Potential subjects were not to stop any chronic, prescribed medication being taken at the direction of a physician, without obtaining agreement from that physician
-Regular treatment with over-the-counter medications. Subjects were to end over-the-counter medication on the date of the screening visit but no less than 2 days prior to administration of study drug. Occasional use of acetaminophen or ibuprofen was allowed during the study for the treatment of pain (under supervision of the investigator)
-Subjects who consumed herbal medications or dietary medications, dietary supplements (e.g., St. John's Wort, ginkgo biloba, garlic supplements), vitamins, and grapefruit or grapefruit juice within 14 days before administration of study drug (Day 1). Subjects were not to consume these items until the last PK sample following the last dose of study drug
-Subjects who consumed more than 2 units of alcoholic beverages per day or more than 14 units per week. Subjects were not to consume any alcohol 72 hours before or after study drug administration through the follow-up visit
-Subjects who consumed an average of more than 8 cups of coffee or other caffeinated beverage, or 7 cans of cola per day. Additionally, subjects were not allowed any caffeinated beverages 72 hrs prior to dosing until the collection of the last PK samples at each dosing occasion
-Subjects who had a history of drug or alcohol abuse or addiction within 2 years prior to dosing, or who tested positive for alcohol or drugs of abuse such as cannabis, cocaine, amphetamines or opiates during the screening period
-Subjects who had participated in a clinical study involving administration of either an investigational or a marketed drug within 2 months or 5 half lives (whichever is longer) prior to the screening visit
-Subjects who tested positive for any of the following infectious disease tests: hepatitis B antigen (HBsAg), hepatitis C virus antibody (HCVAb), human immunodeficiency virus 1 antibody (HIV1Ab), or human immunodeficiency virus 2 antibody (HIV2Ab)
-Subjects who had a female partner who was pregnant, nursing, or planning to become pregnant during the study or within 90 days of the VX-950 dose.

PK Sampling

For the fed arm, blood samples for the determination of TVR and VRT-127394 concentrations were collected on days 1 and 8 at the following times: pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, and 24 hours post-dose. For the fasting arm, blood samples for the determination of TVR and VRT-127394 concentrations were collected on days 1, 8, 15, and 22 at the following times: pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, and 24 hours post-dose.

Bioanalytical Results

All bioanalytical assays for this study were conducted at (b) (4) . Plasma samples were analyzed for TVR by HPLC with tandem mass spectrometric detection. Samples were received between May 3, 2007 and December 12, 2007. The samples were analyzed between May 14, 2007 and December 30, 2007. The samples were stored at between -60 and -80°C. At the time of this report, the long-term frozen stability for TVR and VRT-127394 had only been validated for 6 months. The total storage time from the

first sample receipt date until the last day of analysis exceeded 6 months. However, in a subsequent validation report, long-term frozen stability was validated for 702 days.

Two analytical methods were used in the analysis of study samples: V9LHPP and V9HHPP. The nominal calibration and QC concentrations as well as accuracy and precision results will be presented separately for each method. The V9LHPP calibration standard concentrations for both TVR and VRT-127394 were 2.0, 4.0, 10.0, 50.0, 200.0, 500, 800, and 1000 ng/mL. The V9HHPP calibration standard concentrations for both TVR and VRT-127394 were 20, 40, 100, 250, 650, 1600, 4000, and 5000 ng/mL. The mean accuracy and precision estimates at each TVR and VRT-127394 standard concentration are presented in Tables 3 through 6, below. All accuracy and precision (%CV) values were within the acceptable range (≤20% from nominal at the LLOQ concentration and ≤15% from nominal at all other concentrations). Quality control concentrations using the V9LHPP method for both analytes were 6.0, 60, 250, and 750 ng/mL. Quality control concentrations using the V9HHPP method for both analytes were 60, 500, and 3750 ng/mL. For the V9LHPP method, the mean accuracy ranged from 100 to 102.5% for TVR and 99.2 to 101.8% for VRT-127394. The mean precision ranged from 3.5 to 4.5% for TVR and 4.0 to 7.4% for VRT-127394. For the V9HHPP method, the mean accuracy ranged from 95.2 to 99.2% for TVR and 95.3 to 99.5% for VRT-127394. The mean precision ranged from 3.2 to 3.6% for TVR and 4.8 to 5.6% for VRT-127394.

**Table 3 TVR Calibration Standard Summary Statistics for V9LHPP Method**

| Analysis Group | Theoretical Concentration (ng/mL) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 2.00 | 4.00 | 10.0 | 50.0 | 200 | 500 | 800 | 1000 |
| n | 281 | 273 | 277 | 278 | 277 | 276 | 278 | 279 |
| Mean | 2.00 | 4.00 | 10.0 | 50.4 | 202 | 495 | 801 | 991 |
| SD | 0.100 | 0.192 | 0.446 | 1.90 | 7.21 | 16.1 | 25.6 | 32.9 |
| RSD (%) | 5.0 | 4.8 | 4.5 | 3.8 | 3.6 | 3.3 | 3.2 | 3.3 |
| Accuracy (%) | 100.0 | 100.0 | 100.0 | 100.8 | 101.0 | 99.0 | 100.1 | 99.1 |

**Table 4 VRT-127394 Calibration Standard Summary Statistics for V9LHPP Method**

| Analysis Group | Theoretical Concentration (ng/mL) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 2.00 | 4.00 | 10.0 | 50.0 | 200 | 500 | 800 | 1000 |
| n | 273 | 255 | 258 | 257 | 258 | 252 | 269 | 266 |
| Mean | 2.00 | 4.00 | 10.0 | 49.9 | 200 | 501 | 814 | 985 |
| SD | 0.149 | 0.263 | 0.649 | 3.01 | 11.4 | 30.8 | 47.3 | 49.9 |
| RSD (%) | 7.5 | 6.6 | 6.5 | 6.0 | 5.7 | 6.1 | 5.8 | 5.1 |
| Accuracy (%) | 100.0 | 100.0 | 100.0 | 99.8 | 100.0 | 100.2 | 101.8 | 98.5 |

**Table 5 TVR Calibration Standard Summary Statistics for V9HHPP Method**

| Analysis Group | Theoretical Concentration (ng/mL) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 20.0 | 40.0 | 100 | 250 | 650 | 1600 | 4000 | 5000 |
| n | 112 | 112 | 112 | 111 | 112 | 113 | 112 | 112 |
| Mean | 19.8 | 40.3 | 103 | 253 | 678 | 1600 | 3870 | 4770 |
| SD | 0.624 | 1.42 | 3.51 | 7.40 | 19.4 | 43.0 | 124 | 165 |
| RSD (%) | 3.2 | 3.5 | 3.4 | 2.9 | 2.9 | 2.7 | 3.2 | 3.5 |
| Accuracy (%) | 99.0 | 100.8 | 103.0 | 101.2 | 104.3 | 100.0 | 96.8 | 95.4 |

**Table 6 VRT-127394 Calibration Standard Summary Statistics for V9HHPP Method**

| Analysis Group | Theoretical Concentration (ng/mL) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 20.0 | 40.0 | 100 | 250 | 650 | 1600 | 4000 | 5000 |
| n | 112 | 110 | 110 | 103 | 112 | 113 | 111 | 111 |
| Mean | 20.1 | 39.9 | 99.6 | 240 | 647 | 1600 | 4080 | 5100 |
| SD | 1.20 | 2.15 | 5.23 | 12.8 | 36.1 | 74.5 | 168 | 276 |
| RSD (%) | 6.0 | 5.4 | 5.3 | 5.3 | 5.6 | 4.7 | 4.1 | 5.4 |
| Accuracy (%) | 100.5 | 99.8 | 99.6 | 96.0 | 99.5 | 100.0 | 102.0 | 102.0 |

*Reviewer's Comments:*
*-The bioanalytical results are acceptable.*

Results

A total of 115 subjects were enrolled in this study and 95 completed the study. There were 20 discontinuations: 8 tested positive for prohibited drugs or alcohol during the study, 5 did not show up for scheduled visits, 3 withdrew consent, 2 were lost to follow-up, 1 withdrew due to family reasons, and 1 withdrew due to an adverse event of vasovagal syncope.

*Demographics*

| | Treatment Sequence[a] | | | | |
|---|---|---|---|---|---|
| | Arm 1 | | Arm 2 | | Total |
| | (1-1) (N=13) | (1-2) (N=13) | (2-1) (N=46) | (2-2) (N=43) | (N=115) |
| **Gender (n [%])** | | | | | |
| Male | 13 (100) | 11 (84.6) | 43 (93.5) | 42 (97.7) | 109 (94.8) |
| Female | -- | 2 (15.4) | 3 (6.5) | 1 (2.3) | 6 (5.2) |
| **Ethnicity (n [%])** | | | | | |
| Hispanic or Latino | -- | -- | 1 (2.2) | 2 (4.7) | 3 (2.6) |
| Not Hispanic or Latino | 13 (100) | 13 (100) | 45 (97.8) | 41 (95.4) | 112 (97.4) |
| **Race (n [%])** | | | | | |
| Black | 2 (15.4) | 4 (30.8) | 13 (28.3) | 10 (23.3) | 29 (25.2) |
| Caucasian | 11 (84.6) | 9 (69.2) | 31 (67.4) | 30 (69.8) | 81 (70.4) |
| Asian | -- | -- | 1 (2.2) | -- | 1 (0.9) |
| American Indian | -- | -- | 1 (2.2) | 2 (4.7) | 3 (2.6) |
| Hispanic | -- | -- | -- | 1 (2.3) | 1 (0.9) |
| **Age (years)** | | | | | |
| Mean | 33.2 | 37.5 | 31.9 | 28.5 | 31.4 |
| SD | 11.13 | 12.39 | 10.14 | 10.81 | 10.98 |
| Median | 31.0 | 42.0 | 33.5 | 24.0 | 29.0 |
| Min | 21.0 | 21.0 | 18.0 | 18.0 | 18.0 |
| Max | 55.0 | 52.0 | 52.0 | 53.0 | 55.0 |
| **Weight (kg)** | | | | | |
| Mean | 80.7 | 82.6 | 82.6 | 83.9 | 82.9 |
| SD | 10.98 | 8.95 | 13.21 | 13.18 | 12.45 |
| Median | 83.0 | 82.4 | 83.7 | 81.1 | 82.4 |
| Min | 57.7 | 64.8 | 58.2 | 60.7 | 57.7 |
| Max | 98.7 | 96.2 | 108.3 | 113.0 | 113.0 |
| **Height (cm)** | | | | | |
| Mean | 179.6 | 175.3 | 176.9 | 178.4 | 177.6 |
| SD | 7.71 | 8.60 | 6.65 | 7.68 | 7.40 |
| Median | 181.0 | 173.0 | 177.5 | 178.0 | 178.0 |
| Min | 157.0 | 162.3 | 158.0 | 164.0 | 157.0 |
| Max | 188.0 | 190.0 | 190.0 | 198.0 | 198.0 |
| **BMI ($kg/m^2$)** | | | | | |
| Mean | 25.1 | 26.9 | 26.2 | 26.5 | 26.3 |
| SD | 3.76 | 2.06 | 3.69 | 3.34 | 3.42 |
| Median | 25.7 | 27.4 | 26.2 | 26.4 | 26.4 |
| Min | 18.2 | 23.0 | 19.5 | 20.0 | 18.2 |
| Max | 31.0 | 29.2 | 32.0 | 32.0 | 32.0 |

[a] Sequence 1-1: Day 1, Formulation A; Day 8, Formulation B
Sequence 1-2: Day 1, Formulation B, Day 8, Formulation A
Sequence 2-1: Day 1, Formulation A; Day 8, Formulation B; Day 15, Formulation A; Day 22, Formulation B
Sequence 2-2: Day 1, Formulation B; Day 8, Formulation A; Day 15, Formulation B; Day 22, Formulation A
Arm 1 = Fed State; Arm 2 = Fasted State
Formulation A = 250-mg Tablet, Formulation B = 375-mg Tablet

*Safety*

Overall, the most common adverse events were headache, fatigue, diarrhea, neutropenia, and increased bilirubin. There were no serious adverse events (SAE). One subject discontinued due to an adverse event (vasovagal syncope). Up to 23.6% subjects within a given group had adverse events related to the study drug.

*Pharmacokinetics*

In the subgroup of subjects (n=26) who took TVR in the fed state, exposures following a 750-mg dose using formulation B (375-mg tablet) were higher than for formulation A (250-mg tablet). $AUC_{0\text{-}24h}$ was ~36% higher and Cmax was ~34% higher following dosing with formulation B (Table 7). Two subjects discontinued the study prior to administration of formulation B; thus, there are only 24 subjects included in the statistical analysis of that arm and in the final bioequivalence analysis. The intra-subject variabilities in the fed state in this study were estimated as 16% for Cmax, 16% for $AUC_{0\text{-}24h}$ and 17% for $AUC_{inf}$. Analysis of bioequivalence between the two formulations shows that the 90% confidence intervals for all three parameters are outside the standard BE limits of 80-125% (Table 8).

**Figure 1 Mean Plasma TVR Concentration-Time Profiles: Fed State**

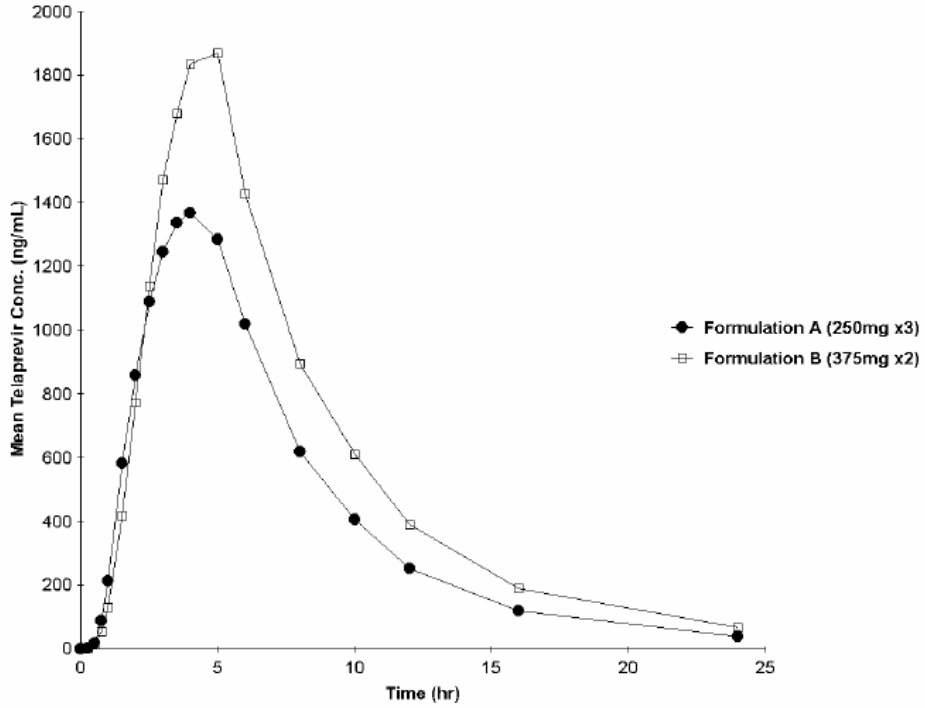


**Table 7 Summary TVR PK Parameters: Fed State**

| Pharmacokinetic Parameter | Formulation A (N=26) | Formulation B (N=24) |
|---|---|---|
| $AUC_{0-\infty}$ (ng*hr/mL) | 10223.75 (5322.05) | 14038.82 (8454.18) |
| $C_{max}$ (ng/mL) | 1602.58 (704.99) | 2143.88 (901.03) |
| $AUC_{0\text{-last}}$ (ng*hr/mL) | 9975.25 (5067.30) | 13522.09 (7572.13) |
| $t_{max}$ (hr)[a] | 3.5 (2, 6) | 4 (2.5, 6) |
| $t_{1/2}$ (hr) | 3.95 (0.83) | 3.96 (1.12) |

**Table 8 BE Statistical Analysis: Fed State**

| Comparison | Parameter | Point Estimate (%) of geometric mean ratio | 90% Confidence interval |
|---|---|---|---|
| Formulation B vs. Formulation A | $C_{max}$ Ratio | 131.8 | 121.6, 142.8 |
| | $AUC_{0\text{-last}}$ Ratio | 132.0 | 121.7, 143.2 |
| | $AUC_{0-\infty}$ Ratio | 132.6 | 122.1, 144.0 |

A total of 88 subjects' PK data were included in the TVR plasma concentration descriptive summaries and 71 subjects were included in the BE analysis. The mean plasma concentrations between subjects who took formulation A and subjects who took formulation B are similar. Mean PK parameters are presented in Table 9 below. The 90% confidence intervals are within the standard BE limits of 80-125% (Table 10). The intra-subject variability of PK parameters in the fasted state was 51% for Cmax, 41% for $AUC_{0\text{-}24h}$ and 41% for $AUC_{inf}$, which are considerably higher than in the fed state.

**Figure 2 Mean Plasma TVR Concentration-Time Profiles: Fasted State**

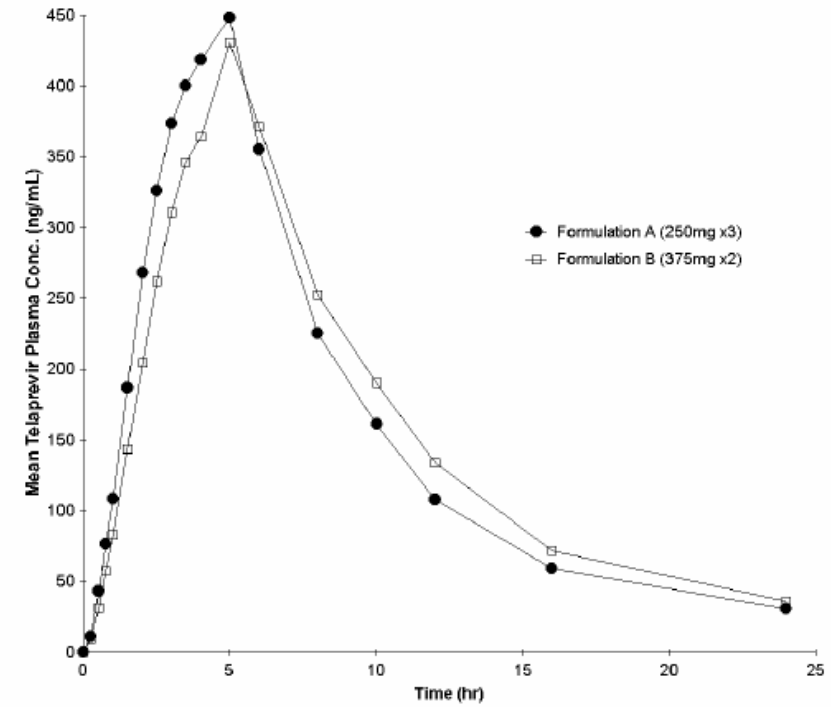


**Table 9 Summary TVR PK Parameters: Fasted State**

| Pharmacokinetic Parameter | Formulation A (N=156) | Formulation B (N=155) |
|---|---|---|
| $AUC_{0-\infty}$ (ng*hr/mL) | 3977.82 (2788.78) | 4151.42 (3195.53) |
| $C_{max}$ (ng/mL) | 509.56 (368.90) | 481.19 (338.22) |
| $AUC_{0-last}$ (ng*hr/mL) | 3665.56 (2596.45) | 3771.89 (2794.96) |
| $t_{max}$ (hr)[a] | 4 (1.5, 10) | 5 (2, 10) |
| $t_{1/2}$ (hr) | 6.05 (3.92) | 5.75 (2.64) |

**Table 10 BE Statistical Analysis: Fasted State**

| Comparison | Parameter | Point Estimate (%) of geometric mean ratio | 90% Confidence interval |
|---|---|---|---|
| Formulation B vs. Formulation A | $C_{max}$ Ratio | 95.8 | 86.9,105.6 |
| | $AUC_{0-last}$ Ratio | 102.6 | 94.8,111.0 |
| | $AUC_{0-\infty}$ Ratio | 102.6 | 94.9,111.0 |

*Reviewer's Comments:*
*-TVR PK parameters following administration of a single dose of TVR (375-mg tablet) in the fed state are similar to PK parameters in other studies where a single dose of TVR was administered following a meal (studies VX06-950-006 and VX-950-TiDP24-C132). In addition, variability is lower when TVR is administered in the fed state.*

Conclusions

In the fed state, dosing with the 375-mg tablet resulted in about 32% higher exposure compared to the 250-mg tablet. The 90% CIs for the ratios of geometric least square means of TVR Cmax, $AUC_{0-24h}$, and $AUC_{inf}$ between the 2 formulations did not fall within the standard bioequivalence limits, and therefore the 2 formulations are not bioequivalent in the fed state. When subjects were dosed in the fasted state, the 90% CIs for the ratios of geometric least square means of telaprevir Cmax, $AUC_{0-24h}$, and $AUC_{inf}$ between the 2 formulations fell within the standard bioequivalence limits. Therefore, the 2 formulations were bioequivalent when given in the fasted state.

**Individual Study Review—VX-950-TiDP24-C121**

Title (Study VX-950-TiDP24-C121)

"The effect of different types of food on the bioavailability of telaprevir (VX-950) after a single oral dose of 750 mg, formulated as the 375-mg tablet, in healthy subjects."

Objective

- To determine the effect of different types of meals on the bioavailability of telaprevir after a single oral dose of 750 mg, formulated as the 375-mg tablet, in healthy subjects

Study Dates and Location(s):
Study initiation: September 24, 2007
Study completion: January 11, 2008
Clinical Site: PAREXEL International GmbH, Berlin, Germany

Study Design

This was a phase I, open-label, randomized, 5-way crossover trial in healthy subjects. A total of 30 subjects were enrolled and each received 5 different treatments in 5 separate phases. Each of the phases was separated by a 6-day washout period. The type of food administered in each phase is detailed below.

- Treatment A: telaprevir intake after a standard breakfast (4 slices of bread, 1 slice of ham, 1 slice of cheese, butter, jelly and 2 cups of decaffeinated coffee or tea with milk and/or sugar, if desired)
- Treatment B: telaprevir intake under fasting conditions
- Treatment C: telaprevir intake after a high-calorie, high-fat breakfast (2 eggs fried in butter, 2 strips of bacon, 2 slices of white bread with butter, 1 croissant with 1 slice of cheese and 240 mL of whole milk)
- Treatment D: telaprevir intake after a low-calorie, high-protein breakfast (115 g turkey without skin, 1 slice of bread and 1 teaspoon fat [mayo or butter])
- Treatment E: telaprevir intake after a low-calorie, low-fat breakfast (2 slices of white bread, jam [20 g] and low-calorie low-fat yogurt [100 g])

| Treatment | Fat (g) | Total kcal | kcal From Fat | kcal From Carbohydrates | kcal From Proteins |
|---|---|---|---|---|---|
| A (standard breakfast) | 21 | 533 | 189 | 268 | 76 |
| B (fasting) | 0 | 0 | 0 | 0 | 0 |
| C (high-calorie high-fat breakfast) | 56 | 928 | 504 | 260 | 164 |
| D (low-calorie high-protein breakfast) | 9 | 260 | 80 | 60 | 120 |
| E (low-calorie low-fat breakfast) | 3.6 | 249 | 32 | 180 | 37 |

Study Dose Used and Dose Rationale

A single oral dose of 750 mg (2 X 375-mg tablet) was used in this study. This is the same dose used in the phase 3 studies (as part of a q8h regimen).

Formulation(s) Used

TVR was provided as 375-mg white to off-white oval tablets for oral administration (b) (4) This is the same formulation used in the pivotal Phase 3 trials.

*Key Inclusion Criteria:*

-Male or female, aged between 18 and 55 years, extremes included
-Females had to be postmenopausal for at least 2 years or had to have had a hysterectomy or tubal ligation (without reversal operation)
-Nonsmoking for at least 1 year before screening
-Normal weight as defined by a body mass index (BMI; weight in kg divided by the square of height in meters) of 18 to 30 $kg/m^2$, extremes included, at screening
-Healthy on the basis of a medical evaluation that revealed the absence of any clinically relevant abnormality

*Key Exclusion Criteria:*

-A history of any illness that, in the opinion of the investigator, could confound the results of the trial or pose an additional risk in administering study medication to the subject
-A hemoglobin value of <12.0 g/dL
-Regular treatment with prescription medications. Subjects were to have ended any short courses of prescription medications at least 14 days prior to the screening visit. Prescription medications were not to be administered during the study.
-Regular treatment with over-the-counter medications. Subjects were to end over-the-counter medication on the date of the screening visit but no less than 2 days prior to administration of study drug. Occasional use of acetaminophen or ibuprofen was allowed during the study for the treatment of pain (under supervision of the investigator)
-Subjects who consumed herbal medications or dietary medications, dietary supplements (e.g., St. John's Wort, ginkgo biloba, garlic supplements), vitamins, and grapefruit or grapefruit juice within 14 days before administration of study drug (Day 1). Subjects were not to consume these items until the last PK sample following the last dose of study drug
-Subjects who consumed more than 2 units of alcoholic beverages per day or more than 14 units per week. Subjects were not to consume any alcohol 72 hours before or after study drug administration through the follow-up visit
-Subjects who consumed an average of more than 8 cups of coffee or other caffeinated beverage, or 7 cans of cola per day. Additionally, subjects were not allowed any caffeinated beverages 72 hrs prior to dosing until the collection of the last PK samples at each dosing occasion
-Subjects who had a history of drug or alcohol abuse or addiction within 2 years prior to dosing, or who tested positive for alcohol or drugs of abuse such as cannabis, cocaine, amphetamines or opiates during the screening period
-Subjects who had participated in a clinical study involving administration of either an investigational or a marketed drug within 2 months or 5 half lives (whichever is longer) prior to the screening visit

-Subjects who tested positive for any of the following infectious disease tests: hepatitis B antigen (HBsAg), hepatitis C virus antibody (HCVAb), human immunodeficiency virus 1 antibody (HIV1Ab), or human immunodeficiency virus 2 antibody (HIV2Ab)
-Subjects who had a female partner who was pregnant, nursing, or planning to become pregnant during the study or within 90 days of the VX-950 dose.

PK Sampling

Blood samples for assessment of TVR and VRT-127394 plasma concentrations were collected at pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, and 24 hours post-dose.

Bioanalytical Results

All bioanalytical assays for this study were conducted at (b) (4) . Plasma samples were analyzed for TVR by HPLC with tandem mass spectrometric detection (LC-MS/MS). Samples were received between November 13, 2007 and November 30, 2007. The samples were analyzed between December 3, 2007 and January 18, 2009. The samples were stored at -70°C. The maximum sample storage time until analysis (66 days) did not exceed the maximum time during which long-term frozen stability was validated (6 months).

The calibration standard concentrations for both TVR and VRT-127394 were 2.0, 4.0, 10.0, 50.0, 200.0, 500, 800, and 1000 ng/mL. The mean accuracy and precision estimates at each TVR and VRT-127394 standard concentration are presented in Tables 1 and 2, respectively, below. All accuracy and precision (%CV) values were within the acceptable range (≤20% from nominal at the LLOQ concentration and ≤15% from nominal at all other concentrations). Quality control concentrations for both analytes were 6.0, 250, and 800 ng/mL. The mean accuracy ranged from 93.1 to 101.6% for TVR and 96.6 to 100.7% for VRT-127394. The mean precision ranged from 3.6 to 5.7% for TVR and 4.4 to 6.7% for VRT-127394.

**Table 1 Mean Calibration Standard Concentrations and Statistics for TVR**

| | VX-950, ng/ml | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Analytical batch | 2.00 | 4.00 | 10.0 | 50.0 | 200 | 500 | 800 | 1000 |
| n | 58 | 57 | 56 | 58 | 58 | 58 | 56 | 57 |
| mean | 1.98 | 4.13 | 9.73 | 48.3 | 206 | 516 | 824 | 943 |
| std. dev. | 0.1 | 0.2 | 0.3 | 1.9 | 7.4 | 18.3 | 28.3 | 36.4 |
| %CV | 5.6 | 4.3 | 3.0 | 4.0 | 3.6 | 3.5 | 3.4 | 3.9 |
| % accuracy | 99.0 | 103.2 | 97.3 | 96.6 | 103.2 | 103.3 | 103.1 | 94.3 |

**Table 2 Mean Calibration Standard Concentrations and Statistics for VRT-127394**

| | VX-950, ng/ml | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Analytical batch | 2.00 | 4.00 | 10.0 | 50.0 | 200 | 500 | 800 | 1000 |
| n | 56 | 56 | 55 | 56 | 56 | 56 | 53 | 54 |
| mean | 1.96 | 4.14 | 10.1 | 49.9 | 199 | 507 | 808 | 954 |
| std. dev. | 0.1 | 0.2 | 0.4 | 2.7 | 7.6 | 23.9 | 32.3 | 38.3 |
| %CV | 5.5 | 5.2 | 3.8 | 5.5 | 3.8 | 4.7 | 4.0 | 4.0 |
| % accuracy | 98.1 | 103.4 | 101.3 | 99.8 | 99.6 | 101.3 | 101.0 | 95.4 |

*Reviewer's Comments:*
*-The bioanalytical results are acceptable.*

Results

A total of 30 subjects were randomized and assigned to treatment. Twenty-eight subjects completed the trial. One subject (121-0015) discontinued treatment due to noncompliance (disallowed drug intake) and 1 subject (121-0048) discontinued treatment due to AEs (ALT elevation grade 3 and AST elevation grade 2).

*Demographics*

| Parameter | All Subjects N = 30 |
|---|---|
| Age, years<br>Median (range) | 39.5<br>(23-54) |
| Height, cm<br>Median (range) | 178.5<br>(167-196) |
| Weight, kg<br>Median (range) | 78.5<br>(67-96) |
| BMI, $kg/m^2$<br>Median (range) | 24.5<br>(20.2-27.8) |
| Sex, n (%)<br>Female<br>Male | <br>2 (6.7)<br>28 (93.3) |

*Safety*

Overall, 13 (43.3%) subjects experienced at least 1 AE during the trial. The most frequently reported AEs in this trial (reported for at least 10% of the subjects during the whole trial) were related to the body systems nervous system disorders (6 subjects, 20%), general disorders and administration site conditions (3 subjects, 10%), and blood and lymphatic system disorders (3 subjects, 10%). The most commonly reported AEs were headache (5 subjects, 16.7%) and neutropenia (3 subjects, 10%). One subject (121-0048) discontinued in the washout period of phase 2 (treatment C) due to AEs (ALT elevation grade 3 and AST elevation grade 2).

*Pharmacokinetics*

Fasting conditions resulted in the lowest exposure to TVR compared with any other type of meal. A high-fat breakfast resulted in the highest Cmax and AUC values; however, Tmax was also longer by an average of 1 hour as compared with the other types of meals (Table 3). Based on the ratios of the LSmeans, Cmax, $AUC_{last}$, and $AUC_{inf}$ of telaprevir were decreased by 83%, 75%, and 73%, respectively, when TVR was administered under fasting conditions compared to administration after a standard breakfast. The 90% confidence intervals of the LSmeans ratios fell below the 80-125% limits.

**Figure 1 Mean Plasma Concentration-Time Curves of TVR Under Different Food Conditions**

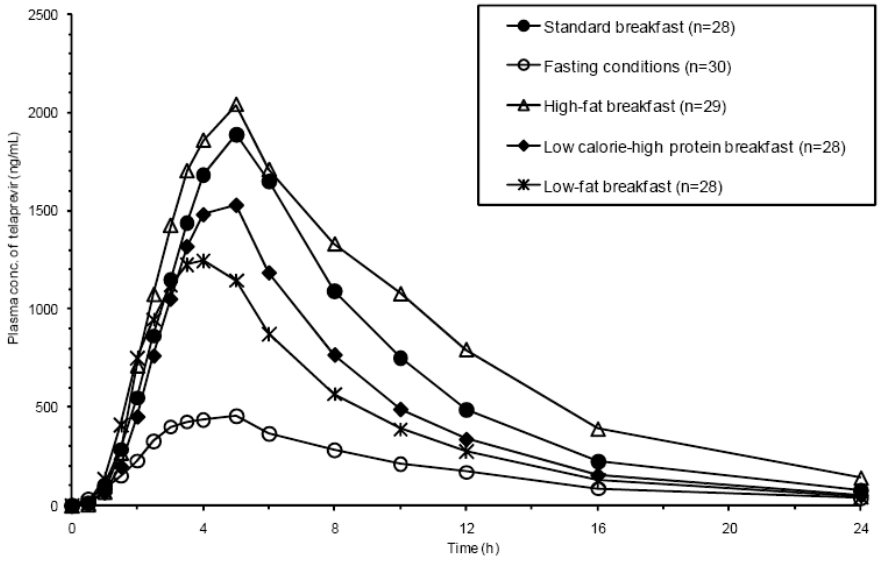



**Table 3 Summary TVR PK Parameters Under Different Food Conditions**

| Pharmacokinetics of Telaprevir (mean±SD, $t_{max}$: median [range]) | Standard Breakfast (Treatment A) | Fasting Conditions (Treatment B) | High-Calorie High-Fat Breakfast (Treatment C) | Low-Calorie High-Protein Breakfast (Treatment D) | Low-Calorie Low-Fat Breakfast (Treatment E) |
|---|---|---|---|---|---|
| n | 28 | 30 | 29 | 28 | 28 |
| $t_{max}$, h | 4.0 (1.5 – 6.0) | 4.0 (1.5 – 6.0) | 5.0 (2.5 – 10.0) | 4.5 (2.5 – 6.0) | 3.5 (2.0 – 6.0) |
| $C_{max}$, ng/mL | 2217 ± 836.2 | 508.8 ± 502.5 | 2310 ± 1007 | 1707 ± 662.1 | 1479 ± 668.2 |
| $AUC_{last}$ ng.h | 14350 ± 6547 | 4264 ± 3562 | 18320 ± 11590 | 10820 ± 4602 | 9248 ± 4665 |
| $AUC_{\infty}$, ng.h | 14930 ± 7297 | 4662 ± 3943 | 19370 ± 12980 | 11220 ± 4986 | 9604 ± 4999 |
| $t_{1/2term}$, h | 4.044 ± 1.118 | 5.385 ± 2.446 | 4.392 ± 1.199 | 4.135 ± 1.269 | 4.292 ± 1.110 |

With the exception of fasting conditions, the inter-subject variability (%CV) of Cmax was comparable for all treatments, with values ranging from 38 to 45%. The inter-subject variability for TVR administered after a standard breakfast, after a high-calorie high-fat breakfast, after a low-calorie high-protein breakfast, or after a low-calorie low-fat breakfast was higher for $AUC_{last}$ and $AUC_{inf}$, ranging from 43 to 67%. A higher inter-subject variability was observed for Cmax, $AUC_{last}$, and $AUC_{inf}$ when telaprevir was administered under fasting conditions, 99%, 84%, and 85%, respectively.

Similar to TVR PK, exposure to VRT-127394 was highest with a high-calorie, high-fat breakfast than with any other meal condition. A standard breakfast resulted in the next highest exposures. Again, fasting conditions resulted in the lowest $AUC_{last}$, $AUC_{inf}$, and Cmax of any meal condition (Table 4).

**Table 4 Summary VRT-127394 PK Parameters Under Different Food Conditions**

| Pharmacokinetics of VRT-127394 (mean±SD, $t_{max}$: median [range]) | Standard Breakfast (Treatment A) | Fasting Conditions (Treatment B) | High-Calorie High-Fat Breakfast (Treatment C) | Low-Calorie High-Protein Breakfast (Treatment D) | Low-Calorie Low-Fat Breakfast (Treatment E) |
|---|---|---|---|---|---|
| n | 28 | 30[a] | 29[c] | 28 | 28 |
| $t_{max}$, h | 5.0 (2.5 – 8.0) | 8.0 (3.5 – 12.0) | 5.0 (4.0 – 12.0) | 5.0 (3.5 – 6.0) | 5.0 (3.0 – 8.0) |
| $C_{max}$, ng/mL | 730.9 ± 278.5 | 145.5 ± 141.2 | 875.1 ± 435.9 | 633.8 ± 232.6 | 413.0 ± 201.7 |
| $AUC_{last}$ ng.h/mL | 6520 ± 3204 | 1753 ± 1450 | 8857 ± 5863 | 5249 ± 2360 | 3796 ± 2016 |
| $AUC_{\infty}$, ng.h/mL | 7019 ± 3900 | 2438[b] ± 1890[b] | 8902 ± 4530 | 5616 ± 2762 | 4137 ± 2404 |
| $t_{1/2term}$, h | 4.416 ± 1.428 | 5.886[b] ± 2.015[b] | 4.729 ± 1.395 | 4.512 ± 1.647 | 4.955 ± 1.704 |

[a] For $AUC_{\infty}$ and $t_{1/2\ term}$, n = 16

[b] Accurate determination not possible

[c] n = 27 for $AUC_{\infty}$ and $t_{1/2term}$

Conclusions

The results of this trial demonstrate that compared to a standard breakfast, exposure to TVR decreased by 73-83%, 25-26% and 38-39% when telaprevir was administered under fasting conditions, after a low-calorie, high-protein breakfast and after a low-calorie, low-fat breakfast, respectively. Administration of TVR after a high-calorie high-fat breakfast resulted in similar Cmax values while $AUC_{last}$ and $AUC_{inf}$ increased by 19-20% compared to administration after a standard breakfast. The PK characteristics of VRT-127394 following the different types of meals were generally consistent with TVR.

**Individual Study Review—VX07-950-017**

Title (Study VX07-950-017)

"A Phase 1, Open-label, Randomized, Single Dose Escalation, and Relative Bioavailability Study of Telaprevir in Healthy Subjects"

Objectives

- To evaluate dose proportionality of uncoated 375-mg tablets of telaprevir (TVR)
- To evaluate relative bioavailability of coated and uncoated 375-mg tablets of TVR
- To assess the safety and tolerability of single escalating doses of uncoated 375-mg tablets of TVR given to healthy volunteers in the fed state
- To assess the safety and tolerability of a single dose of coated 375-mg tablets of TVR given to healthy volunteers in the fed state

Study Dates and Location(s):
Study initiation: August 8, 2007
Study completion: November 8, 2007
Clinical Sites: Covance Clinical Research Unit, Austin, TX

Study Design

This study was a randomized, open-label, single ascending dose, phase 1 study with TVR alone. The study included 4 groups (N=5 subjects per group) with 6 dosing occasions in each group. There was a 5-7 day washout period between each dosing occasion. The relative bioavailability of TVR administered as film-coated and uncoated 375-mg tablets was assessed as a nested study in a 2 x 2 crossover design using a 750-mg single-dose regimen during the first 2 dosing occasions. In the subsequent dosing occasions, dose proportionality of the uncoated 375-mg tablet formulation of TVR was assessed by administration of single escalating doses of 375, 750, 1125, 1500, and 1875 mg to healthy subjects in the fed state. Since dosing occasions 6, 7, and 8 represent the dosing occasion in which the sixth dose was administered to subjects within a specific treatment group, they are collectively referred to as dosing occasion 6. See Figure 1 below for dosing scheme.

**Figure 1 Dosing Occasion Scheme**

| | | Dose (mg) on Dosing Occasion | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| 1 | 5 | 750 | 750[a] | 375 | 750 | 1125 | 1500[b] | --- | --- |
| 2 | 5 | 750 | 750[a] | 375 | 750 | 1125 | --- | 1500 | --- |
| 3 | 5 | 750[a] | 750 | 375 | 750 | 1125 | --- | 1875 | --- |
| 4 | 5 | 750[a] | 750 | 375 | 750 | 1125 | --- | --- | 1875 |

[a] Coated 375-mg tablets of TVR for assessment of relative bioavailability; all other doses were with the uncoated 375-mg tablets
[b] The remaining dosing occasions were staggered to assess adverse events before proceeding to the next dosing occasion.

Study Doses Used and Dose Rationale

At the time of this study, doses up to 1250 mg of an earlier formulation of TVR have been previously administered to healthy subjects and were well-tolerated. Doses of 375, 750, and

1125 mg were chosen for this study to ensure that sufficient data would be obtained from at least 3 dose levels to evaluate dose proportionality. High doses of TVR (1500 and 1875 mg) were chosen to evaluate tolerability and exposure to TVR at higher doses to allow for future instances where a dose adjustment (to a higher TVR dose) may be necessary.

*Reviewer's Comments:*
*-The Applicant has conducted their statistical analysis of BE between the coated (Test) and uncoated (Ref) tablets using average BE methods. In a traditional average BE test, dosing occasions 1 and 2 would serve as either the Test or Ref arms (depending on whether the subject received the coated or uncoated tablet in each dosing occasion). In the case of a scaled average BE approach, the first two dosing occasions would be included along with dosing occasion 4, which is Ref for everyone (essentially a 3-way crossover design with Ref on two occasions, due to high inter-subject variability).*

Formulation(s) Used

The uncoated TVR 375-mg tablet formulation used in this study is the same formulation as has been used for most phase 1 studies and for all the phase 3 studies. The coated 375 mg tablet is the proposed commercial formulation. A comparative components and composition table is presented below for both the uncoated and coated tablets. The only substantive difference between the 2 formulations is (b) (4) .

**Table 1 Components and Composition of 375-mg Core (Uncoated) Tablet vs. 375-mg Film-Coated Tablet**

(b) (4)

*Reviewer Comments:*
*-As this is the only study comparing the BE of the Phase 3 and proposed commercial formulations, the comparison of the two formulations on dosing occasions 1 and 2 will be reviewed as a pivotal BE study. The study site was inspected by the Division of Scientific Investigation (DSI).*

*Key Inclusion Criteria:*
-Subjects between 18 and 55 years of age (inclusive)
-Female subjects must have been of documented non-childbearing potential. Nonchildbearing potential for female subjects was defined as postmenopausal (12 months of spontaneous amenorrhea at screening) or surgically sterile (bilateral oophorectomy with or without hysterectomy at screening) or hysterectomy without oophorectomy
-Male subjects agreed to use at least 1 method of contraception that is highly effective, including a barrier method, during the dosing period and for 90 days after the last dosing of study drug (unless the subject is a male with documented surgical sterilization). Female partners of male subjects agreed to use the same precautions and were not pregnant or nursing
-BMI from 18 to 29 $kg/m^2$ (inclusive) at screening
-Medical history, physical examination, ECG, and laboratory evaluations must have been without major or clinically significant findings

*Key Exclusion Criteria:*
-Subjects with a history of any illness that, in the opinion of the investigator or the subject's general practitioner, confounded the results of the study or posed an additional risk in administering study drug(s) to the subject
-Regular treatment with prescription medications. Subjects were to have ended any short courses of prescription medications at least 14 days prior to the screening visit. Prescription medications were not to be administered during the study. (Potential subjects were not to stop any chronic, prescribed medication being taken at the direction of a physician, without obtaining agreement from that physician)
-Regular treatment with over-the-counter medications. Subjects were to end over-the-counter medication on the date of the screening visit but no less than 2 days prior to administration of study drug. Occasional use of acetaminophen or ibuprofen was allowed during the study for the treatment of pain (under supervision of the investigator)
-Subjects who consumed herbal medications or dietary medications, dietary supplements (e.g., St. John's Wort, ginkgo biloba, garlic supplements), vitamins, and grapefruit or grapefruit juice within 14 days before administration of study drug (Day 1).
-Subjects who consumed more than 2 units of alcoholic beverages per day or more than 14 units per week.
-Subjects who consumed an average of more than 5 cups of coffee or other caffeinated beverage
-Subjects who had a history of drug or alcohol abuse or addiction within 2 years prior to dosing, or who tested positive for alcohol or drugs of abuse such as cannabis, cocaine, amphetamines or opiates during the screening period
-Subjects who had participated in a clinical study involving administration of either an investigational or a marketed drug within 2 months or 5 half lives (whichever is longer) prior to the screening visit
-Subjects who tested positive for any of the following infectious disease tests: hepatitis B antigen (HBsAg), hepatitis C virus antibody (HCVAb), human immunodeficiency virus 1 antibody (HIV1Ab), or human immunodeficiency virus 2 antibody (HIV2Ab)
-Illness within 5 days before the start of study drug dosing ("illness" is defined as a recent non-serious, non-acute condition, e.g., the flu or the common cold). Such subjects could be enrolled at the discretion of the investigator

Blood Sampling for PK

Blood samples for determination of TVR and VRT-127394 plasma concentrations were collected at pre-dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, and 24 hours post-dose after each single dose of TVR in each dosing occasion.

Bioanalytical Results

Plasma samples were analyzed for TVR and VRT-127394 by HPLC with tandem mass spectrometric detection (LC-MS/MS) by (b) (4)
Samples were analyzed between September 26, 2007 and December 29, 2007. The samples were stored between -60° and -80° C. The maximum sample storage time until analysis was ~108 days, which is within the validated long-term frozen stability duration of 6 months.

The calibration standard concentrations for both TVR and VRT-127394 were 2.0, 4.0, 10.0, 50.0, 200.0, 500, 800, and 1000 ng/mL. The mean accuracy and precision estimates at each TVR and VRT-127394 standard concentration are presented in Tables 2 and 3, respectively, below. All accuracy and precision (%CV) values were within the acceptable range (≤20% from nominal at the LLOQ concentration and ≤15% from nominal at all other concentrations). Quality control concentrations for both analytes were 6.0, 250, and 750 ng/mL. The mean accuracy ranged from 98.7to 104.3% for TVR and 96.9 to 101.8% for VRT-127394. The mean precision ranged from 3.0 to 3.9% for TVR and 6.6 to 7.4% for VRT-127394.

**Table 2 Mean Calibration Standard Concentrations and Statistics for TVR**

| Analysis Group | Theoretical Concentration (ng/mL) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 2.00 | 4.00 | 10.0 | 50.0 | 200 | 500 | 800 | 1000 |
| n | 102 | 101 | 102 | 101 | 100 | 101 | 101 | 101 |
| Mean | 1.99 | 4.03 | 10.1 | 49.2 | 207 | 499 | 793 | 979 |
| SD | 0.0920 | 0.192 | 0.349 | 2.03 | 6.30 | 16.0 | 25.9 | 32.8 |
| RSD (%) | 4.6 | 4.8 | 3.5 | 4.1 | 3.0 | 3.2 | 3.3 | 3.4 |
| Accuracy (%) | 99.5 | 100.8 | 101.0 | 98.4 | 103.5 | 99.8 | 99.1 | 97.9 |

**Table 3 Mean Calibration Standard Concentrations and Statistics for VRT-127394**

| Analysis Group | Theoretical Concentration (ng/mL) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 2.00 | 4.00 | 10.0 | 50.0 | 200 | 500 | 800 | 1000 |
| n | 94 | 91 | 88 | 83 | 92 | 89 | 92 | 91 |
| Mean | 2.00 | 3.99 | 10.1 | 49.4 | 205 | 500 | 809 | 969 |
| SD | 0.131 | 0.277 | 0.646 | 3.04 | 14.5 | 32.9 | 53.2 | 63.1 |
| RSD (%) | 6.6 | 6.9 | 6.4 | 6.2 | 7.1 | 6.6 | 6.6 | 6.5 |
| Accuracy (%) | 100.0 | 99.8 | 101.0 | 98.8 | 102.5 | 100.0 | 101.1 | 96.9 |

*Reviewer's Comments:*
*-The bioanalytical results are acceptable.*

Results

A total of 18 subjects completed the study (two subjects discontinued due to an AE). Due to the discontinuation of these 2 subjects, 19 subjects received a 375-mg dose, 19 subjects received a 750-mg dose, 18 subjects received an 1125-mg dose, 9 subjects received a 1500-mg dose, and 9 subjects received a 1875-mg dose.

*Demographics*

| | Group | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | Total |
| **Number of Subjects** | 5 | 5 | 5 | 5 | 20 |
| **Sex (n [%])** | | | | | |
| Male | 5 (100) | 4 (80) | 5 (100) | 5 (100) | 19 (95) |
| Female | --- | 1 (20) | --- | --- | 1 (5) |
| **Race (n [%])** | | | | | |
| Caucasian | 4 (80) | 3 (60) | 3 (60) | 3 (60) | 13 (65) |
| Black | 1 (20) | --- | 2 (40) | 2 (40) | 5 (25) |
| American Indian / Alaskan Native | --- | 1 (20) | --- | --- | 1 (5) |
| Other | --- | 1 (20) | --- | --- | 1 (5) |
| **Age (years)** | | | | | |
| Mean (SD) | 39 (8.3) | 32 (8.4) | 35 (7.5) | 35 (10.3) | 35 (8.3) |
| Median | 41 | 30 | 36 | 29 | 36 |
| Min, Max | 26, 48 | 23, 45 | 24, 45 | 27, 51 | 23, 51 |
| **Body Mass Index ($kg/m^2$)** | | | | | |
| Mean (SD) | 24.4 (3.3) | 23.8 (2.7) | 25.3 (3.3) | 27.2 (2.0) | 25.2 (2.9) |
| Median | 25.2 | 23.6 | 25.4 | 26.4 | 25.7 |
| Min, Max | 19.1, 27.5 | 20.6, 27.1 | 20.4, 28.5 | 24.8, 29.8 | 19.1, 29.8 |

*Safety*

Three subjects had 1 or 2 adverse events of mild intensity, 3 subjects had 1 adverse event of moderate intensity, and 1 subject had 1 mild and 1 moderate adverse event. There were no SAEs or deaths in this study. Two subjects discontinued due to adverse events (anemia and viral respiratory infection). In both cases, the adverse events were classified as unrelated to study drug. (Please refer to the medical officer's review for further details.)

*TVR Pharmacokinetics-Dose Proportionality Study*

Following a single dose of TVR at doses between 375 mg and 1875 mg, the general profile of plasma concentration vs. time appear similar for all doses (Figure 2). The mean Tmax remained the same irrespective of the dose (~5 hours). Increases in Cmax, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ were greater than dose proportional between the 375-mg and the 1875 mg doses (Table 4). However, at dose levels between 750 and 1500 mg, the increases in Cmax were closer to dose proportional, although increases in AUC values remained non-proportional. The 1875-mg dose produced a nearly identical Cmax value as the 1500-mg dose and an $AUC_{0\text{-last}}$ value that is only ~16.8% higher, despite the 25% higher dose. Apparent oral clearance trended lower as the dose increased, while half-life increased with increasing dose. However, the volume of distribution remained relatively similar across all doses (with the exception of the 1875-mg dose).

**Figure 2 Mean TVR Plasma-Concentration vs. Time Profiles by Dose**

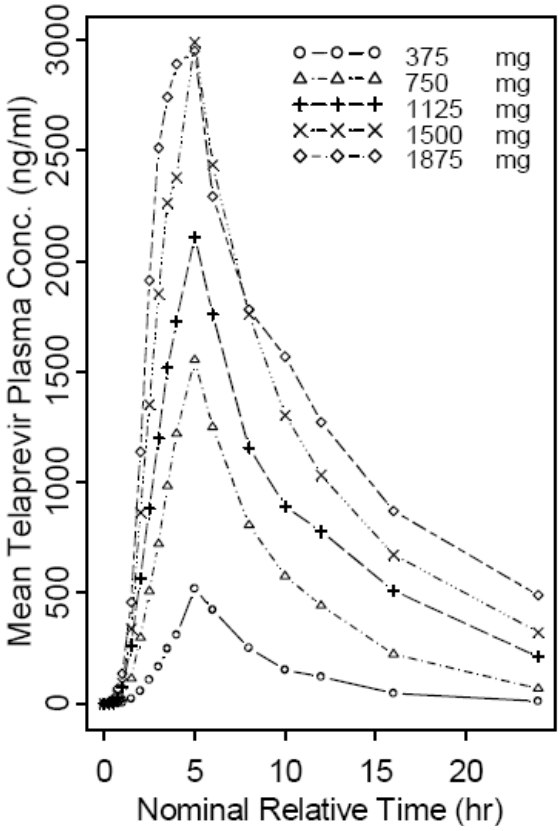



**Table 4 Arithmetic Means (SD) of TVR PK Parameters by Dose**

| PK Parameter | 375 mg (N=19) | 750 mg (N=19) | 1125 mg (N=18) | 1500 mg (N=9) | 1875 mg (N=9) |
|---|---|---|---|---|---|
| $C_{max}$ (ng/mL) | 539.79 | 1740.84 | 2346.67 | 3232.22 | 3259.44 |
| | (217.75) | (785.28) | (917.21) | (1496.90) | (1661.71) |
| $AUC_{0\text{-last}}$ (hr*ng/mL) | 3084.24 | 11102.16 | 18297.72 | 25991.47 | 30393.76 |
| | (1513.28) | (6692.22) | (8941.90) | (14006.59) | (17129.77) |
| $AUC_{0\text{-}\infty}$ (hr*ng/mL) | 3146.52 | 11749.10[b] | 19362.18[c] | 24250.23[d] | 34944.13[e] |
| | (1579.56) | (7484.56) | (11199.97) | (10194.68) | (22574.69) |
| $t_{max}$ (hr)[a] | 5 (3.55,6) | 5 (3.5,12) | 5 (3.5,12) | 5 (3,8) | 5 (2.5,8) |
| $t_{1/2}$ (hr) | 3.23 | 3.96[b] | 5.44[c] | 6.49 | 8.31 |
| | (0.70) | (1.10) | (1.79) | (2.20) | (3.30) |
| Cl/F (L/hr) | 157.43 | 100.61 | 77.96 | 68.88 | 92.83 |
| | (98.82) | (85.44) | (55.60) | (40.39) | (115.75) |
| Vz/F (L) | 692.80 | 522.53 | 560.09 | 574.30 | 1102.52 |
| | (367.89) | (342.80) | (293.69) | (281.23) | (1634.82) |

[a] median (range)
[b] Subject 1001 had indeterminable $\lambda_z$ and not included in statistic (N=18).
[c] Subject 1001 and Subject 1008 had indeterminable $\lambda_z$ and not included in statistic (N=16).
[d] Subject 1012 had >25 % extrapolated $AUC_{0\text{-}\infty}$ and not included in statistic (N=8).
[e] Subject 1001 had >25 % extrapolated $AUC_{0\text{-}\infty}$ and not included in statistic (N=8).

*VRT-127394 Pharmacokinetics-Dose Proportionality Study*

The PK profiles for VRT-127394 were also similar across the different dose levels. Similar to TVR PK, increases in mean Cmax, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ were greater than dose proportional between the 375-mg and the 1875 mg doses (Table 5).

**Table 5 Arithmetic Means (SD) of VRT-127394 PK Parameters by Dose**

| PK Parameter | 375 mg (N=19) | 750 mg (N=19) | 1125 mg (N=18) | 1500 mg (N=9) | 1875 mg (N=9) |
|---|---|---|---|---|---|
| $C_{max}$ (ng/mL) | 155.39 | 510.95 | 759.17 | 1049.33 | 1169.56 |
| | (68.78) | (255.26) | (305.36) | (386.35) | (637.41) |
| $AUC_{0\text{-last}}$ (hr*ng/mL) | 1222.96 | 4711.72 | 7966.15 | 12360.75 | 15178.37 |
| | (717.95) | (3260.71) | (4209.67) | (6398.52) | (9658.12) |
| $AUC_{0\text{-}\infty}$ (hr*ng/mL) | 1285.44[b] | 5202.70[b] | 7486.66[c] | 11609.39[d] | 8380.28[e] |
| | (819.84) | (3959.47) | (3883.37) | (4457.19) | (4718.41) |
| $t_{max}$ (hr)[a] | 6 (4,12) | 5 (4,12) | 5 (4,16) | 5 (5,10) | 5 (3,16) |
| $t_{1/2}$ (hr) | 3.43[b] | 4.77[b] | 7.38[f] | 9.28 | 10.01[g] |
| | (0.10) | (1.33) | (3.60) | (5.12) | (4.24) |
| $AUC_{950}$[h] (%) | 72.32 | 71.41 | 70.37 | 67.71 | 67.98 |
| | (3.02) | (3.39) | (2.54) | (1.70) | (3.29) |

[a] median (range)
[b] Subject 1001 had indeterminable $\lambda_z$ and was not included in analysis. Therefore, N=18.
[c] Subjects 1001 and 1008 had indeterminable $\lambda_z$ and were not included in analysis. Subjects 1005 and 1012 had >25% extrapolated $AUC_{0\text{-}\infty}$ and were not included in analysis. (N=14)
[d] Subjects 1012 and 1016 had >25% extrapolated $AUC_{0\text{-}\infty}$ and were not included in analysis. ( N=7)
[e] Subject 1001 had indeterminable $\lambda_z$ and was not included in analysis. Subjects 1004, 1005, 1018, and 1020 had >25% extrapolated $AUC_{0\text{-}\infty}$ and were not included in analysis. ( N=4)
[f] Subjects 1001 and 1008 had indeterminable $\lambda_z$ and were not included in analysis. (N=16)
[g] Subject 1001 had indeterminable $\lambda_z$ and was not included in analysis. (N=8)
[h] $AUC_{950}$ (%) = $AUC_{0\text{-last telaprevir}}$ / ($AUC_{0\text{-last telaprevir}}$ + $AUC_{0\text{-last VRT-127394}}$) * 100

*TVR Dose Proportionality Assessment*

The Applicant performed two different analyses of dose proportionality: 1.) power model assessment using S-Plus and 2.) ANOVA assessment in WinNonlin. The results of both analyses show that $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ increased greater than dose proportionally between the 375-mg and 1875-mg doses. In the power model, dose proportionality in Cmax between the 750-mg and 1500-mg doses could be concluded while in the ANOVA method, dose proportionality in Cmax could not be ruled out in that dose range.

*TVR Pharmacokinetics-Comparative BA/BE Study*

The plasma concentration vs. time profiles for the uncoated and coated tablets appear similar in shape (Figure 3). However, mean TVR $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and Cmax were 15%, 14%, and 12% higher, respectively, following administration of the coated tablet (intended commercial formulation) than with the uncoated tablet (used in all phase 3 studies, Table 6). Similar results were obtained for VRT-127394 (results not shown). Statistical analysis of BE conducted by the Applicant between the two tablet formulations demonstrated that the tablets are not bioequivalent (Table 7). The upper bound of the 90% confidence intervals for all three TVR parameters' point estimate of least square means ratio were above the 80-125% boundary, indicating that the coated tablet could provide meaningfully higher exposures than the uncoated tablet.

The Applicant conducted a second statistical analysis of BE to further explore the difference in bioavailability between the two formulations. Since dosing occasion 4 of this study

included a single 750-mg dose using the uncoated tablet (as part of the dose proportionality study), the Applicant used dosing occasion 4 as the "reference" product in the BE analysis in lieu of the crossover reference product PK data from dosing occasions 1 and 2. According to those results, the formulations are bioequivalent (Table 8). However, this analysis is post-hoc and not prospectively planned. The reviewer re-calculated the BE statistics using only the data from dosing occasions 1 and 2, included subject 1001 in the dataset, and dropped subject 1009. The results show that the two formulations are still not bioequivalent. The reviewer-calculated results are presented in Table 9.

*Reviewer's Comments:*
*-Due to the withdrawal of subject 1009 following dosing occasion 1, the Applicant included a total of 19 subjects in the reference group (uncoated tablets), and 20 subjects in the test group (coated tablets) during the comparative bioavailability portion of the study. However, in the reviewer-calculated analysis, this subject's data was dropped from study. Since this subject did not receive the reference product in this study, inclusion of his/her PK data would not maintain a balanced two-way crossover design. In addition, subject 1001 should be included in the dataset. All subjects including subject 1001 had calculable Kel values.*
*-Because the subject number was relatively small and the inter-subject variability was higher than expected, treating the study as a 2-sequence, 3-way crossover design with scaled average BE was initially evaluated as an alternative to analyzing the data. This would require that TVR demonstrate characteristics of a highly variable drug (≥30% CV in PK parameters for the reference product). However, in this study, the reference product %CV values for $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, and Cmax were 18%, 22%, and 19%, respectively. Thus, the scaled BE approach could not be applied to this dataset.*

**Figure 3 Mean TVR Plasma Concentration vs. Time Profiles by Formulation**

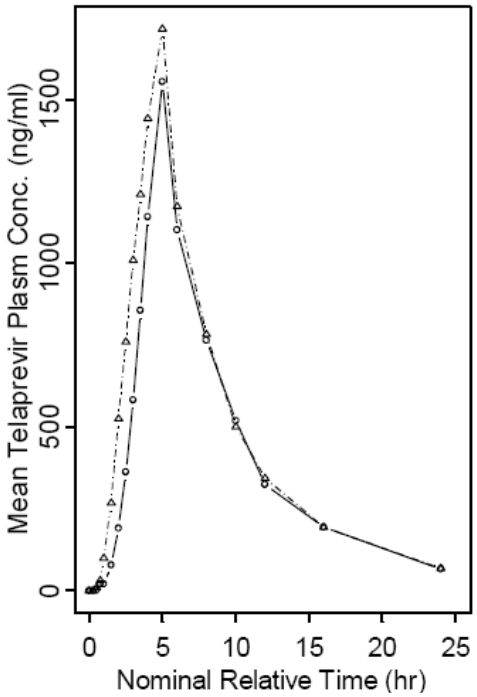


**Table 6 Arithmetic Means (SD) of TVR PK Parameters by Formulation**

| PK Parameter | Uncoated (N=19) | Coated (N=20) |
|---|---|---|
| $C_{max}$ (ng/mL) | 1692.00 (750.9) | 1887.80 (830.5) |
| $AUC_{0\text{-}last}$ (hr*ng/mL) | 9871.12 (5780.11) | 11304.61 (6293.44) |
| $AUC_{0\text{-}\infty}$ (hr*ng/mL) | 10414.42 (6395.59) | 11920.95[b] (6840.44) |
| $t_{max}$ (hr)[a] | 5 (4,8) | 5 (2,8) |
| $t_{1/2}$ (hr) | 4.72 (1.37) | 4.78 (1.53) |
| Cl/F (L/hr) | 99.43 (57.91) | 94.72 (81.35) |
| Vz/F (L) | 652.05 (393.24) | 620.41 (516.08) |

**Table 7 BE Statistical Analysis—Test vs. Reference in Dosing Occasions 1 and 2 (conducted by the Applicant)**

| Comparison | Parameter | Point Estimate (%) of geometric least squares mean ratio | 90% Confidence interval |
|---|---|---|---|
| Coated (test) versus. Uncoated (reference) | $C_{max}$ Ratio | 107.41 | [89.94, 128.26] |
| | $AUC_{0\text{-}last}$ Ratio | 110.70 | [94.52, 129.65] |
| | $AUC_{0\text{-}\infty}$ Ratio[a] | 111.93 | [94.99, 131.90] |

[a] Subject 1001 had >25% extrapolated AUC0-∞ with coated tablet and an indeterminable λz with uncoated tablet

**Table 8 BE Statistical Analysis—Test vs. Reference in Dosing Occasions 1, 2, and 4 (conducted by the Applicant)**

| Comparison | Parameter | Point Estimate (%) of geometric least squares mean ratio | 90% Confidence interval |
|---|---|---|---|
| Coated (test) versus Uncoated (reference) | $C_{max}$ Ratio | 106.66 | [94.11, 120.89] |
| | $AUC_{0\text{-}last}$ Ratio | 102.30 | [93.39, 112.06] |
| | $AUC_{0\text{-}\infty}$ Ratio[a] | 102.50 | [93.04, 112.91] |

[a] Subject 1001 had >25% extrapolated AUC0-∞ with coated tablet and an indeterminable λz with uncoated tablet

**Table 9 BE Statistical Analysis (reviewer-calculated)**

| Parameter | Point estimate of LSM ratio (coated to uncoated) | 90% Confidence interval |
|---|---|---|
| **Cmax** | 1.06 | 89.04-127.36 |
| **$AUC_{0\text{-}last}$** | 1.08 | 91.51-127.61 |
| **$AUC_{0\text{-}inf}$** | 1.09 | 92.10-128.26 |

Although the reviewer-calculated results demonstrate that the two tablets are not statistically bioequivalent, it does not preclude the acceptability/approvability of the coated tablet. Since the coated tablet has higher exposures relative to the uncoated tablet, an issue of

concern would be safety. Since anemia is the only safety issue that has been found to be associated with higher TVR exposure, an examination of the exposure-safety relationship between TVR $AUC_{\tau,ss}$ and probability of anemia provides some rationale in support of the use of the coated tablet as the intended commercial formulation. In a multivariate analysis of the relationship between TVR exposure and probability of anemia in HCV-infected patients, because RBV's regimen in the background primarily drives the relationship, the added contribution of TVR is relatively low. Thus the slope of the relationship between TVR AUC and probability of anemia would be expected to be relatively shallow in the therapeutic range for TVR. A 15% upward shift in AUC exposure would not be expected to significantly change the probability of patients developing anemia (please see the pharmacometrics review in the appendix for further details).

The results of the clinical and bioanalytical study site inspections by DSI indicate that no Form 483s were issued at the clinical site. Several 483s were issued for the bioanalytical site; however, they were either resolved by the bioanalytical site or do not impact the results of the study. (The plasma samples from period 4 [dosing occasion 4] were not used in the determination of bioequivalence in this study.) The final recommendations from the DSI inspector regarding plasma samples are as follows:

- *"Plasma sample data from subjects 01014, 01015, 01016, 01017, 01018, 01019 and 01020 collected 24 hours post-dose in period 4, should be discarded because the integrity of these samples was likely compromised. These plasma samples were stored at room temperature for approximately 8 days, and the stability under these conditions was not evaluated.*
- *The telaprevir plasma concentration for subject 01011, Period 2, 1.5 hrs post-dose, should be 27.4 ng/mL and not 28.1 ng/mL."*

Conclusions

Based on the results of the dose proportionality portion of the study, $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ increased greater than dose proportionally between the 375-mg and 1875-mg doses. However, no conclusions could be made regarding dose proportionality in Cmax in that dose range.

The BA/BE portion of the study showed that the uncoated tablet and the coated tablet are not bioequivalent. However, the acceptability of the to-be-marketed coated tablet would depend on available exposure-safety data for TVR at the potentially higher exposure that would be expected following administration with the coated tablet. A 15% upward shift in AUC exposure would not be expected to significantly change the probability of patients acquiring anemia (please see the pharmacometrics review in the appendix for further details). Thus, the coated tablet is acceptable as it would not be expected to cause a change in efficacy or a significant shift in safety as compared with the uncoated tablet.

**Individual Study Review—VX04-950-101**

Title (Study VX04-950-101)

"A Phase 1b Multiple Dose, Dose-Escalation Study of VX-950 in Healthy Subjects and Hepatitis C Positive Subjects"

Objectives

- To evaluate the safety and tolerability following ascending multiple doses of VX-950 administered to healthy subjects and subjects with hepatitis C
- To investigate the pharmacokinetics of VX-950, following ascending multiple doses of VX-950 administered to healthy subjects and subjects with hepatitis C
- To examine HCV kinetics following ascending multiple doses of VX-950 administered in subjects with hepatitis C

Study Dates and Location(s):
Study initiation: October 21, 2004
Study completion: May 10, 2005
Clinical Sites:

- Pharma Bio-Research Group B.V. (The Netherlands)
- PBR, Clinical Research Unit, University Hospital Groningen (The Netherlands)
- PBR, Medical Screening Center, Zuidlaren (The Netherlands)
- Academic Medical Center (AMC), Department of Gastroenterology and Hepatology (The Netherlands)
- Saarland University Hospital (SUH), Department of Internal Medicine II (Germany)

Study Design

This study was a randomized, 2-part, multiple-dose, blinded, dose-escalation, placebo-controlled study that included 24 healthy subjects in part A and 36 subjects with hepatitis C in part B. Subjects in part A received 1 of the dose regimens below (randomized 6:2, VX-950:placebo). All treatments in both parts were administered in the fasted state.

- Panel 1: VX-950 450 mg q8h X 5 days (or placebo)
- Panel 2: VX-950 750 mg q8h X 5 days (or placebo)
- Panel 3: VX-950 1250 mg q8h X 5 days (or placebo)

HCV-infected subjects in part B received 1 of the following dose regimens (randomized 10:2, VX-950:placebo):

- Panel 4: VX-950 450 mg q8h X 14 days (or placebo)
- Panel 5: VX-950 750 mg q8h X 14 days (or placebo)
- Panel 6: VX-950 1250 mg q8h X 14 days (or placebo). However, this was amended such that each subject was dosed q12h for 14 consecutive days.

*Reviewer's Comments:*
*-The Applicant states that it was expected that adequate plasma concentrations would be achieved when VX-950 was dosed q12h, rather than q8h in panel 6 of part B. Although a 1250 mg q8h regimen was expected to be well tolerated, 1250 mg q12h was expected to yield concentrations within the predicted therapeutic range. Therefore, the dosing frequency was amended to twice daily instead of three times daily.*

Study Doses Used and Dose Rationale

The primary goal of the study was to investigate multiple-dose PK of VX-950 across a range of doses. Thus, these doses (both above and below the therapeutic dose of 750 mg) were chosen in order to explore a range of doses approaching or exceeding the therapeutic limit. VX-950 $IC_{50}$ (240 ng/mL) and $IC_{90}$ (476 ng/mL) values from the replicon assay were used to determine doses that were anticipated to produce therapeutic benefit. A dose of 450 mg was anticipated to yield a median average liver concentration of 4104 ng/mL, which would be approximately 9 times the $IC_{90}$ in 50% of subjects, assuming a liver to plasma ratio of 17. A dose of 750 mg was expected to yield an average liver concentration of 11,906 ng/mL, which would be approximately 25 times the $IC_{90}$ in 50% of subjects, while the 1250 mg dose was expected to yield average liver concentration values up to 57-fold of the replicon assay $IC_{90}$ (27,132 ng/mL).

Formulation(s) Used

VX-950 was provided as a powder formulated as the amorphous form of VX-950 with PVP K30 in an aqueous suspension.

*Key Inclusion Criteria:*

Part A:

-Male and female subjects of non-childbearing potential (defined in females as subjects who were postmenopausal, surgically sterile or hysterectomy without oophorectomy)
-Subjects between 18 to 65 years (inclusive)
-Subjects with a body mass index (BMI) range of 18.5 and 29.0 $kg/m^2$ (inclusive for males) or 18.5 and 32.5 $kg/m^2$ (inclusive for females)
-Subjects judged to be in good health on the basis of medical history, physical examination, and routine laboratory measurements
-Male subjects must have agreed to use a barrier method of contraception during the study and for 90 days following the last dose of study drug
-Subjects whose hematology and clinical chemistry of blood was within normal range or showed no clinically significant deviations (as judged by the investigator)
-Subjects who did not have clinically significant abnormalities in 12-lead ECG, arterial blood pressure (90 to 150 mmHg) and pulse rate (40 to 100 beats per minute [bpm])
-Subjects who agreed to refrain from the concomitant use of herbal dietary supplements, or vitamins during the study dosing period

Part B (all inclusion criteria from above apply in addition to the following):

-Subjects whose alanine aminotransferase (ALT) level was ≤4.0 times the upper limit of the normal (ULN)
-Subjects who had HCV genotype 1 (all subtypes)
-Subjects who had levels of HCV RNA of $\geq 1 \times 10^5$ IU/mL by Roche COBAS TaqMan HCV test® (confirmed by repeat measures of 2 separate samples taken during the prestudy screening period, both of which must have met the defined criteria).

*Key Exclusion Criteria:*

Part A:

-Subjects who tested positive for hepatitis B antigen (HBsAg), HCV antibody, or HIV 1/2 antibody.

-Subjects who had concurrent antiviral therapy (except for antiviral agents approved for the treatment of herpes viruses) within the previous 3 months preceding entry, or the anticipated use of any such therapy during the course of this study
-Subjects with a history of any illness that, in the opinion of the investigator or the subject's general practitioner, might have confounded the results of the study, or posed an additional risk in administering study drugs to the subject
-Subjects who had regular treatment with non-topical medications during 4 weeks before drug administration or topical medications with known systemic absorption (e.g., hydrocortisone cream), with the exception of estrogen replacement therapy (females)
-Subjects who consumed on average more than 2 units of alcoholic drinks per day
-Subjects who regularly consumed an average of more than 8 cups of coffee per day
-Subjects who had a history of drug abuse within 6 months of study entry
-Subjects who had a history of methadone use within 3 months of study entry
-Subjects who had a positive urine screen for drugs of abuse
-Subjects who had participated in an investigational drug study within 90 days before drug administration, or more than 2 drug studies within the past 12 months
-Subjects who had participated in prior clinical studies with VX-950
-Subjects who had donated more than 1 unit of blood (500 mL) within 60 days of the first administration of study drug
-Subjects who had an illness within 5 days before receiving the first dose of study drug, that in the judgment of the investigator, would jeopardize subject safety or study outcome

Part B (all inclusion criteria from above apply in addition to the following):
-Subjects with uncompensated liver disease as shown by the following:

- international normalized ratio [INR] of ≥2.0,
- serum albumin less than the lower limit of normal,
- serum total bilirubin >1.8 times the ULN,
- history of ascites, hepatic encephalopathy or bleeding esophageal varices

-Subjects who had alcohol-related cirrhosis or primary biliary cirrhosis
-Subjects who tested positive for either HBsAg or the HIV antibody

Blood Sampling for PK

Part A: Blood samples for determination of VX-950 and VRT-127394 (R-diastereomer of TLP) plasma concentrations were collected on Days 1 and 5 at pre-dose, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, and 8 (pre-dose 2), 10, 12, 16 hours (pre-dose 3), and 24 hours (pre-dose 1 on Days 2 and 6) post-dose. A trough plasma sample was taken on day 3 at pre-dose.

Part B: Blood samples for determination of VX-950 and VRT-127394 (R-diastereomer of TLP) plasma concentrations were collected on days 1 and 14 at pre-dose, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, and 8 (pre-dose 2 for Panels 4 and 5), 10, 12 hours post-dose 1 (pre-dose 2 for Panel 6), 16 (pre-dose 3 for Panels 4 and 5), and 24 hours (pre-dose 1 on days 2 and 15) post-dose. A trough plasma sample was taken on days 3, 7, and 11 (pre-dose 1).

Bioanalytical Results

Plasma samples were analyzed for VX-950 by HPLC with tandem mass spectrometric detection (LC-MS/MS) by (b) (4). Samples were received in frozen condition from November 8, 2004 through April 15, 2005. Samples were analyzed between November 8, 2004 and June 1, 2005. The samples were stored at -70°C. The

maximum sample possible storage time until analysis was 205 days, which is within the validated long-term frozen stability duration of 638 days.

The calibration standard concentrations for both VX-950 and VRT-127394 were 2.0, 4.0, 10.0, 50.0, 200.0, 500, 800, and 1000 ng/mL. The mean accuracy and precision estimates at each TLP standard concentration are presented in Tables 1 and 2 below. All accuracy and precision (%CV) values were within the acceptable range (≤20% from nominal at the LLOQ concentration and ≤15% from nominal at all other concentrations). Quality control concentrations were 6.0, 250, and 800 ng/mL. The mean accuracy ranged from 102 to 108.4% for VX-950 and 102.3 to 110.5% for VRT-127394. The mean precision ranged from 7.1 to 10.6% for VX-950 and 8 to 8.6% for VRT-127394.

**Table 1 Mean Calibration Standard Concentrations and Statistics for TLP**

| Nominal Concentrations (ng/ml) | | 2.00 | 4.00 | 10.0 | 50.0 | 200 | 500 | 800 | 1000 |
|---|---|---|---|---|---|---|---|---|---|
| mean | (ng/ml) | 1.98 | 4.09 | 9.88 | 48.6 | 204 | 499 | 820 | 983 |
| SD | (ng/ml) | 0.13 | 0.26 | 0.57 | 2.7 | 12 | 23 | 48 | 59 |
| CV | (%) | 6.5 | 6.5 | 5.7 | 5.6 | 5.8 | 4.6 | 5.8 | 6.0 |
| accuracy | (%) | 99.2 | 102.3 | 98.8 | 97.1 | 101.9 | 99.8 | 102.5 | 98.3 |
| n | | 49 | 49 | 49 | 49 | 49 | 47 | 50 | 50 |

**Table 2 Mean Calibration Standard Concentrations and Statistics for VRT-127394**

| Nominal Concentrations (ng/ml) | | 2.00 | 4.00 | 10.0 | 50.0 | 200 | 500 | 800 | 1000 |
|---|---|---|---|---|---|---|---|---|---|
| mean | (ng/ml) | 1.99 | 4.07 | 9.82 | 49.1 | 204 | 504 | 824 | 959 |
| SD | (ng/ml) | 0.13 | 0.25 | 0.62 | 2.0 | 13 | 27 | 47 | 53 |
| CV | (%) | 6.7 | 6.2 | 6.3 | 4.1 | 6.3 | 5.4 | 5.8 | 5.5 |
| accuracy | (%) | 99.5 | 101.6 | 98.2 | 98.2 | 102.1 | 100.8 | 103.0 | 95.9 |
| n | | 46 | 47 | 45 | 45 | 47 | 48 | 47 | 47 |

*Reviewer's Comments:*
*-The bioanalytical results for this study are acceptable.*

Results

In Part A, 24 subjects were enrolled and completed the study. In Part B, 37 subjects were enrolled in the study and 34 subjects completed the study. Two subjects withdrew before receiving their first dose of study drug and one subject was withdrawn at the discretion of the investigator due to acute gastrointestinal illness on the night before dosing. One subject in panel 6 who discontinued was replaced by a subject who completed the study.

*Demographics*

| Variable | Placebo (N=6) | VX-950 450 mg q8h (N=6) | VX-950 750 mg q8h (N=6) | VX-950 1250 mg q8h (N=6) | VX-950 Total (N=18) | Total (N=24) |
|---|---|---|---|---|---|---|
| Sex, n (%) | | | | | | |
| Male | 6 (100) | 5 (83.3) | 6 (100) | 5 (83.3) | 16 (88.9) | 22 (91.7) |
| Female | -- | 1 (16.7) | -- | 1 (16.7) | 2 (11.1) | 2 (8.3) |
| Race, n (%) | | | | | | |
| Caucasian | 6 (100) | 6 (100) | 4 (66.7) | 6 (100) | 16 (88.9) | 22 (91.7) |
| Black | -- | -- | 1 (16.7) | -- | 1 (5.6) | 1 (4.2) |
| Other | -- | -- | 1 (16.7) | -- | 1 (5.6) | 1 (4.2) |
| Age (years) | | | | | | |
| Mean | 29.0 | 38.8 | 39.2 | 41.0 | 9.7 | 37.04 |
| SD | 16.70 | 16.09 | 19.59 | 19.68 | 17.43 | 17.54 |
| Median | 22.5 | 36.0 | 32.5 | 38.0 | 36.0 | 26.5 |
| Min, Max | 21, 63 | 23, 62 | 22, 64 | 19, 65 | 19, 65 | 19, 65 |
| BMI ($kg/m^2$) | | | | | | |
| Mean | 22.13 | 22.98 | 23.15 | 23.62 | 23.25 | 22.97 |
| SD | 1.835 | 2.454 | 2.226 | 1.991 | 2.114 | 2.069 |
| Median | 22.50 | 22.35 | 23.30 | 23.95 | 23.30 | 23.15 |
| Min, Max | 19.6, 24.2 | 19.9, 26.4 | 20.5, 26.9 | 20.1, 25.8 | 19.9, 26.9 | 19.6, 26.9 |

*Safety*

In part A, 20 of the 24 subjects (83.3%) reported at least 1 AE during the study, although these were all, with 1 exception, mild in severity and resolved without treatment. One subject (750 mg VX-950) experienced a severe AE of syncope vasovagal, however, this event was not considered to be related to the study drug. No SAEs were reported for subjects in part A, and there were no discontinuations because of AEs. The number of subjects reporting AEs that were considered to be at least possibly drug-related was higher at the 750 and 1250 mg dose levels compared to placebo and 450 mg dose level, although all AEs considered at least possibly related to study drug were mild in severity.

In part B, 28 of the 34 subjects (82.4%) reported at least 1 AE during the study. With the exception of 4 moderate AEs, all events were considered to be mild in severity, and resolved without treatment. No serious or SAEs were reported for subjects in part B and there were no discontinuations because of AEs. The number of subjects reporting AEs, which were at least possibly or probably drug-related, was generally similar at each dose level of VX-950 and was comparable to placebo. All of those events were mild in severity. (Please see the medical officer's review for further details.)

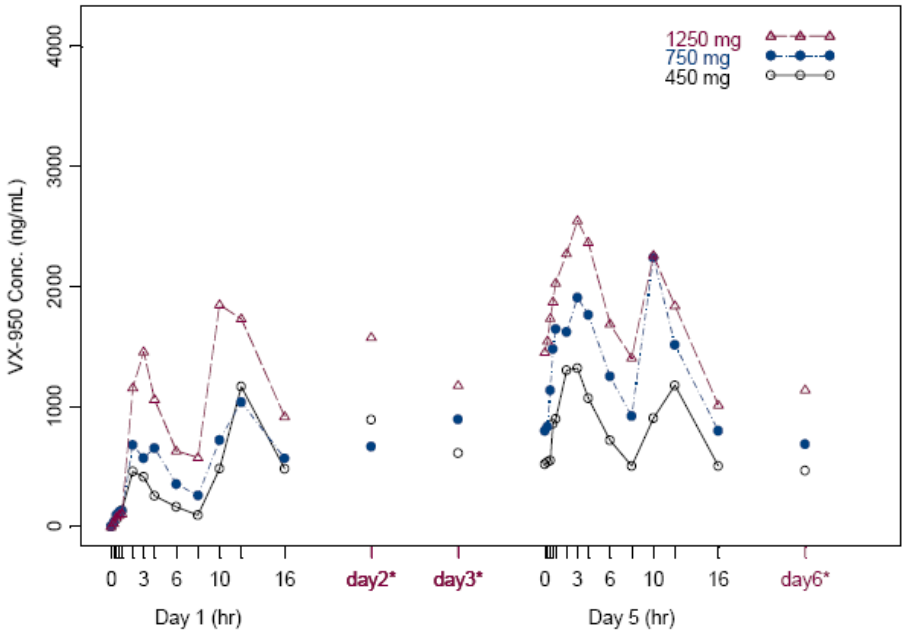
*Pharmacokinetics*

Based on noncompartmental analysis of VX-950 PK, $AUC_{0\text{-}8h}$ increased with increasing dose for both healthy subjects and HCV-infected subjects (Tables 3 and 4). However, the increase was more proportional with dose in healthy subjects than in infected subjects. The accumulation ratio at the therapeutic dose (750 mg) was higher for healthy subjects from day 1 to day 5 than in infected subjects from day 1 to day 14 (accumulation ratios were 3.1 vs. 1.8, respectively). Additionally, mean day 5 $AUC_{8h}$ exposure increased by 47% and 30% while the dose increased (by 67%) from 450 mg to 750 mg and from 750 mg to 1250 mg, respectively, in healthy subjects. In HCV-infected subjects, mean day 14 $AUC_{8h}$ exposure increased by 5% and 9% while the dose increased (by 67%) from 450 mg to 750 mg and from 750 mg to 1250 mg, respectively.

Based on the Ctrough values obtained in part A, steady-state does not appear to be reached until day 6 for the therapeutic dose. The peak Ctrough was observed at day 3 (similar to

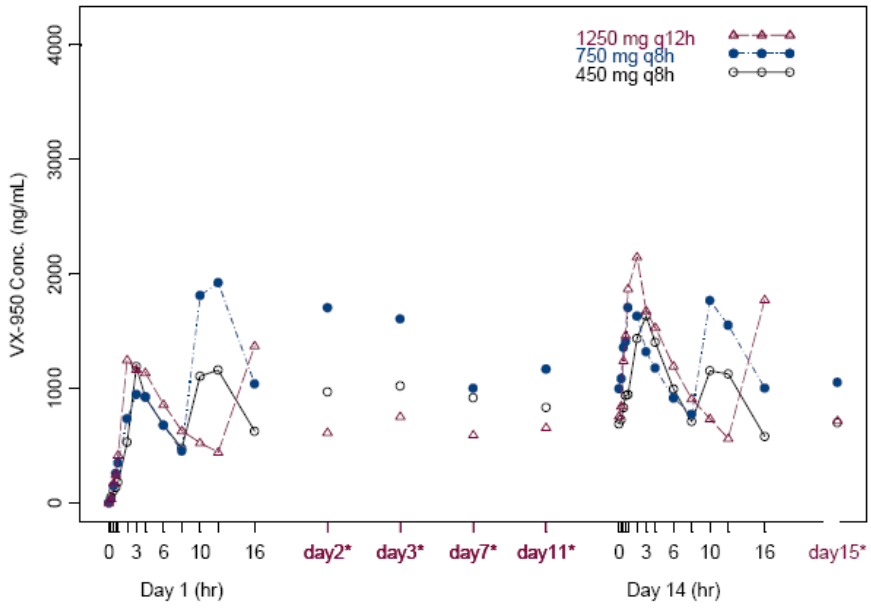
VX-950 multiple-dose results in other studies in healthy subjects) and declined until the last day of collection on day 6 (Figure 1). Similarly, in HCV-infected subjects, Ctrough values did not appear to stabilize until after day 7 (Figure 2).

**Figure 1 Median VX-950 Concentration-Time Profile for Healthy Subjects (Part A)**




* Values for Days 2, 3, and 6 are trough concentrations.

**Figure 2 Median VX-950 Concentration-Time Profile for HCV-Infected Subjects (Part B)**




* Values for Days 2, 3, 7, 11, and 15 are trough concentrations.

Although the elimination half-lives were generally similar between the two populations (Table 5), the number of evaluable subjects for this parameter was limited due to the sampling

scheme that was limited to the dosing interval only. (Thus, only subjects whose ratio of AUC to $AUC_{inf}$ did not exceed 30% were included in the calculation.) The median Cmax values at steady-state for part A were 1344, 1997, 2655 ng/mL for the 450 mg q8h, 750 mg q8h, and 1250 mg q8h regimen, respectively. The median Cmax values at steady-state for part B were 1919, 1722, 2147 ng/mL for the 450 mg q8h, 750 mg q8h, and 1250 mg q12h regimens, respectively (data not shown).

Exposure to VRT-127394 was generally proportional to dose at steady-state in healthy subjects. Similar to VX-950, mean $AUC_{0-8h}$ increased less proportionally with dose in HCV-infected subjects (Table 4).

A population PK analysis was also performed for this study. The results of that analysis and a review of the appropriateness of the selected model will be discussed in the pharmacometrics portion of this review (Appendix 2**).

**Table 3 VX-950 and VRT-127394 $AUC_{0-8}$ Values (ng*hr/mL) for Healthy Subjects (Part A)**

| Analyte, Time Point | VX-950 Dose | n | Median | Mean | CV |
|---|---|---|---|---|---|
| VX-950, Day 1 | 450 | 6 | 1996 | 2039 | 64% |
| | 750 | 6 | 3478 | 3766 | 45% |
| | 1250 | 6 | 6626 | 6619 | 51% |
| VX-950, Day 5 | 450 | 6 | 6991 | 7854 | 37% |
| | 750 | 6 | 10520 | 11554 | 33% |
| | 1250 | 6 | 15923 | 15045 | 26% |
| VRT-127394, Day 1 | 450 | 6 | 468 | 645 | 80% |
| | 750 | 6 | 1062 | 1024 | 41% |
| | 1250 | 6 | 2471 | 2435 | 54% |
| VRT-127394, Day 5 | 450 | 6 | 3574 | 3937 | 35% |
| | 750 | 6 | 5201 | 5630 | 40% |
| | 1250 | 6 | 10580 | 10117 | 33% |

**Table 4 VX-950 and VRT-127394 $AUC_{last}$ Values (ng*hr/mL) for HCV-infected Subjects (Part B)**

| Analyte, Time Point | VX-950 Dose | N | $t_{last}$ | Median | Mean | CV |
|---|---|---|---|---|---|---|
| VX-950, Day 1 | 450 | 10 | 8 | 5512 | 5593 | 51% |
| | 750 | 8 | 8 | 5612 | 5699 | 39% |
| | 1250[a] | 10 | 8 | 7135 | 7194 | 30% |
| | | | 12 | 9224 | 9426 | 29% |
| VX-950, Day 14 | 450 | 10 | 8 | 9276 | 9626 | 37% |
| | 750 | 8 | 8 | 9476 | 10078 | 36% |
| | 1250[a] | 10 | 8 | 11231 | 11021 | 29% |
| | | | 12 | 13923 | 13867 | 26% |
| VRT-127394, Day 1 | 450 | 10 | 8 | 2501 | 2360 | 43% |
| | 750 | 8 | 8 | 2039 | 2254 | 43% |
| | 1250[a] | 10 | 8 | 2194 | 2372 | 29% |
| | | | 12 | 3489 | 3557 | 28% |
| VRT-127394, Day 14 | 450 | 10 | 8 | 5088 | 5705 | 50% |
| | 750 | 8 | 8 | 6129 | 6174 | 34% |
| | 1250[a] | 10 | 8 | 5606 | 5469 | 27% |
| | | | 12 | 7196 | 7291 | 23% |

[a] AUC data for the 1250 mg group are shown for a $t_{last}$ of 8 hours to facilitate comparison with the other dose groups and for a $t_{last}$ of 12 hours because that was the dosing interval for the 1250 mg group. $t_{last} = 8$ then $AUC_{last} = AUC_{0-8}$ ; $t_{last} = 12$ then AUClast = $AUC_{0-12}$

**Table 5 Summary Table for VX-950 Apparent Elimination Half-life (Part A and Part B)**

| Part | Day | Dose | n | Median | Mean | CV | |
|---|---|---|---|---|---|---|---|
| A | 1 | 450 | 4 | 2.61 | 2.76 | 17% | Healthy subjects |
| | | 750 | 4 | 2.53 | 2.60 | 17% | |
| | | 1250 | 3 | 2.74 | 2.68 | 6% | |
| | 5 | 450 | 3 | 3.46 | 3.58 | 8% | |
| | | 750 | 1 | 3.20 | 3.20 | | |
| | | 1250 | 2 | 3.93 | 3.93 | 20% | |
| B | 1 | 450 | 4 | 2.78 | 2.68 | 24% | HCV-infected subjects |
| | | 750 | 4 | 3.18 | 3.20 | 15% | |
| | | 1250 | 7 | 5.04 | 4.68 | 22% | |
| | 14 | 450 | 5 | 3.04 | 3.34 | 19% | |
| | | 750 | 1 | 3.68 | 3.68 | | |
| | | 1250 | 8 | 4.36 | 4.69 | 22% | |

*Reviewer's Comments:*
*-Cmax values at the 750 mg q8h dose are lower than for the 450 mg q8h dose in HCV-infected subjects, suggesting that the extent of absorption of VX-950 decreases with increasing dose in that population.*
*-In both populations, Ctrough values increased to a maximum around day 3 and then declined to steady-state by day 6 or after. This is a similar PK profile for ritonavir where there is a known mixed effect on CYP3A4 metabolism. RTV's inhibition of the enzyme predominates initially (causing an increase in plasma concentrations) until the CYP3A4 induction property of RTV begin to manifest itself (causing a decline in the initial increase in plasma concentrations). Overall, the net effect of RTV on CYP3A4 is inhibition, as is the case for VX-950.*

*Efficacy (Analysis of HCV RNA Levels)*

Median HCV RNA levels in the VX-950 dose groups decreased rapidly and substantially in part B of the study (Figure 3). The mean maximal change in HCV RNA from baseline during the treatment phase were -3.7, -4.6, and -3.4 $\log_{10}$ IU/mL for the 450 mg q8h, 750 mg q8h, and 1250 mg q12h dosing regimens, respectively (Table 6). In contrast, the median HCV RNA levels in subjects dosed with placebo showed little change during the dosing period. All 3 VX-950 dosing regimens showed similar declines up to day 3 of dosing. However, the 450 mg q8h and 1250 mg q12h groups showed evidence of rebound during the treatment period (within 14 days). In the 750 mg q8h group, the median HCV RNA levels continued to decrease throughout the treatment period of the trial. As expected, median HCV RNA levels rebounded in all dose groups following treatment cessation at day 14. (Please see the clinical virologist's review for further discussion.)

**Figure 3 Median HCV RNA Levels by Dose Group Through 2-Week Follow-up, Part B**

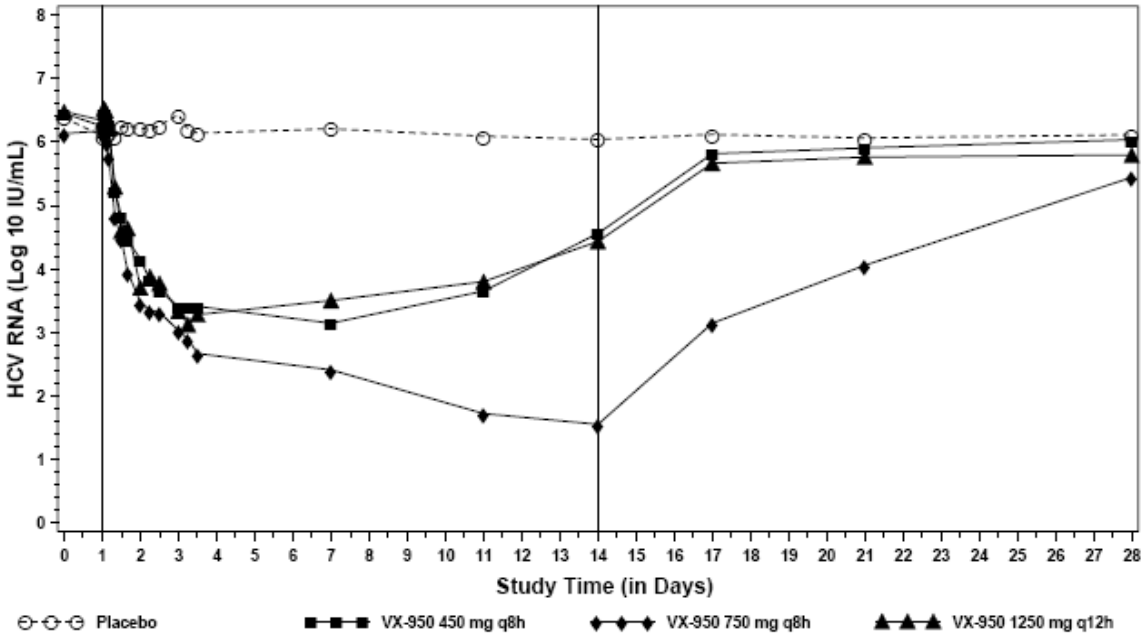



**Table 6 Mean Maximal Change from Baseline in HCV RNA During the Dosing Period (Through Day 14)**

| Parameter | Placebo (N=6) | VX-950 450 mg q8h (N=10) | VX-950 750 mg q8h (N=8) | VX-950 1250 mg q12h (N=10) |
|---|---|---|---|---|
| Mean | -0.3973 | -3.7040 | -4.6529 | -3.4539 |
| SD | 0.09040 | 0.78078 | 0.96417 | 0.34018 |
| Median | -0.4263 | -3.4556 | -4.7718 | -3.4947 |
| Min, Max | -0.484, -0.268 | -5.125, -2.977 | -6.305, -3.488 | -3.833, –2.787 |
| 95% CI | -0.4922, -0.3025 | -4.2625, -3.1455 | -5.4590, -3.8469 | -3.6973, -3.2106 |

*Reviewer's Comments:*
*-The results of this study provide a sufficient comparison of PK between the two populations as well as information on the relative differences in PK at different dose levels. However, the absolute exposure values are not as relevant to the overall characterization of PK/PD relationships for TVR since the suspension used in this study has substantially lower bioavailability than the tablet formulation that was used in the phase 2 and 3 studies. Thus, the dose/exposure relationship observed in this study would not directly apply to studies conducted with the tablet. For instance, in this study, the Ctrough values for the 1250 mg q12h regimen were substantially lower than the 750 mg q8h regimen at all Ctrough assessment periods (although it is still higher than the reported in vitro $IC_{90}$ value of ~476 ng/mL for VX-950). This lower Ctrough translated into lower antiviral activity throughout the treatment period and detection of viral rebound as early as day 7 on treatment in the 1250 mg q12h group. However, in a phase 2 study using TVR tablets (C208) comparing the 750 mg q8h and 1125 mg q12h regimens, although the Ctrough values were still lower for the 1125 mg q12h regimen, the*

*$SVR24_{actual}$ rates were similar (ranging from 81.0% to 85.0%) between the two groups. Thus, a q12 regimen has the potential to provide similar efficacy as the 750 mg q8h regimen, provided the Ctrough values are substantially higher than the in vitro $IC_{90}$ value. Note: based on these phase 2 study results, the Applicant has proposed a phase 3 study comparing these two regimens.*

Conclusions

This multiple-dose, dose escalation study in healthy subjects and HCV-infected subjects provided comparisons of PK data between the two different populations as well as formed the basis for dose selection for phase 3 studies with TVR. The PK data indicate that TVR most likely has mixed effects on CYP3A4 metabolism and takes 7 days or longer to reach steady-state in HCV-infected patients. PK in HCV-infected subjects is non-linear as exposures increase less than dose proportionally in that population. The accumulation factor in infected patients (1.8) is also lower than in healthy subjects (3.1).

The HCV RNA data show that the 750 mg q8h regimen appeared to provide the most robust antiviral activity during the 14-day treatment period. This regimen provided the highest mean maximal decline in HCV RNA as well as continued decline in mean HCV RNA throughout the dosing period (without evidence of rebound). Based on the safety and viral decline data from this study, it appears that the 750 mg q8h regimen is the most appropriate dose for further study.

### 3.2.3 Intrinsic Factors

**Individual Study Review—VX06-950-006**

Title (Study VX06-950-006)

"A Phase 1 Study to Assess the Safety and Pharmacokinetics of Telaprevir (VX-950) in Subjects with Mild Hepatic Impairment"

Objectives

- To compare the pharmacokinetics of telaprevir following multiple oral doses in healthy subjects and subjects with mild hepatic impairment.
- To compare the pharmacokinetics of telaprevir following a single oral dose in healthy subjects and subjects with mild hepatic impairment.
- To assess the safety of single and multiple doses of telaprevir in subjects with mild hepatic impairment.

Study Dates and Location(s):
Study initiation: July 18, 2006 (first subject's first dose)
Study completion: February 1, 2007 (date last subject completed follow-up)
Clinical Sites: Applied Analytical Industries (AAI) Deutschland GmbH & Co KG and Universitätsklinikum Universität Ulm (University of Ulm), Germany.

Study Design

This was an open-label study that included 10 subjects with mild hepatic impairment (defined as Child-Pugh A; group A) and 10 healthy subjects (group B). The first 5 Child-Pugh A subjects that were enrolled received a single 750-mg dose of telaprevir on day 1 (single-dose day 1). The single-dose Day 1 PK results from these subjects were compared to the highest telaprevir exposure obtained in prior telaprevir studies to determine whether a dose reduction was required for continuation in the multiple dose treatment period. Following confirmation of the dose level subjects initiated telaprevir dosing every 8 hours (q8h) on multiple-dose day 1 through multiple-dose day 5. The final dose was administered on the morning of multiple-dose day 6. The remaining subjects received the same number of doses (single dose followed by multiple doses through day 6). After the second set of 5 Child-Pugh A subjects completed multiple-dose day 7, the 10 healthy subjects were enrolled in the study. Again, all doses were administered in the same fashion as group A.

Study Doses Used

| Group - Subjects<br>Subject Numbers | Single-dose<br>Day 1 | Multiple-dose Day 1-5 | Multiple-dose Day 6[a] |
|---|---|---|---|
| **Group B – Healthy Subjects** | | | |
| 01011-01020 | 750 mg | 750 mg q8h | 750 mg |
| **Group A- Child-Pugh A Subjects** | | | |
| 01001-01005 | 750 mg | 750 mg q8h | 750 mg |
| 01006-01010 | 750 mg | 750 mg q8h | 750 mg |

Dose Rationale

The dose chosen for this study is the clinical dose used in the phase 3 studies. However, the Applicant did have a provision to modify the dose if the exposure was higher than expected in the first 5 Child-Pugh A subjects.

Formulation(s) Used

A 250-mg telaprevir tablet was used for this study. The 375-mg tablet was used in the phase 3 studies. A bioequivalence study showed that the 2 tablet formulations of telaprevir were bioequivalent when given as a single 750-mg dose in the fasted state. However, in the presence of food (medium-fat breakfast of 472 kcal, 34% kcal fat), the 375-mg tablet resulted in approximately 32% higher telaprevir exposure compared to the 250-mg tablet. In the current study, the 250-mg tablets were administered with a medium-fat meal or large snack.

**C-P A subjects**

*Key Inclusion Criteria:*

-Hepatically impaired male subjects 18 to 65 years of age
-Hepatically impaired female subjects 18 to 65 years of age who were not of child-bearing potential defined as postmenopausal (12 months of spontaneous amenorrhea at screening) or surgically sterile (bilateral oophorectomy with or without hysterectomy at screening) or hysterectomy without oophorectomy
-Had a Child-Pugh total score of 5 or 6 (for Child-Pugh A classification) based on assessment of liver function at screening
-Male subjects must have used 2 forms of contraception, including 1 barrier method (e.g., a condom with spermacide) while receiving telaprevir and for 90 days after last dose of telaprevir

*Key Exclusion Criteria:*

-Participated in a clinical study involving the administration of either an investigational or a marketed drug within 2 months or 5 half-lives (whichever is longer) before the screening visit
-Participated in a study with a new molecular entity during the previous 3 months or in more than 4 studies with an investigational drug within the last 12 months
-Had taken any drug known to be an enzyme inducer or inhibitor, especially CYP3A enzymes or any drug known to affect drug absorption, within 4 weeks of the start of dosing to the end of the study
-Consumed herbal medications or dietary supplements (e.g., St. John's Wort, ginkgo biloba, garlic supplements), vitamins, grapefruit, or grapefruit juice within 14 days before the first administration of study drug
-Tested positive for HCV Ab, HBsAg, HIV1 Ab, HIV2 Ab, or drug screen.

**Healthy subjects**

*Key Inclusion Criteria:*

-Healthy male subjects 18 to 65 years of age
-Healthy female subjects 18 to 65 years of age who were not of child-bearing potential defined as postmenopausal (12 months of spontaneous amenorrhea at screening) or surgically sterile (bilateral oophorectomy with or without hysterectomy at screening) or hysterectomy without oophorectomy

-Matching with the Child-Pugh A subjects (Group A) for sex, body mass index (BMI; ±4 kg/m2), and age (±5 years).
-Male subjects must have used 2 forms of contraception, including 1 barrier method (e.g., a condom with spermacide) of contraception while receiving telaprevir and for 90 days after the last dose of telaprevir

*Key Exclusion Criteria:*
-Participated in a clinical study involving administration of either an investigational or a marketed drug within 2 months or 5 half-lives (whichever is longer) before the screening visit.
-Participated in a study with a new molecular entity during the previous 3 months or in more than 4 studies with an investigational drug within the last 12 months
-Currently taking a course of medication or medication on a regular basis, regardless of whether it was prescribed
-Had taken any drug known to be an enzyme inducer or inhibitor, especially of CYP3A enzymes or any drug known to affect drug absorption, within 4 weeks of the start of dosing to the end of the clinical phase of the study
-Consumed herbal medications or dietary supplements (e.g., St. John's Wort, ginkgo biloba, garlic supplements), vitamins, grapefruit, or grapefruit juice within 14 days before the first dose of study drug
-Tested positive for HCV Ab, HBsAg, HIV1 Ab, HIV2 Ab, or drug screen.

Blood Sampling for PK

Blood samples for determination of telaprevir and VRT-127394 (R-diastereomer of TVR) plasma concentrations were collected at predose and 0.25, 0.5, 0.75, 1, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 16, and 24 hours post-dose after the first dose on study (single-dose Day 1) and the last dose on study (multiple-dose Day 6). In addition, predose blood samples were collected before the morning dose on multiple-dose Days 1, 2, 3, 4, and 5.

Bioanalytical Results

Plasma samples were analyzed for TVR and VRT-127394 by HPLC with tandem mass spectrometric detection. Samples were received in frozen condition on four separate dates: August 1, 2006, August 30, 2006, November 7, 2006 and February 1, 2007. The samples were stored at -70°C. The maximum sample storage until analysis was 19 days, which is within the validated long-term frozen stability duration of 6 months.

The calibration standard concentrations for both TVR and VRT-127394 were 2.0, 4.0, 10.0, 50.0, 200.0, 500, 800, and 1000 ng/mL. The mean accuracy and precision estimates at each TVR and VRT-127394 standard concentration are presented in Tables 1 and 2, respectively, below. All accuracy and precision (%CV) values were within the acceptable range (≤20% from nominal at the LLOQ concentration and ≤15% from nominal at all other concentrations). Quality control concentrations for both analytes were 6.0, 250, and 800 ng/mL. The mean accuracy ranged from 99.3 to 101.3% for TVR and 98.3 to 100.9% for VRT-127394. The mean precision ranged from 3.6 to 4.9% for TVR and 6.7 to 10.1% for VRT-127394.

**Table 1 Mean Calibration Standard Concentrations and Statistics for TVR**

| Nominal Concentrations (ng/ml) | 2.00 | 4.00 | 10.0 | 50.0 | 200 | 500 | 800 | 1000 |
|---|---|---|---|---|---|---|---|---|
| Mean (ng/ml) | 2.04 | 3.97 | 9.33 | 49.4 | 206 | 505 | 802 | 1031 |
| SD (ng/ml) | 0.1 | 0.2 | 0.3 | 2.2 | 4.7 | 14.0 | 24.0 | 52.4 |
| CV (%) | 7.3 | 4.5 | 3.5 | 4.4 | 2.3 | 2.8 | 3.0 | 5.1 |
| Accuracy (%) | 101.8 | 99.2 | 93.3 | 98.7 | 102.8 | 100.9 | 100.2 | 103.1 |
| n | 22 | 22 | 22 | 22 | 22 | 21 | 22 | 22 |

**Table 2 Mean Calibration Standard Concentrations and Statistics for VRT-127394**

| Nominal Concentrations (ng/ml) | 2.00 | 4.00 | 10.0 | 50.0 | 200 | 500 | 800 | 1000 |
|---|---|---|---|---|---|---|---|---|
| Mean (ng/ml) | 2.02 | 3.95 | 9.82 | 50.3 | 202 | 501 | 810 | 992 |
| SD (ng/ml) | 0.1 | 0.2 | 0.6 | 3.0 | 9.6 | 26.0 | 37.0 | 44.4 |
| CV (%) | 5.7 | 5.3 | 5.9 | 5.9 | 4.7 | 5.2 | 4.6 | 4.5 |
| Accuracy (%) | 101.0 | 98.8 | 98.2 | 100.6 | 100.8 | 100.2 | 101.3 | 99.2 |
| n | 17 | 18 | 18 | 18 | 17 | 17 | 18 | 17 |

*Reviewer's Comments:*
*-The bioanalytical results for this study are acceptable.*

Results

A total of 20 subjects, 10 Child-Pugh A subjects and 10 healthy subjects were planned for this study. Ten subjects in each group received at least 1 dose of telaprevir and were included in the safety analysis. Two subjects in each group discontinued study drug due to adverse events; thus only 8 subjects in each group (16 total) completed the study.

*Demographics*

| Healthy Subjects | | | | Child-Pugh A Subjects | | | |
|---|---|---|---|---|---|---|---|
| **Subject Number** | **Age (years)** | **Sex** | **BMI ($kg/m^2$)** | **Subject Number** | **Age (years)** | **Sex** | **BMI ($kg/m^2$)** |
| 1011 | 62 | Male | 30.4 | 1001 | 61 | Male | 36.4 |
| 1013 | 62 | Male | 28.4 | 1002 | 65 | Male | 25.6 |
| 1012 | 50 | Male | 28.4 | 1004 | 55 | Male | 28.7 |
| 1014 | 62 | Female | 27.3 | 1006 | 65 | Female | 31.2 |
| 1016 | 63 | Male | 25.8 | 1007 | 57 | Male | 25.6 |
| 1019 | 53 | Female | 38.7 | 1008 | 53 | Female | 39.4 |
| 1017 | 52 | Male | 29.8 | 1009 | 52 | Male | 30.6 |

*Safety*

A total of 18 AEs in 7 subjects were moderate in severity and considered related to study drug. The most common moderate AEs were diarrhea (4 subjects), headache (3 subjects), and pollakiuria, hemorrhagic diarrhea, and rash (2 subjects each). The remaining moderate AEs of vomiting, hematochezia, painful defecation, erythema, and muscle spasms occurred in 1 subject each. Mild and moderate rash (1 of each severity in different body locations) and erythema (2 of each severity in different body locations) and a mild adverse event of pruritus all reported in

subject 01005 and 2 mild adverse events of erythema (in 2 different body locations) in subject 01003 required treatment with concomitant medication and led to premature discontinuation of study drug during the multiple-dose treatment period.

Two healthy subjects (group B) discontinued prematurely due to adverse events. These adverse events included moderate pruritus and mild papular rash in 1 subject and moderate peripheral edema in the other subject. In Child-Pugh A subjects (group A), 1 subject discontinued due to mild erythema and a second subject discontinued due to mild pruritus, moderate rash (exanthema both arms), mild rash (exanthema upper body), and mild and moderate erythema (2 body locations for each severity).

*Pharmacokinetics*

Several PK analyses were performed within this study. First, single-dose PK parameters for both TVR and VRT-127394 were assessed (Tables 3 and 4 below). The results show that for TVR Tmax, $AUC_{inf}$, half-life, and clearance, mean values between healthy subjects and subjects with mild hepatic impairment were similar. Cmax and $AUC_{0-8h}$ values were approximately 18% and 12% lower, respectively, in C-P A subjects as compared with healthy subjects. However, these differences would likely not be considered clinically significant. Similarly, VRT-127394 exposures were not significantly different between the two groups of subjects. Again, the largest differences were in VRT-127394 Cmax and $AUC_{0-8h}$ values, which were approximately 20% and 15% lower, respectively, in the C-P A subjects than the healthy subjects.

**Table 3 Summary TVR PK Parameters—Single dose**

| **Mean ± SD** | **Cmax** (ng/mL) | **Tmax** (hr) | **$AUC_{0-8h}$** (ng*hr/mL) | **$AUC_{inf}$** (ng*hr/mL) | **$T_{1/2}$** (hr) | **Cl/F** (L/hr) |
|---|---|---|---|---|---|---|
| Healthy (n=10) | 2070 ± 673 | 3.55 ± 1.09 | 9643 ± 3757 | 14406 ± 5708 | 4.5 ± 0.67 | 61 ± 25 |
| C-P A (n=10) | 1699 ± 549 | 3.56 ± 1.14 | 8530 ± 3131 | 14368 ± 5277 | 5.6 ± 0.97 | 59 ± 24 |

**Table 4 Summary VRT-127394 PK Parameters—Single dose**

| **Mean ± SD** | **Cmax** (ng/mL) | **Tmax** (hr) | **$AUC_{0-8h}$** (ng*hr/mL) | **$AUC_{inf}$** (ng*hr/mL) | **$T_{1/2}$** (hr) | **Cl/F** (L/hr) |
|---|---|---|---|---|---|---|
| Healthy (n=10) | 666 ± 268 | 4.95 ± 1.46 | 3207 ± 1388 | 6461 ± 2793 | 5.4 ± 0.99 | ND |
| C-P A (n=10) | 525 ± 207 | 5.55 ± 2.11 | 2725 ± 1084 | 6884 ± 2697 | 6.6 ± 1.31 | ND |

ND=not determined

Following six days of dosing with TVR 750 mg q8h, an approximately 2-fold accumulation was observed with respect to $AUC_{0-8h}$ for both TVR and its diastereomer when compared to a single dose. This accumulation ratio is similar between the two groups, suggesting that no additional accumulation occurs in subjects with mild impairment as compared with healthy subjects. Following multiple dosing, C-P A subjects had slightly lower TVR exposure than healthy subjects (Table 5). Cmax was lower by ~12% and $AUC_{0-8h}$ was lower by ~16% in subjects with mild hepatic impairment. Based on geometric least squares analysis, the 90% confidence intervals were outside the routine bioequivalence limits of 80-125% (Table 7).

However, it is unlikely that the differences between the two populations following multiple dosing are clinical relevant.

**Table 5 Summary TVR PK Parameters—Multiple dose**

| **Mean ± SD** | **Cmax** (ng/mL) | **Tmax** (hr) | **$AUC_{0-8h}$** (ng*hr/mL) | **$AUC_{inf}$** (ng*hr/mL) | **$T_{1/2}$** (hr) | **Cl/F** (L/hr) |
|---|---|---|---|---|---|---|
| Healthy (n=8) | 3425 ± 907 | 1.75 ± 0.93 | 20170 ± 5036 | ND | 6.2 ± 1.26 | 22 ± 6 |
| C-P A (n=8) | 3009 ± 505 | 1.50 ± 0.54 | 16879 ± 2944 | ND | 8.3 ± 2.21 | 23 ± 7 |

**Table 6 Summary VRT-127394 PK Parameters— Multiple dose**

| **Mean ± SD** | **Cmax** (ng/mL) | **Tmax** (hr) | **$AUC_{0-8h}$** (ng*hr/mL) | **$AUC_{inf}$** (ng*hr/mL) | **$T_{1/2}$** (hr) | **Cl/F** (L/hr) |
|---|---|---|---|---|---|---|
| Healthy (n=8) | 1814 ± 407 | 2.94 ± 1.50 | 12514 ± 3062 | ND | 6.5 ± 1.21 | ND |
| C-P A (n=8) | 1636 ± 369 | 1.69 ± 1.13 | 10759 ± 2546 | ND | 9.4 ± 3.08 | ND |

ND=not determined

**Table 7 Geometric Least Squares Mean Ratios and 90% Confidence Intervals for TVR PK Parameters in Child-Pugh A Subjects and Healthy Subjects**

| Day | Parameters | Units | Nobs | GLS Mean Ratio (CPA:HS) [%Ref] | 90% Confidence Interval Lower | Upper |
|---|---|---|---|---|---|---|
| 1 | $C_{max}$ | ng/mL | 10 | 81.8 | 62.0 | 107.9 |
| | $AUC_{0-8}$ | hr*ng/mL | 10 | 89.4 | 65.7 | 121.7 |
| | $AUC_{0-\infty}$ | hr*ng/mL | 10 | 101.0 | 74.4 | 137.2 |
| 6 | $C_{max}$ | ng/mL | 8 | 89.5 | 73.0 | 109.8 |
| | $AUC_{0-8}$ | hr*ng/mL | 8 | 84.8 | 70.3 | 102.4 |

The effect of mild hepatic impairment on the PK of TVR was assessed between matched pairs of subjects (match based on age, sex, and BMI). A total of seven matched pairs were included in the analysis. The GLS mean ratio and 90% confidence intervals suggest that there were no significant differences in Cmax and $AUC_{0-8h}$ between subjects with mild hepatic impairment and healthy subjects following multiple dosing (Table 8).

**Table 8 Geometric Least Squares Mean Ratios and 90% Confidence Intervals for TVR PK Parameters in Child-Pugh A Subjects and Healthy Subjects—Subjects Matched by Age, Sex, and BMI**

| Day | Parameter | Units | Nobs | GLS Mean Ratio (CPA:HS) [%Ref] | 90% Confidence Interval | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| 1 | $C_{max}$ | ng/mL | 7 | 86.9 | 59.3 | 127. 5 |
| | $AUC_{0-8}$ | hr*ng/mL | 7 | 94.7 | 63.1 | 142.0 |
| | $AUC_{0-\infty}$ | hr*ng/mL | 7 | 106.4 | 72.5 | 156.0 |
| 6 | $C_{max}$ | ng/mL | 7 | 97.5 | 79.7 | 119.4 |
| | $AUC_{0-8}$ | hr*ng/mL | 7 | 90.8 | 74.6 | 110.5 |

*Reviewer's Comments:*
*-Six total subjects were excluded from the PK analysis to determine the effect of mild hepatic impairment on TVR PK (subjects 01003, 01005, 01010, 01015, 01018, 01020). Four of these subjects discontinued the study due to an adverse event. Two of those subjects were matches of each other; the remaining two subjects had matches that were excluded from the analysis to maintain a balanced study:*

- *Subject 01003 matched Subject 01020 (both discontinued due to AEs)*
- *Subject 01005 matched Subject 01018 (01005 discontinued due to an AE)*
- *Subject 01010 matched Subject 01015 (01015 discontinued due to an AE)*

Conclusions

The results of this study show that there were no significant differences in PK between subjects with mild hepatic impairment (C-P A) as compared with healthy subjects after multiple dosing. However, slightly lower Cmax and AUC values were observed in subjects with mild hepatic impairment. Since clearance values did not differ between groups, this could be a reflection of lower absorption in C-P A subjects. Of note, an early 250-mg tablet was used in this study and it has been shown to have lower bioavailability than the 375-mg tablet used in the phase 3 studies. It is possible that the poorer bioavailability observed in the C-P A subjects in this study could be improved with dosing with the 375-mg tablet. Either way, this study confirms that dose modification in subjects with mild hepatic impairment is not necessary.

**Individual Study Review—VX06-950-012**

Title (Study VX06-950-012)

"A Phase 1 Study to Assess the Safety and Pharmacokinetics ofTelaprevir (VX-950) in Subjects with Moderate and Severe Degrees of Hepatic Impairment"

Objectives

- To assess the PK of telaprevir following administration of multiple oral doses to subjects with moderate and severe hepatic impairment
- To assess the PK of telaprevir following administration of a single oral dose to subjects with moderate and severe hepatic impairment
- To assess the safety of single and multiple doses of telaprevir in subjects with moderate and severe hepatic impairment

Study Dates and Location(s):

Study initiation: June 6, 2007 (first subject's first dose)
Study completion: March 11, 2008 (date last subject completed follow up)
Clinical Sites: Indiana University Department of Medicine Division of Gastroenterology/Hepatology, Indiana University, 550 N. University Blvd, Indianapolis, IN

Study Design

This was a Phase 1, open-label study in which subjects received single and multiple oral doses of telaprevir. Subjects were administered a single dose of telaprevir on day 1 and received multiple doses of telaprevir from day 2 to day 5. The last dose of telaprevir was administered the morning of day 6 and subjects were discharged from the clinic on day 7. The following 2 groups were planned for enrollment:

- Group A: 10 Child-Pugh B subjects (moderate hepatic impairment)
- Group B: 10 Child-Pugh C subjects (severe hepatic impairment)

*Reviewer's Comments:*
*-Initially, Child-Pugh B (C-P B) subjects were to complete follow-up prior to the enrollment of Child-Pugh C (C-P C) subjects. However, based on the results of the PK analysis for the C-P B cohort that showed decreased telaprevir plasma levels compared to healthy subjects enrolled in previous studies, the study was discontinued and no subjects were screened or enrolled in the C-P C cohort.*

Study Doses Used

Subjects received a single 750-mg dose of telaprevir on day 1, multiple doses (750 mg q8h) of telaprevir on days 2 to 5, and a final 750-mg dose of telaprevir on the morning of day 6.

Dose Rationale

The dose chosen for this study is the clinical dose used in the phase 3 studies.

Formulation(s) Used

A 250-mg telaprevir tablet was used for this study. The 375-mg tablet was used in the phase 3 studies. A bioequivalence study showed that the 2 tablet formulations of telaprevir were

bioequivalent when given as a single 750-mg dose in the fasted state. However, in the presence of food (medium-fat breakfast of 472 kcal, 34% kcal fat), the 375-mg tablet resulted in approximately 32% higher telaprevir exposure compared to the 250-mg tablet. In the current study, the 250-mg tablets were administered with a "regular meal" or large snack.

**C-P B subjects**

*Key Inclusion Criteria:*

-Women of non-childbearing potential and male subjects between 18 and 65 years of age. Non-childbearing potential was defined as postmenopausal (12 months of spontaneous amenorrhea at screening) or surgically sterile (bilateral oopherectomy with or without hysterectomy, or hysterectomy without oopherectomy)
-Child Pugh score of 7 to 9 (CPB, moderate) or ≥10 (CPC, severe)
-Male subjects agreed to use 2 methods of contraception, including 1 barrier method (e.g., a condom and spermicide or a diaphragm and a second barrier method), during the study and for 90 days following the last dose of study drug
-Body mass index (BMI) ≤35 kg/m2 (inclusive) at screening
-Hematology and clinical chemistry values without clinically significant deviations and physical examination results (including vital signs and screening ECG) without clinically significant abnormalities, except for those expected related to liver disease, as judged by the investigator

*Key Exclusion Criteria:*

-Not clinically stable or who had a history of any illness that, in the opinion of the investigator or the subject's general practitioner, might have confounded the results of the study or pose an additional risk in administering study drug(s) to the subject
-Tested positive for HCV Ab, HBsAg, HIV1 Ab, HIV2 Ab, or drug screen
-Had sclerosing cholangitis or primary biliary cirrhosis
-Current encephalopathy grade of 3 at screening
-Consumed more than 50 g of alcohol per day prior to the study. Subjects must be able to abstain from alcohol consumption 72 hours prior to dosing through the follow-up visit.
-Subjects must not have a history of drug or alcohol abuse or addiction within 6 months (protocol version 4.0) or 2 years (protocol versions 1.0 to 3.0) prior to dosing, or test positive for alcohol or drugs of abuse such as cannabis, cocaine, amphetamines, or opiates during the screening period.
-Male subjects with female partners that were pregnant, nursing, planning to become pregnant during the study or within 90 days of the last telaprevir dose, or were unwilling to comply with the contraception requirements.
-Had a smoking habit
-Regular treatment with prescription medications. Subjects were to end any short courses of prescription medications at least 14 days before the screening visit. Prescription medications were not to be administered during the study.
-Regular treatment with over-the-counter medications. Subjects were to stop over-the-counter medication 2 days before the first administration of study drug.
-Used herbal medications, dietary supplements (e.g., St. John's Wort, ginkgo biloba, garlic supplements), vitamins, grapefruit or grapefruit juice, or orange juice within 14 days before the first administration of study drug (Day 1).
-Consumed an average of more than five 8 ounce servings of coffee or other caffeinated beverage, or seven 8 ounce servings of cola per day. Subjects were not to consume any caffeinated beverages within the 72 hours before study drug administration through the follow-up visit.

-Participated in a clinical study involving administration of either an investigational or a marketed drug within 2 months or 5 half lives (whichever is longer) before the screening visit.
-Had an illness within 5 days before receiving the first dose of study drug.

Blood Sampling for PK

Blood samples for determination of telaprevir and VRT-127394 (R-diastereomer of TVR) plasma concentrations were collected at predose and 0.25, 0.5, 0.75, 1, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 16, and 24 hours post-dose after the first dose on study (single-dose day 1) and the last dose on study (multiple-dose day 6). In addition, predose blood samples were collected before the morning dose on days 2, 3, 4, and 5.

Bioanalytical Results

Plasma samples were analyzed for TVR and VRT-127394 by HPLC with tandem mass spectrometric detection. Samples were received in frozen condition on two dates: October 5, 2007 and March 14, 2008. The samples were stored at -70°C. The maximum sample storage until analysis was 90 days, which is within the validated long-term frozen stability duration of 6 months.

The calibration standard concentrations for both TVR and VRT-127394 were 2.0, 4.0, 10.0, 50.0, 200.0, 500, 800, and 1000 ng/mL. The mean accuracy and precision estimates at each TVR and VRT-127394 standard concentration are presented in Tables 1 and 2, respectively, below. All accuracy and precision (%CV) values were within the acceptable range (≤20% from nominal at the LLOQ concentration and ≤15% from nominal at all other concentrations). Quality control concentrations for both analytes were 6.0, 250, and 800 ng/mL. The mean accuracy ranged from 97.8 to 99.4% for TVR and 94.6 to 99.6% for VRT-127394. The mean precision ranged from 3.2 to 5.3% for TVR and 3.9 to 22.3% for VRT-127394.

**Table 1 Mean Calibration Standard Concentrations and Statistics for TVR**

| Nominal Concentrations (ng/ml) | 2.00 | 4.00 | 10.0 | 50.0 | 200 | 500 | 800 | 1000 |
|---|---|---|---|---|---|---|---|---|
| Mean (ng/ml) | 2.01 | 4.01 | 9.70 | 49.4 | 202 | 509 | 812 | 992 |
| SD (ng/ml) | 0.1 | 0.2 | 0.4 | 1.7 | 7.1 | 22.2 | 26.8 | 38.8 |
| CV (%) | 6.4 | 4.9 | 4.3 | 3.5 | 3.5 | 4.4 | 3.3 | 3.9 |
| Accuracy (%) | 100.5 | 100.2 | 97.0 | 98.8 | 101.0 | 101.7 | 101.5 | 99.2 |
| n | 12 | 11 | 12 | 11 | 12 | 12 | 12 | 12 |

**Table 2 Mean Calibration Standard Concentrations and Statistics for VRT-127394**

| Nominal Concentrations (ng/ml) | 2.00 | 4.00 | 10.0 | 50.0 | 200 | 500 | 800 | 1000 |
|---|---|---|---|---|---|---|---|---|
| Mean (ng/ml) | 2.02 | 3.97 | 9.77 | 49.9 | 202 | 503 | 811 | 993 |
| SD (ng/ml) | 0.1 | 0.2 | 0.5 | 2.6 | 8.7 | 19.1 | 27.4 | 40.6 |
| CV (%) | 4.6 | 4.5 | 5.0 | 5.3 | 4.3 | 3.8 | 3.4 | 4.1 |
| Accuracy (%) | 100.8 | 99.2 | 97.7 | 99.7 | 101.2 | 100.6 | 101.4 | 99.3 |
| n | 12 | 11 | 12 | 12 | 12 | 12 | 12 | 12 |

*Reviewer's Comments:*
*-One VRT-127394 QC sample (above the LLOQ concentration) fell outside of the acceptable criteria, which led the mean precision value to be above the acceptable limit of ≤15%. However,*

*that result was still included in the summary statistics. Plasma samples for subjects 1008, 1009, and 1010 were included in the run that contained the failed QC sample (run AQ12-002a). However, only subjects 1009 and 1010 had multiple dose data. If the concentration data for these 2 subjects were excluded from the PK analysis, the resulting $AUC_{0-8h}$ and Cmax values would not differ by more than 2% (based on noncompartmental analysis). Thus, the inclusion of this data did not have an impact on the overall conclusions of this study.*

Results

A total of 10 subjects with moderate hepatic impairment (C-P B) and 10 subjects with severe hepatic impairment (C-P C) were planned for this study. The 10 C-P B subjects were enrolled and received at least 1 dose of telaprevir (4 subjects had C-P score of 7; 2 subjects had C-P score of 8; 4 subjects had C-P score of 9). Nine of these subjects completed the study and 1 subject prematurely discontinued due to a serious adverse event (subject experienced syncope on day 4). The PK results for the C-P B cohort showed that telaprevir plasma concentrations were significantly lower as compared to healthy subjects enrolled in previous studies. Thus, the study was discontinued and no subjects were screened or enrolled for the C-P C cohort.

*Demographics*

| Variable | Child-Pugh B Subjects N = 10 |
|---|---|
| Sex, n | |
| Female | 2 |
| Male | 8 |
| Age (years) | 57 (47, 62) |
| Body weight (kg) | 98.5 (91, 112) |
| Height (cm) | 1.75 (1.63, 1.85) |
| BMI ($kg/m^2$) | 32.15 (27.1, 36.3) |

*Safety*

With the exception of 2 adverse events (AEs), all AEs were mild in severity. One day following the last dose of telaprevir, Subject 01003 experienced 2 episodes of confusional state. One episode was considered moderate and the other was considered mild in intensity. One subject experienced a severe AE. Subject 01008 experienced an episode of vasovagal syncope that was considered not related to telaprevir. This event was considered serious and led to premature discontinuation from the study.

Four subjects had 6 mild AEs that were considered related (possible or probable) to telaprevir and did not require interruption of dosing. These events included rash in Subject 01001, photosensitivity reaction in subject 01002, pruritus in subject 01005, and dyspepsia and headache (2 separate events) in subject 01009. Subject 01009 was treated with acetaminophen for headache. All of the other related adverse events resolved without treatment. Please refer to the medical officer's review for further details.

*Pharmacokinetics*

Since this study did not include healthy subjects, a cross-study comparison of PK parameters was made to the healthy subject cohort in study VX06-950-006 (Tables 3 and 4). A non-compartmental model analysis was performed to obtain the PK parameters for this study. Subjects with moderate hepatic impairment (C-P B) had approximately 50% lower Cmax and $AUC_{0-8h}$ exposure to TVR at steady-state than healthy subjects. Similarly, VRT-127394 Cmax and

$AUC_{0-8h}$ values were both ~38% lower in C-P B subjects than healthy subjects. The Cmax was lower and Tmax significantly delayed in C-P B subjects, suggesting that hepatic impairment decreased the extent and rate of absorption. However, the apparent volume of distribution was also higher in subjects with moderate hepatic impairment.

The box plots in Figure 1 show that when both C-P A and C-P B subjects are compared to healthy volunteers (HV), there is a consistent and steady decrease in exposure to TVR and steady increase in half-life and volume of distribution based on the degree of hepatic impairment. Because the only significant covariate affecting TVR exposure in phase 2 studies was weight, the subjects in the datasets used for the PK parameters and box plots presented below were matched based on weight. The PK subset of subjects matched for weight included 7 C-P B subjects with the lowest weight from the current study and 4 HVs and 5 C-P A subjects from study 012. However, when compared across studies and across the different populations, these results were similar to those observed for the whole dataset (when not matched for weight).

**Table 3 Summary TVR PK Parameters—Multiple Dose (Matched by Weight)**

| **Mean ± SD** | **Cmax** (ng/mL) | **Cmin** (ng/mL) | **Tmax** (hr) | **$AUC_{0-8h}$** (ng*hr/mL) | **$T_{1/2}$** (hr) | **CL/F** (L/hr) | **V/F** (L) |
|---|---|---|---|---|---|---|---|
| Healthy (n=4) | 3272 ± 951 | 1505 ± 445 | 1.88 ± 1.18 | 18410 ± 4120 | 6.2 ± 1.5 | 25 ± 5 | 227 ± 100 |
| C-P B (n=6) | 1865 ± 587 | 1068 ± 167 | 4.33 ± 1.36 | 11706 ± 3685 | 8.3 ± 2.4 | 33 ± 16 | 371 ± 138 |

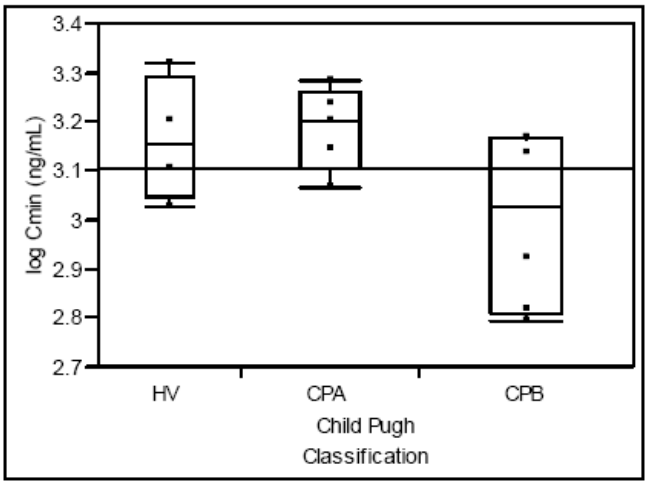
**Table 4 Summary VRT-127394 PK Parameters— Multiple Dose (Matched by Weight)**

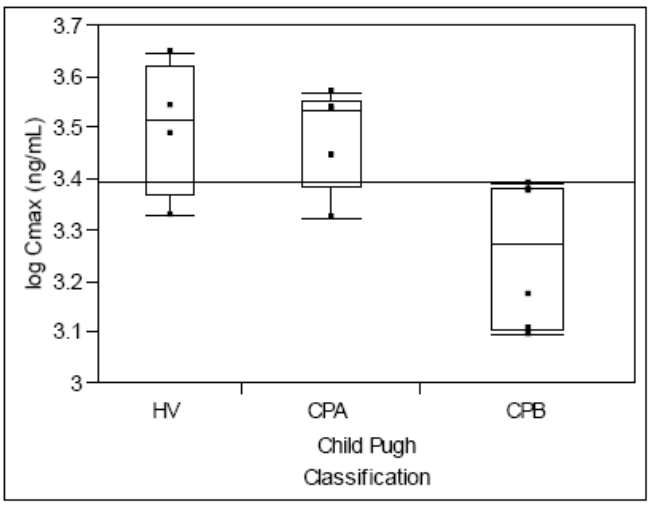
| **Mean ± SD** | **Cmax** (ng/mL) | **Cmin** (ng/mL) | **Tmax** (hr) | **$AUC_{0-8h}$** (ng*hr/mL) | **$T_{1/2}$** (hr) |
|---|---|---|---|---|---|
| Healthy (n=4) | 1595 ± 364 | 1130 ± 377 | 3.25 ± 1.89 | 11075 ± 2799 | 5.5 ± 0.55 |
| C-P B (n=6) | 998 ± 251 | 718 ± 272 | 4.16 ± 1.43 | 6977 ± 2061 | 9.3 ± 5.9 |

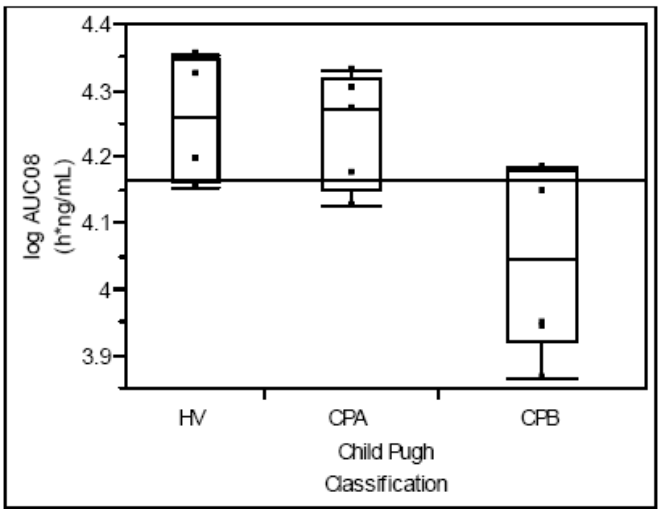
**Table 5 Statistical Analysis of TVR PK Parameters for Healthy Subjects (N=8) (Study 006) and C-P B Subjects (N=9) (Study 012) – Full PK Dataset**

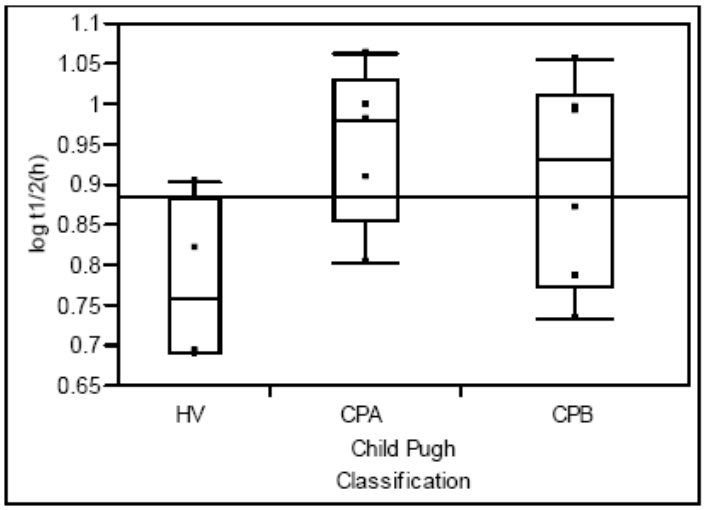
| | | | | 90% Confidence Interval | |
|---|---|---|---|---|---|
| **Treatment** | **Parameters** | **Units** | **Ratio CPB:HS [%Ref]** | **Lower** | **Upper** |
| Single Dose | $Ln(C_{max})$ | ng/mL | 59 | 45 | 78 |
| | $Ln(AUC_{0-8})$ | hr*ng/mL | 63 | 47 | 86 |
| | $Ln(AUC_{0-\infty})$ | hr*ng/mL | 83 | 60 | 114 |
| | $Ln(t_{1/2})$ | hr | 150 | 123 | 184 |
| | Ln(V/F) | L | 182 | 132 | 251 |
| | Ln(CL/F) | L/hr | 121 | 88 | 167 |
| Multiple Dose | $Ln(C_{min})$ | ng/mL | 56 | 42 | 73 |
| | $Ln(C_{max})$ | ng/mL | 51 | 41 | 63 |
| | $Ln(AUC_{0-8})$ | hr*ng/mL | 54 | 43 | 66 |
| | $Ln(t_{1/2})$ | hr | 132 | 106 | 164 |
| | Ln(V/F) | L | 201 | 154 | 263 |
| | Ln(CL/F) | L/hr | 152 | 114 | 203 |

**Figure 1 Box Plots of TVR Cmin, Cmax, $AUC_{0-8h}$, $T_{1/2}$, and V/F in Healthy Subjects, C-P A Subjects, and C-P B Subjects Following Multiple Dosing (Matched by Weight)**





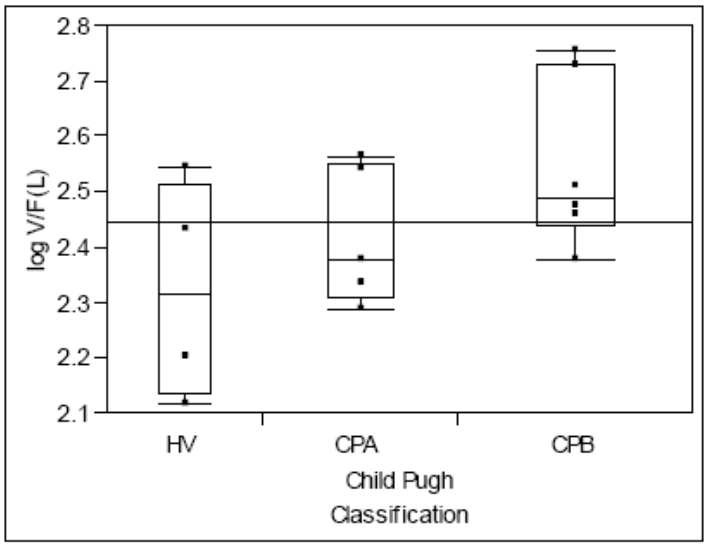




**Table 6 Statistical Analysis of TVR PK Parameters for Healthy Subjects (N=4) (Study 006) and C-P B Subjects (N=6) (Study 012) - Matched by Weight**

| Treatment | Parameters | Units | HS GeoLSM | CPB GeoLSM | Ratio CPB:HS [%Ref] | 90% Confidence Interval | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower | Upper |
| Multiple Dose | Ln($C_{min}$) | ng/mL | 1457 | 999 | 69 | 47 | 99 |
| | Ln($C_{max}$) | ng/mL | 3163 | 1785 | 56 | 40 | 79 |
| | Ln($AUC_{0-8}$) | hr*ng/mL | 18060 | 11207 | 62 | 46 | 84 |
| | Ln($t_{1/2}$) | hr | 6 | 8 | 133 | 99 | 180 |
| | Ln(V/F) | L | 211 | 352 | 167 | 110 | 253 |
| | Ln(CL/F) | L/h | 24 | 30 | 125 | 83 | 188 |

The Applicant further explored the reduction in exposure to TVR and VRT-127394 in C-P B subjects by examining the relationship between TVR concentrations and the following covariates:

- Continuous: albumin, alkaline phosphatase, bilirubin total, creatinine, PT INR, MELD score, AST, ALT, AST/ALT, hepatic blood flow, weight, BMI, and age. Values were the

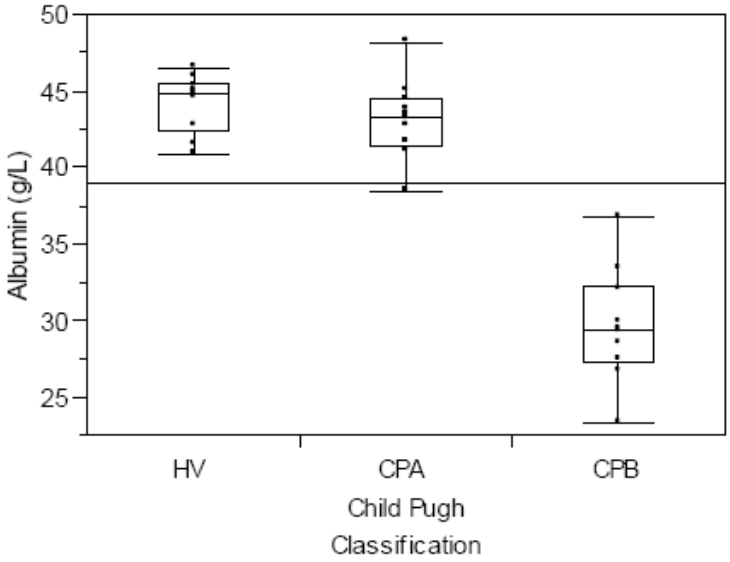
average of all available measurements, and did not show any trends before and after dosing.

- Categorical: sex, ascites, hepatic encephalopathy, and concomitant treatment with laxative and with diabetes medication.

The correlations between relevant PK parameters and covariates were examined using bivariate correlation for continuous covariates and using Wilcoxon rank sum test for categorical covariates. None of the categorical covariates including sex, ascites, hepatic encephalopathy, and concomitant treatment with laxatives or diabetes medication were consistently correlated to either AUC0-8h or Cmax. However, laboratory values known to be markers of hepatic impairment including albumin, AST, bilirubin, and INR, as well as MELD score and weight, correlated with TVR Cmax, $AUC_{0\text{-}8h}$ and T1/2.

Of particular interest is the potential reduction of protein binding in subjects with moderate hepatic impairment. As expected, C-P B subjects had significantly lower average albumin levels (see Figure 2 below). There was a positive correlation between albumin levels and Cmax as well as $AUC_{0\text{-}8h}$, after both single and multiple doses.

**Figure 2 Average Albumin Levels by Severity of Hepatic Impairment: Comparison of Levels in Studies 006 and 012**




In *in vitro* testing, TVR binding to human plasma proteins ranged between 59.1% and 75.6% at TVR concentrations between 0.1 and 20 μM, with decreased binding at higher concentrations. TVR also binds to alpha-1-acid glycoprotein (AAG) *in vitro*; however, the binding decreases with decreasing concentrations of AAG. The concentrations of both albumin and AAG have been reported to be reduced by 68% and 74% in subjects with cirrhosis, a marker of hepatic impairment (Franeyman, NF, 1988). Thus, it is plausible that a lower albumin concentration contributed to the higher apparent volume of distribution due to increased distribution of TVR to nonvascular compartments in the body. The higher volume of distribution would also explain the increased clearance. These changes in ADME may partially account for the reduced Cmax and $AUC_{0\text{-}8h}$ in C-P B subjects.

*Reviewer's Comments:*
*-Unbound concentrations of TVR were not determined in this study due to the* (b) (4) *that is used to stabilize TVR from epimerizing. (The* (b) (4) *would have denatured any plasma proteins that were bound to TVR.) Thus, it is unclear how similar TVR unbound concentrations are between subjects with moderate hepatic impairment and subjects with normal hepatic function. Based on the lower Cmax values in subjects with moderate hepatic impairment, there is a possibility that the extent of absorption is lower and would require a higher dose to reach therapeutic concentrations. However, without information on TVR unbound concentrations, it is difficult to discern whether the lower TVR exposure is due to decreased protein binding or an issue with absorption.*
*-Although multiple dosing in study VX06-950-006 consisted of dosing for 5.5 days and in this study the multiple dosing period lasted only 4.5 days, this difference is not expected to affect the steady-state concentrations of TVR.*
*-Since hepatic impairment generally results in reduced clearance of hepatically metabolized drugs and subsequently increases drug exposure, the opposite was observed with TVR exposure. Thus, other mechanisms such as lowered absorption, increased volume of distribution, or changes in protein binding likely play a role in explaining the reduced TVR concentrations.*
*-Although the results of this study are not consistent with a drug that is extensively metabolized in the liver, it is not uncommon for protease inhibitors to exhibit these PK characteristics or have unchanged PK parameters as a result of moderate hepatic impairment (e.g., patients with moderate hepatic impairment demonstrated a 30% lower exposure to saquinavir; dose-normalized steady-state ritonavir exposures in subjects with moderate hepatic impairment were ~40% lower than those in subjects with normal hepatic function; subjects with moderate hepatic impairment exhibited similar exposure to darunavir as compared with healthy subjects).*

Conclusions

TVR was generally well-tolerated in subjects with moderate hepatic impairment in this study. Exposure to TVR in C-P B subjects in this study was significantly lower (~50%) than in subjects with normal hepatic function in study 006. It is unclear at this point whether the effect is due to an alteration in absorption or indirectly related to decreased protein binding and an increased Vd. Because the effect of moderate hepatic impairment on the PK of TVR is substantial and the unbound concentration of TVR is unknown, dosing with TVR should not be recommended for patients with moderate or severe hepatic impairment.

**Individual Study Review—VX-950-TiDP24-C132**

Title (Study VX-950-TiDP24-C132)

"A Phase I open-label trial to investigate the effect of severe renal impairment on the single-dose pharmacokinetics of telaprevir."

Objectives

- To investigate the effect of severe renal impairment on the single-dose pharmacokinetics of telaprevir
- To investigate the effect of severe renal impairment on the total and unbound plasma concentrations of the sum of telaprevir and VRT-127394
- To determine the safety and tolerability of a single dose of telaprevir in subjects with severe renal impairment compared to matched healthy subjects

Study Dates and Location(s):
Start: May 27, 2009
End: February 26, 2010
Clinical Sites: APEX GmbH, München, Germany and CRS Clinical Research, Kiel, Germany

Study Design

This was a phase I, open-label study that included 24 male and female subjects in 2 cohorts: 1.) 12 healthy subjects and 2.) 12 subjects with severe renal impairment. Since the expected impact of renal impairment on TVR PK is minimal, the Applicant chose to use a reduced study design. Healthy subjects were matched to a subject with severe renal impairment with regards to sex, race, age (±10 years), and BMI (±20%). All subjects received a single dose of 750 mg TVR following a meal. Complete PK profiles of TVR up to 24 hours post-dose were determined following administration of a single dose of telaprevir 750 mg to healthy subjects and subjects with severe renal impairment. Twenty-four hour urine was collected for estimation of CrCl.

Study Dose Used and Dose Rationale

A single 750-mg dose of TVR was used for this study. This is the same dose that is used in a single administration (as part of a q8h regimen) as the dose used in the phase 3 studies.

Formulation(s) Used

TVR was formulated as the 375-mg oral tablet formulation (caplet-shaped tablets) containing 375 mg of TVR in combination with HPMC-AS, dibasic calcium phosphate, croscarmellose, microcrystalline cellulose, colloidal silicon dioxide, and sodium stearyl fumarate. This is the same formulation used in the pivotal Phase 3 trials.

*Key Inclusion Criteria:*
For all subjects:
-Male or female, aged between 18 and 75 years, extremes included
-Females of childbearing potential were allowed if adequate contraception was used. Females of nonchildbearing potential had to be amenorrheal for at least 2 years, or had to have undergone

tubal ligation (or other permanent birth control methods), (total) hysterectomy, or (bilateral) oophorectomy
-Nonsmoking or smoking no more than 10 cigarettes, or 2 cigars, or 2 pipes per day for at least 3 months before study screening
-A BMI, of 18 to 32 kg/$m^2$, extremes included, at study screening

For subjects with severe renal impairment:
-Consistent with the disease process of chronic renal failure and associated symptoms, otherwise judged to be in good health in the opinion of the investigator on the basis of a medical evaluation including a physical examination, medical history, ECG, vital signs, and the results of blood biochemistry, blood coagulation and hematology tests and a urinalysis carried out at screening, with any concomitant medical conditions under stable medical control
-Creatinine clearance <30 mL/min (Cockcroft-Gault)
-Severity of renal disease had to be stable: i.e., having no significant change in renal function as evidenced from serum creatinine value not having changed by more than 20% between the value obtained at screening, and the last determination, obtained at least within 6 months before study entry
-Stable treatment regimen for renal impairment from 2 months prior to treatment start
-Concomitant medications to treat underlying disease states or medical conditions related to renal insufficiency could be used, except when specifically excluded by name or pharmacological class, and provided that dosages were stable for at least 2 months prior to telaprevir dosing

For healthy subjects:
-Healthy on the basis of a medical evaluation that revealed the absence of any clinically relevant abnormality and included a physical examination, medical history, ECG, vital signs, and the results of blood biochemistry, blood coagulation and hematology tests, and a urinalysis carried out at screening
-Normal renal function, i.e., CrCl > 80 mL/min (Cockcroft-Gault)
-Matched to a subject with severe renal impairment with regards to sex, race, age (±10 years) and BMI (±20%).

*Key Exclusion Criteria:*
For all subjects:
-A history of any illness (unrelated to renal impairment, as appropriate) that, in the opinion of the investigator, could confound the results of the study or pose an additional risk in administering study medication to the subject
-Consumption of herbal medications or dietary supplements (including vitamins, products containing *Hypericum perforatum* (St. John's wort), *Ginkgo biloba*, or garlic supplements) and grapefruit or grapefruit juice, apple juice, or orange juice within 14 days before the administration of study medication
-Consumption of more than 2 units of alcoholic beverages per day, or more than 14 units per week
-Consumption of an average of more than five 240-mL servings of coffee or other caffeinated beverage per day
-History of alcohol or drug abuse or addiction within 2 years prior to dosing, or a positive test for alcohol or drugs such as amphetamines, cocaine, cannabinoids, methadone, barbiturates, benzodiazepines, or opioids during the screening period

-Participation in a clinical study involving administration of an investigational drug within 2 months or 5 half-lives (whichever is longer) prior to the screening visit
-A positive test for any of the following infectious disease tests: hepatitis A infection, hepatitis B antigen (HBsAg), hepatitis C virus RNA, human immunodeficiency virus 1 antibody (HIV-1Ab), or human immunodeficiency virus 2 antibody (HIV-2Ab);
-Male subjects having female partners who were planning to become pregnant during the study or within 90 days of intake of study medication
-Females of childbearing potential who were pregnant or planning to become pregnant within 90 days of the completion of the study, who were not using adequate contraception, or who were breastfeeding

For subjects with severe renal impairment:
-History of renal transplant or renal carcinoma. Subjects with a history of renal carcinoma who had been cancer-free for at least 5 years could be included
-Subjects with End Stage Renal Disease (ESRD) requiring dialysis

Note: Subjects with severe renal impairment were allowed to use concomitant medications as medically necessary (including vitamin D products), except for drugs that were inducers/inhibitors of CYP3A4 activity or CYP3A4 substrates with a narrow therapeutic index

For healthy subjects:
-Current use of prescription medication. Subjects had to stop any short-duration courses of prescription medications at least 14 days before the screening visit
-Regular treatment with over-the-counter medications. Subjects could stop over-the-counter medications on the date of the screening visit, but had to stop no less than 7 days prior to the administration of study medication

Blood Sampling for PK

Blood samples for the determination of total TVR and total and unbound TVR+VRT-127394 concentrations were collected at pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, and 24 hours post-dose.

Bioanalytical Results

All bioanalytical assays for this study were conducted at (b) (4) . Plasma samples were analyzed for TVR by HPLC with tandem mass spectrometric detection. Samples were received between June 30, 2009 and February 3, 2010. The samples were analyzed between October 22, 2009 and February 5, 2010. The samples were stored at -70°C. The maximum sample storage time until analysis did not exceed the maximum time during which long-term frozen stability was validated (638 days).

Due to the rapid conversion between the isomers TVR and VRT-127394 in plasma samples without the addition of (b) (4) (which would have denatured plasma proteins bound to TVR), the Applicant stated that it was not possible to accurately determine individual VRT-127394 concentrations or unbound TVR concentrations by itself. Therefore, the Applicant decided to evaluate total TVR (sum of bound and unbound), total TVR+VRT-127394, and unbound TVR+VRT-127394 in this study.

The calibration standard concentrations for TVR were 2.0, 4.0, 10.0, 50.0, 200.0, 500, 800, and 1000 ng/mL. The mean accuracy and precision estimates at each standard concentration

are presented in Table 1 below. All accuracy and precision (%CV) values were within the acceptable range (≤20% from nominal at the LLOQ concentration and ≤15% from nominal at all other concentrations). Quality control concentrations were 6.0, 250, and 800 ng/mL. The mean accuracy of the QC samples ranged from 98.4 to 100% and the mean precision ranged from 3.0 to 5.1%.

**Table 1 TVR Calibration Standard Summary Statistics**

| | VX-950, ng/ml | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Analytical batch** | **2.00** | **4.00** | **10.0** | **50.0** | **200** | **500** | **800** | **1000** |
| n | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 16 |
| mean | 2.00 | 4.07 | 9.52 | 49.2 | 208 | 511 | 807 | 971 |
| std. dev. | 0.0918 | 0.196 | 0.369 | 1.81 | 4.28 | 10.3 | 25.9 | 24.3 |
| %CV | 4.6 | 4.8 | 3.9 | 3.7 | 2.1 | 2.0 | 3.2 | 2.5 |
| % accuracy | 100.0 | 101.8 | 95.2 | 98.4 | 104.0 | 102.2 | 100.9 | 97.1 |

*Reviewer's Comments:*
*-Because the extent of interconversion between the two isomers is not calculable, the utility of the concentration of the sum of the two isomers is limited. However, data for total TVR (bound+unbound) and TVR+VRT-127394 (unbound) will be presented.*
*-The bioanalytical results are acceptable.*

Results

A total of 24 subjects (12 healthy subjects and 12 subjects with severe renal impairment) were enrolled and completed the study. No subject discontinued the study early.

*Demographics*

| Parameter | Healthy subjects N=12 | Subjects with severe renal impairment N=12 | All subjects N=24 |
|---|---|---|---|
| Age, years<br>Median (range) | 62.0 (47; 71) | 68.0 (41; 73) | 62.5 (41; 73) |
| Weight, kg<br>Median (range) | 78.0 (60; 97) | 64.5 (50; 92) | 73.5 (50; 97) |
| Height, cm<br>Median (range) | 177.5 (163; 186) | 171.0 (159; 184) | 176.5 (159; 186) |
| BMI, kg/m²<br>Median (range) | 24.65 (20.8; 29.9) | 22.85 (18.8; 31.8) | 24.40 (18.8; 31.8) |
| Sex, n (%)<br>Female<br>Male | <br>4 (33.3)<br>8 (66.7) | <br>4 (33.3)<br>8 (66.7) | <br>8 (33.3)<br>16 (66.7) |
| Race, n (%)<br>White | <br>12 (100) | <br>12 (100) | <br>24 (100) |
| Ethnicity, n (%)<br>Not hispanic or latino | <br>12 (100) | <br>12 (100) | <br>12 (100) |
| Smoker, n (%)<br>N<br>Y[a] | <br>9 (75.0)<br>3 (25.0) | <br>10 (83.3)<br>2 (16.7) | <br>19 (79.2)<br>5 (20.8) |

N=number of subjects; n=number of subjects with that observation
[a] All smokers were light smokers, i.e., no more than 10 cigarettes or 2 cigars or 2 pipes per day.

*Safety*

No deaths or other SAEs occurred and no AEs led to permanent discontinuation of TVR during this study. Five (41.7%) subjects with severe renal impairment and 7 (58.3%) healthy subjects had at least 1 AE during the whole study, including 4 (33.3%) and 7 (58.3%), respectively, during the treatment phase. During the treatment phase, the most frequently reported AE in the severe renal impairment cohort was fatigue (2 [16.7%] subjects). The most frequently reported AEs in the cohort of healthy subjects were headache, asthenia, and nasopharyngitis (each in 2 [16.7%] subjects). The majority of AEs were grade 1 in severity. No grade 3 AEs were reported. Please refer to the medical officer's review for further details.

*Pharmacokinetics*

Following a single dose of 750 mg TVR, plasma concentrations of TVR were higher in subjects with severe renal impairment than in healthy subjects. Based on the mean concentration-time profile (Figure 1), it appears that subjects with renal impairment experienced slower clearance of TVR since the largest difference between the two curves was in the elimination phase. However, one subject (subject 132-0025) in the severe renal impairment cohort had significantly higher TVR plasma concentrations than other subjects in that cohort from hour 8 and beyond. The shape of this subject's plasma concentration-time profile differed from other subjects with severe renal impairment (Figure 2). The Applicant stated that there was no apparent explanation for these high plasma concentrations in the case report forms. The Applicant submitted descriptive statistics and statistical analysis of the PK parameters for total TVR both with and without this subject's data.

**Figure 1 Mean Plasma Concentration-Time Curves of TVR (Including Standard Deviation Bars) Following Administration of a Single 750-mg Dose of TVR in Subjects with Severe Renal Impairment and in Healthy Subjects**

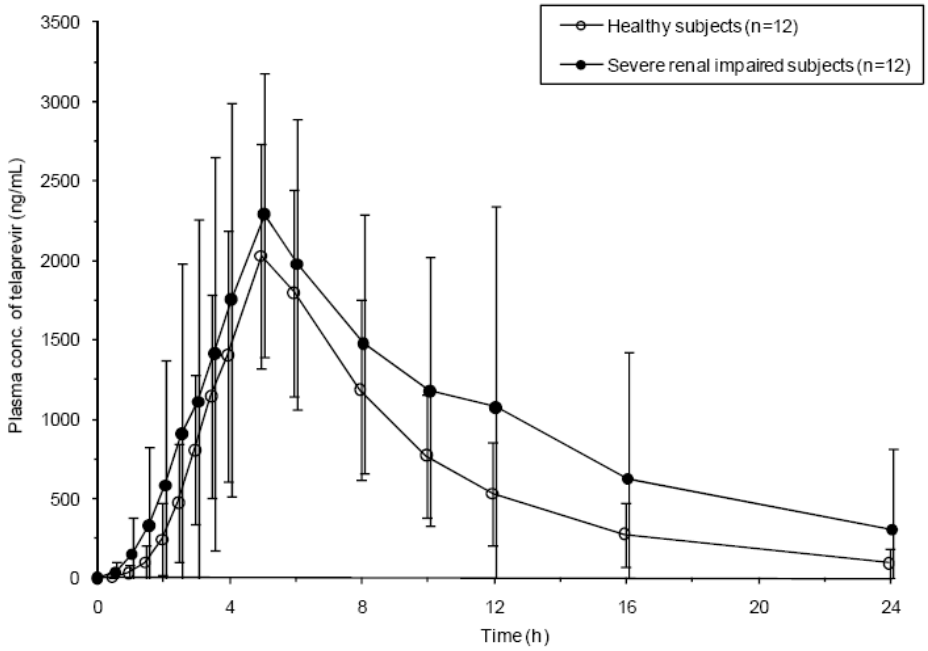
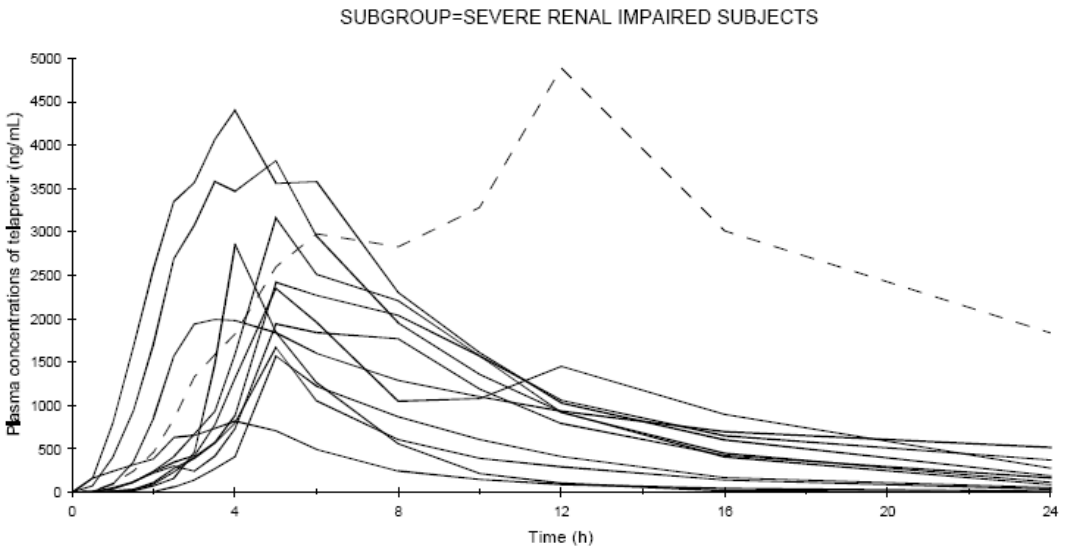


**Figure 2 Combined Individual Concentration-Time Curves for Subjects with Severe Renal Impairment**




The table below shows the mean TVR PK parameters for healthy subjects, all subjects with severe renal impairment, and subjects with severe renal impairment with the exclusion of subject 132-0025. Cmax and $AUC_{inf}$ are higher in subjects with severe renal impairment by approximately 18% and 34%, respectively. However, with the exclusion of outlier subject 132-0025's data, the differences are approximately 9% and 34%, respectively.

**Table 2 Mean TVR (total) PK Parameters Following a Single 750-mg Dose in Subjects with Severe Renal Impairment and in Healthy Subjects**

| *Pharmacokinetics of telaprevir (total)* (mean ± SD, $t_{max}$: median [range]) | Healthy subjects (reference) | Subjects with severe renal impairment (test 1) | Subjects with severe renal impairment, excluding Subject 132-0025[b] (test 2) |
|---|---|---|---|
| n | 12 | 12[a] | 11 |
| $C_{max}$, ng/mL | 2256 ± 635.7 | 2658 ± 1218 | 2455 ± 1043 |
| $t_{max}$, h | 5.0 (3.92-6.0) | 5.0 (3.5-12.0) | 5.0 (3.5-5.0) |
| $AUC_{last}$, ng.h/mL | 14440 ± 5960 | 21980 ± 15650 | 18300 ± 9562 |
| $AUC_{\infty}$, ng.h/mL | 15140 ± 6736 | 20260 ± 11000 | 20260 ± 11000[c] |
| $\lambda_z$, 1/h | 0.1592 ± 0.02549 | 0.1528 ± 0.05882 | 0.1528 ± 0.05882[c] |
| $t_{1/2term}$, h | 4.470 ± 0.8012 | 5.511 ± 3.288 | 5.511 ± 3.288[c] |

[a] n=11 for $AUC_{\infty}$, $\lambda_z$ and $t_{1/2term}$
[b] Subject 132-0025 had a pharmacokinetic profile that differed greatly from that of the other subjects, although a root cause could not be identified.
[c] $\lambda_z$ could not be estimated for Subject 132-0025, consequently descriptive statistics for associated PK parameters are unchanged.

Based on point estimates of the LS means ratio, the inclusion of subject 132-0025's PK data resulted in subjects with renal impairment having ~10% higher Cmax, 30% higher $AUC_{last}$, and 21% higher $AUC_{inf}$ than healthy subjects (Table 3). When subject 132-0025 is excluded

from the statistical analysis, Cmax is 3% higher, $AUC_{last}$ is 16% higher, and $AUC_{inf}$ is 21% higher (Table 4) in subjects with severe renal impairment.

**Table 3 Summary Statistics of TVR PK Parameters (All Subjects Included)**

| *Parameter* | LSmeans[a] | | LSmeans ratio | 90% CI |
|---|---|---|---|---|
| | Healthy subjects (reference) | Subjects with severe renal impairment (test) | | |
| $C_{max}$, ng/mL | 2179 | 2392 | 1.098 | 0.8279 - 1.456 |
| $AUC_{last}$, ng.h/mL | 13470 | 17560 | 1.304 | 0.8719 - 1.950 |
| $AUC_{\infty}$, ng.h/mL[b] | 13990 | 16960 | 1.213 | 0.8179 - 1.798 |
| *Parameter* | Median[a] | | Treatment difference median | 90% CI, h[c] |
| | Healthy subjects (reference) | Subjects with severe renal impairment (test) | | |
| $t_{max}$, h | 5.0 | 5.0 | 0.00 | 0.00 - 1.00 |

[a] n=12 for reference and test
[b] n=11 for test

**Table 4 Summary Statistics of TVR PK Parameters (Subject 132-0025 Excluded)**

| *Parameter* | LSmeans[a] | | LSmeans ratio | 90% CI |
|---|---|---|---|---|
| | Healthy subjects (reference) | Subjects with severe renal impairment (test) | | |
| $C_{max}$, ng/mL | 2179 | 2241 | 1.029 | 0.7838 - 1.350 |
| $AUC_{last}$, ng.h/mL | 13470 | 15650 | 1.162 | 0.8047 - 1.678 |
| $AUC_{\infty}$, ng.h/mL | 13990 | 16960 | 1.213 | 0.8179 - 1.798 |
| *Parameter* | Median[a] | | Treatment difference median | 90% CI, h[b] |
| | Healthy subjects (reference) | Subjects with severe renal impairment (test) | | |
| $t_{max}$, h | 5.0 | 5.0 | 0.00 | (0.00) - (1.00) |

[a] n=12 for reference and n=11 for test

The unbound concentrations of TVR+VRT-127394 are presented in Table 5 below. The trend is similar between the total unbound concentrations of the two moieties combined and total TVR (bound+unbound). Subjects with severe renal impairment had 49% higher $AUC_{last}$ and 17% higher Cmax than healthy subjects. Although the unbound concentrations represent TVR and VRT-127394 combined, the relative change would likely be similar to TVR unbound concentrations.

**Table 5 Mean TVR+VRT127394 (unbound) PK Parameters Following a Single 750-mg Dose in Subjects with Severe Renal Impairment and in Healthy Subjects**

| *Pharmacokinetics of unbound telaprevir + VRT-127394* (mean ± SD, $t_{max}$: median [range]) | Healthy subjects (reference) | Subjects with severe renal impairment (test) |
|---|---|---|
| n | 12 | 12 |
| $C_{max}$, ng/mL | 382.8 ± 68.54 | 449.7 ± 224.8 |
| $t_{max}$, h | 6.0 (4.0-6.0) | 6.0 (4.0-12.0) |
| $AUC_{last}$, ng.h/mL | 2612 ± 669.8 | 3889 ± 2531 |

*Reviewer's Comments:*
*-The $AUC_{last}$ value is higher than $AUC_{inf}$ in severely renally impaired subjects (Table 15-A above). This is because the elimination rate constant could not be estimated for subject 132-0025, thus n=11 for $AUC_{inf}$, $\lambda_z$, and $T_{1/2}$.*
*-Although protein binding is often altered in patients with impaired renal function and the unbound concentration of a drug should be determined if the binding is concentration-dependent (as is the case with TVR), the evaluation of total TVR is acceptable since the extent of plasma protein binding is relatively low (<80%). In* in vitro *testing, TVR binding to human plasma proteins ranged between 59.1% and 75.6% at TVR concentrations between 0.1 and 20 μM.*
*-According to the guidance on conducting PK studies in patients with impaired renal function, a single-dose design may be used when the drug demonstrates linear and time-independent PK. The results of several multiple-dose studies and a dose proportionality study (VX07-950-017) show that TVR exposures are approximately 2-fold higher at steady-state than after a single dose. It is unclear if accumulation of telaprevir would be similar between patients with renal impairment and healthy subjects. However, upon exclusion of subject 132-0025's PK data, the increase in Cmax and AUC in severely renally impaired subjects would not be considered clinically relevant (3% increase in Cmax and 21% increase in $AUC_{inf}$). Even with the contribution of accumulation of TVR at steady-state, it is unlikely that exposure to telaprevir (following multiple doses) would increase to the extent of requiring a dose adjustment, especially considering there are no dose-limiting toxicities associated with TVR. Although anemia has been shown to be associated with TVR exposure, it is even more strongly correlated with RBV exposure. Thus, a more reasonable strategy to manage anemia would be to adjust a patient's RBV dose rather than adjusting their TVR dose. Therefore, a multiple-dose study investigating the effect of severe renal impairment on the PK of TVR is not necessary.*

Conclusions

The results of this study indicate that severe renal impairment increases exposure to TVR by 3% and 21% in Cmax and $AUC_{inf}$ following a single dose. This alteration in TVR PK is not considered clinically relevant and significant increases in TVR exposure due to accumulation at steady-state would not be anticipated. Furthermore, because the only toxicity event associated with TVR exposure (anemia) would be better managed with adjustment in RBV dose, the issue of safety at slightly higher TVR exposure is not a significant concern. Thus, a multiple-dose study evaluating the effect of renal impairment on TVR PK is not needed.

### 3.2.4 Extrinsic Factors

**Individual Study Review—VX05-950-003**

Title (Study VX06-950-003)

"A Phase 1 Study Examining the Effect of Vitamin E TPGS and HPMC, Ketoconazole or Ritonavir on the Pharmacokinetics of VX-950 in Healthy Male Subjects"

Objectives

- To examine the pharmacokinetics of VX-950 tablets co-administered with additional vitamin E alpha-tocopheryl polyethylene glycol-1000 succinate (TPGS) and hydroxypropyl methylcellulase (HPMC E50) (or equivalent) vehicle
- To examine the effects of ketoconazole and low-dose ritonavir on the PK of VX-950
- To assess the safety of a single dose of VX-950 administered with or without ritonavir or ketoconazole

Study Dates and Location(s):
Study initiation: January 27, 2006 (screening)
Study completion: April 2, 2006 (follow-up visit)
Clinical Site: MDS Pharma Services, 621 Rose Street, Lincoln, NE 68502

Study Design

This was a randomized, open-label single dose crossover design with 2 parts. In Part 1 of the study, on each of the 2 dosing occasions, each subject received a single oral dose of VX-950 alone (formulation A) or VX-950 with vitamin E TPGS/HPMC (formulation B) in the fasted state, in randomized order (see Table 1 below). Each dosing occasion was separated by a 7-day washout period. In part 2, all subjects were re-randomized to receive a single dose of 750 mg of VX-950 alone (formulation A) with or without either a single dose of ritonavir 100 mg (RTV) or a single dose of ketoconazole 400 mg (KETO) following a regular breakfast (the regular breakfast contained 431 total calories of which 21%, 60%, and 19% were from fat, carbohydrate, and protein, respectively) on 2 dosing occasions. Part 1 and part 2 were separated by at least a 7-day washout period.

**Table 1 Study Design**

**Part 1**

| Sequence | Dosing Occasion 1 | Dosing Occasion 2 |
|---|---|---|
| A | 750 mg VX-950 fasted | 750 mg VX-950 with vitamin E TPGS/HPMC E50 (or equivalent) fasted |
| B | 750 mg VX-950 with vitamin E TPGS/HPMC E50 (or equivalent) fasted | 750 mg VX-950 fasted |

**Part 2**

| Sequence | Dosing Occasion 1 | Dosing Occasion 2 |
|---|---|---|
| **Ritonavir Coadministration** | | |
| C | 750 mg VX-950 | 750 mg VX-950 with 100 mg ritonavir |
| D | 750 mg VX-950 with 100 mg ritonavir | 750 mg VX-950 |
| **Ketoconazole Coadministration** | | |
| E | 750 mg VX-950 | 750 mg VX-950 with 400 mg ketoconazole |
| F | 750 mg VX-950 with 400 mg ketoconazole | 750 mg VX-950 |

Study Dose Used and Dose Rationale

A single 750-mg dose of VX-950 was used for this study. Previous studies using doses ranging from 25 to 1250 mg have indicated that 750 mg q8h resulted in the highest Ctrough of VX-950 exposure and the greatest median decrease in HCV RNA levels. In addition, a single oral dose of 750 mg was expected to provide sufficient exposure to adequately characterize the pharmacokinetics of VX-950. A dose of 750 mg q8h was used in the phase 3 studies and is the dose proposed for approval.

Formulation(s) Used

The following study drugs were administered during the course of this study:

- VX-950, 250 mg tablets Manufactured by (b) (4)
- Metolose 60SH50 (Hypromellose USP, 50 CPS) Manufactured by (b) (4) Lot No.: 507600
- Eastman Vitamin E TPGS, NF Grade Manufactured by Eastman Chemical Lot No.: 50916-0-01 Batch No.: 50051000
- NORVIR® (ritonavir capsules) SOFT GELATIN 100 mg Manufactured by Abbott Laboratories Lot No.: 342692E21
- NIZORAL® (ketoconazole) TABLETS 200 mg Manufactured by Janssen Pharmaceutica Products, LP Lot No.: 5GG163
- An oral suspension of vitamin E TPGS and HPMC was prepared for administration by (b) (4).

*Reviewer Comments:*
*The 250 mg tablet of VX-950 is not the proposed commercial formulation. The proposed commercial formulation is a coated 375-mg tablet while the formulation used in phase 3 studies was an uncoated 375-mg tablet.*

*Key Inclusion Criteria:*
-Male subjects between 19 and 55 years of age (inclusive)
-Agreed to use 2 methods of contraception, including 1 barrier method (i.e., a condom and spermicide), during and for 90 days after the completion of the study
-Subjects had a BMI from 18 to 29 $kg/m^2$ (inclusive) at screening
-All subjects were judged to be in good health on the basis of medical history, physical examination, and routine laboratory measurement results. Medical history and physical examination were without major or clinically significant findings

-Hematology and clinical chemistry were within normal range or showed no clinically significant deviations from normal range during the screening period (as judged by the investigator)
-Physical examination, including vital signs and screening 12-lead electrocardiogram (ECG), was without clinically significant abnormalities, according to the investigator

*Key Exclusion Criteria:*
-Female subjects
-Subjects with a history of any illness that, in the opinion of the investigator or the subject's general practitioner, confounded the results of the study or posed an additional risk in administering study drug(s) to the subject
-Regular treatment with prescription medications. Subjects were to have ended any short courses of prescription medications at least 14 days prior to the screening visit. Prescription medications were not to be administered during the study. (Potential subjects were not to stop any chronic, prescribed medication being taken at the direction of a physician, without obtaining agreement from that physician)
-Regular treatment with over-the-counter medications. Subjects were to end over-the-counter medication on the date of the screening visit but no less than 2 days prior to administration of study drug. Occasional use of acetaminophen or ibuprofen was allowed during the study for the treatment of pain (under supervision of the investigator)
-Subjects who consumed herbal medications or dietary medications, dietary supplements (e.g., St. John's Wort, ginkgo biloba, garlic supplements), vitamins, and grapefruit or grapefruit juice within 14 days before administration of study drug (Day 1). Subjects were not to consume these items until the last PK sample following the last dose of study drug
-Subjects who consumed more than 2 units of alcoholic beverages per day or more than 14 units per week. Subjects were not to consume any alcohol 72 hours before or after study drug administration through the follow-up visit
-Subjects who consumed an average of more than 8 cups of coffee or other caffeinated beverage, or 7 cans of cola per day. Additionally, subjects were not allowed any caffeinated beverages 72 hrs prior to dosing until the collection of the last PK samples at each dosing occasion
-Subjects who had a history of drug or alcohol abuse or addiction within 2 years prior to dosing, or who tested positive for alcohol or drugs of abuse such as cannabis, cocaine, amphetamines or opiates during the screening period
-Subjects who had participated in a clinical study involving administration of either an investigational or a marketed drug within 2 months or 5 half lives (whichever is longer) prior to the screening visit
-Subjects with a hemoglobin of <12.0 g/dL
-Subjects who tested positive for any of the following infectious disease tests: hepatitis B antigen (HBsAg), hepatitis C virus antibody (HCVAb), human immunodeficiency virus 1 antibody (HIV1Ab), or human immunodeficiency virus 2 antibody (HIV2Ab)
-Subjects who had a female partner who was pregnant, nursing, or planning to become pregnant during the study or within 90 days of the VX-950 dose

Blood Sampling for PK

Blood samples for determination of VX-950 and VRT-127394 (R-diastereomer of VX-950) plasma concentrations were collected at pre-dose and 0.25, 0.5, 0.75, 1, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 16, and 24 hours post-dose at each dosing occasion (days 1, 8, 22, and 36). On Days 22

and 36, additional blood samples were collected to determine plasma ketoconazole and ritonavir concentrations.

Bioanalytical Results

All bioanalytical assays for this study were conducted at (b) (4) . Plasma samples were analyzed for VX-950 and VRT-127394 by HPLC with tandem mass spectrometric detection (LC-MS/MS). Samples were received between: February 7, 2006 and March 29, 2006. The samples were stored at between -60° and -80° C. The samples were analyzed between February 10, 2006 and April 12, 2006. The maximum sample storage time until analysis was 64 days, which is within the validated long-term frozen stability duration of 6 months.

The calibration standard concentrations for both VX-950 and VRT-127394 were 2.0, 4.0, 10.0, 50.0, 200.0, 500, 800, and 1000 ng/mL. The mean accuracy and precision estimates at each VX-950 and VRT-127394 standard concentration are presented in Tables 2 and 3, respectively, below. All accuracy and precision (%CV) values were within the acceptable range (≤20% from nominal at the LLOQ concentration and ≤15% from nominal at all other concentrations). Quality control concentrations for both analytes were 6.0, 250, and 800 ng/mL. The mean accuracy ranged from 96.8 to 100.8% for VX-950 and 94.8 to 100.7% for VRT-127394. The mean precision ranged from 2.5 to 4.6% for VX-950 and 4.8 to 6.6% for VRT-127394.

**Table 2 Mean Calibration Standard Concentrations and Statistics for VX-950**

| Analysis | Theoretical Concentration (ng/mL) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Group | 2.00 | 4.00 | 10.0 | 50.0 | 200 | 500 | 800 | 1000 |
| Range | 1.60-2.40 | 3.40-4.60 | 8.5-11.5 | 42.5-57.5 | 170-230 | 425-575 | 680-920 | 850-1150 |
| n | 71 | 77 | 78 | 77 | 77 | 77 | 78 | 78 |
| Mean | 2.01 | 3.98 | 9.95 | 50.8 | 195 | 507 | 802 | 999 |
| SD | 0.102 | 0.201 | 0.367 | 1.78 | 5.61 | 17.3 | 28.9 | 36.5 |
| RSD (%) | 5.1 | 5.1 | 3.7 | 3.5 | 2.9 | 3.4 | 3.6 | 3.7 |
| Accuracy(%) | 100.5 | 99.5 | 99.5 | 101.6 | 97.5 | 101.4 | 100.3 | 99.9 |

**Table 3 Mean Calibration Standard Concentrations and Statistics for VRT-127394**

| Analysis | Theoretical Concentration (ng/mL) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Group | 2.00 | 4.00 | 10.0 | 50.0 | 200 | 500 | 800 | 1000 |
| n | 68 | 69 | 70 | 67 | 73 | 74 | 74 | 73 |
| Mean | 1.99 | 4.03 | 10.0 | 51.2 | 193 | 507 | 799 | 997 |
| SD | 0.121 | 0.289 | 0.680 | 3.19 | 12.9 | 32.8 | 52.7 | 58.6 |
| RSD (%) | 6.1 | 7.2 | 6.8 | 6.2 | 6.7 | 6.5 | 6.6 | 5.9 |
| Accuracy(%) | 99.5 | 100.8 | 100.0 | 102.4 | 96.5 | 101.4 | 99.9 | 99.7 |

*Reviewer's Comments:*
*-The bioanalytical results are acceptable.*

Results

Of the 36 subjects planned for randomization, 35 subjects were randomized and dosed in part 1 of the study. One randomized subject was discontinued prior to dosing on day 8 due to a positive urine drug test prior to the second dosing occasion. Of the 34 subjects who completed part 1, 32 subjects were randomized and dosed in part 2. Two subjects withdrew consent prior to randomization in part 2.

*Demographics*

| Trait | | |
|---|---|---|
| Sex | Male | 35 (100.0%) |
| Race | Asian | 1 ( 2.9%) |
| | Black | 5 ( 14.3%) |
| | Caucasian | 28 ( 80.0%) |
| | Hispanic | 1 ( 2.9%) |
| Age | N | 35 |
| | Mean | 33.0 |
| | SD | 11.2 |
| | Median | 30.0 |
| | Minimum | 19.0 |
| | Maximum | 55.0 |

*Safety*

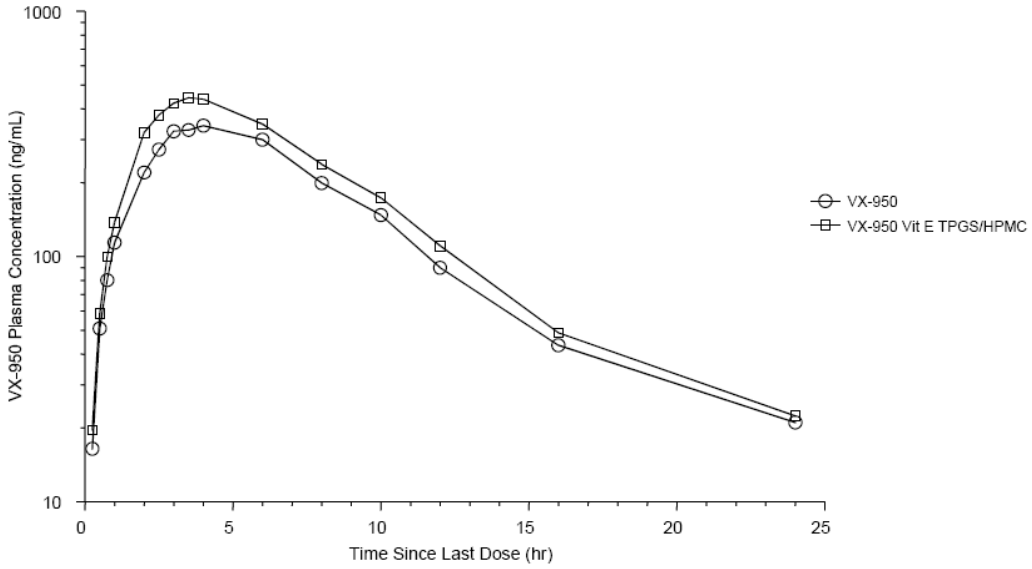
In part 1, all of the adverse events were of mild severity with the exception of 2 incidences of headache. During the second dosing occasion, subject 01102 experienced a moderate headache approximately 7 days after VX-950 + vitamin E TPGS/HPMC dosing, which was not considered related to study drug. Approximately 14 hours after receiving VX-950 alone during the first dosing occasion, subject 01112 experienced a moderate headache that was considered to be possibly related to study drug. In part 2, all adverse events were of mild severity with the exception of 3 incidences of headache. Two of the moderate headaches were considered possibly related to study drug (subjects 01212 and 01234) and 1 event was considered not related to study drug (subject 01226). Please refer to the medical officer's review for further details.

*Effect of vitamin E TPGS and HPMC on VX-950 and VRT-127394 PK*

Noncompartmental analyses of VX-950 and VRT-127394 plasma concentrations were performed on data collected from the 4 treatment periods of the study (Days 1, 8, 22, and 36). Noncompartmental analyses of ketoconazole and ritonavir were performed on data collected from indicated treatment days in Part 2 of the study (Day 22 or Day 36). Because BQL samples were obtained at 24 hours for 3 subjects in part 1, the time used for $t_{last}$ was 16 hours for part 1 and the food effect comparisons for all subjects. For the ketoconazole and ritonavir comparisons in part 2, the time used for $t_{last}$ was 24 hours for all subjects.

When mean VX-950 plasma concentrations between treatments with and without vitamin E TPGS/HPMC in the fasted state were compared, exposures were higher when VX-950 was administered with vitamin E TPGS and HPMC (Table 4). $AUC_{0\text{-}16h}$ was ~24% higher and Cmax was ~29% higher when vitamin E TPGS/HPMC were co-administered with VX-950.

**Figure 1 Mean VX-950 Plasma Concentration-Time Profiles**




*Reviewer's Comments:*
*-Based on the mean concentration-time profile above (and review of the individual concentration-time profiles), and the fact that the half-lives remained relatively unchanged between the two treatments, the addition of vitamin E TPGS and HPMC is most likely improving bioavailability.* (b) (4)

**Table 4 Mean VX-950 PK Parameters for Subjects Administered VX-950 Alone (formulation A) or With Vitamin E TPGS/HPMC (formulation B)**

| VX-950 Pharmacokinetic Parameter | VX-950 Alone | VX-950 With Vitamin E TPGS and HPMC |
|---|---|---|
| $t_{max}$ (hr)[a] | 3.50 (2.00-6.00) | 3.50 (2.00-6.00) |
| $C_{max}$ (ng/mL) | 379 (327) | 489 (396) |
| $t_{1/2}$ (hr) | 5.24 (2.06) | 5.07 (2.11) |
| $AUC_{0-\infty}$ (ng hr/mL) | 3199 (2357) | 3901 (3064) |
| $AUC_{0-16}$ (ng hr/mL) | 2779 (2070) | 3445 (2700) |
| VX-950 $AUC_{0-\infty}$/total $AUC_{0-\infty}$[b] | 0.703 (0.028)[c] | 0.698 (0.021)[c] |
| VX-950 $AUC_{0-16}$/ total $AUC_{0-16}$[b] | 0.725 (0.027) | 0.719 (0.024) |

[a] Median (range)
[b] Total equals the sum of VX-950 and VRT-127394 AUC values
[c] n=29

The results of pairwise statistical analyses show that the 90% confidence intervals for all three VX-950 PK parameters ($AUC_{inf}$, $AUC_{0-16h}$, and Cmax) were outside the standard BE limits (80-125%) (Table 5 below).

**Table 5 Summary Statistics of VX-950 PK Parameters**

| Analyte | Treatment Comparison | Parameter | Point Estimate (%) | 90% Confidence Interval |
|---|---|---|---|---|
| VX-950 | VX - 950 With Vit E TPGS/HPMC / VX - 950 Alone | $AUC_{0-\infty}$ | 120.42 | 104.99, 138.12 |
| VX-950 | VX - 950 With Vit E TPGS/HPMC / VX - 950 Alone | $AUC_{0-16}$ | 121.04 | 104.01, 140.86 |
| VX-950 | VX - 950 With Vit E TPGS/HPMC / VX - 950 Alone | $C_{max}$ | 125.46 | 103.42, 152.19 |

Summary PK parameters for VRT-127394 are listed in Table 6 below. Mean VRT-127394 $AUC_{inf}$ and $AUC_{0-16h}$ values were about 30% higher, and mean VRT-127394 Cmax values were ~28% higher when VX-950 was administered with vitamin E TPGS and HPMC. Thus, the PK characteristics for VRT-127394 were similar to those of VX-950.

**Table 6 Mean VRT-127394 PK Parameters for Subjects Administered VX-950 Alone (formulation A) or With Vitamin E TPGS/HPMC (formulation B)**

| VRT-127394 Pharmacokinetic Parameter | VX-950 Alone | VX-950 With Vitamin E TPGS and HPMC |
|---|---|---|
| $t_{max}$ (hr)[a] | 6.00 (2.51-10.00) | 4.00 (3.00-12.00) |
| $C_{max}$ (ng/mL) | 121 (99.5) | 155 (128) |
| $t_{1/2}$ (hr) | 6.62 (3.93)[b] | 6.72 (4.47) |
| $AUC_{0-\infty}$ (ng hr/mL) | 1407 (1187)[c] | 1827 (1570)[c] |
| $AUC_{0-16}$ (ng hr/mL) | 1077 (876) | 1399 (1184) |

[a] Median (range)
[b] n=34
[c] n=29

*Effect of KETO on VX-950 and VRT-127394 PK*

When VX-950 was co-administered with KETO, mean VX-950 plasma concentrations were higher than when VX-950 was administered alone (Table 7). Mean VX-950 $AUC_{inf}$ and mean $AUC_{0-24h}$ values were about 67% higher, whereas mean VX-950 Cmax values were about 29% higher when VX-950 was administered with KETO. Upon inspection of the concentration-time profiles, elimination was slower for subjects who took VX-950 with KETO (Figure 2). Likewise, mean VRT-127394 plasma concentrations were also higher when VX-950 was administered with KETO as compared with VX-950 administered alone (Table 8). However, the magnitude of change was larger for VRT-127394 than for VX-950. Mean VRT-127394 $AUC_{inf}$ was 96% higher, mean $AUC_{0-24h}$ was 88% higher, and mean VRT-127394 Cmax was ~46% higher when VX-950 was administered with KETO.

**Figure 2 Mean VX-950 Plasma Concentration-Time Profiles With and Without Co-Administration with KETO**

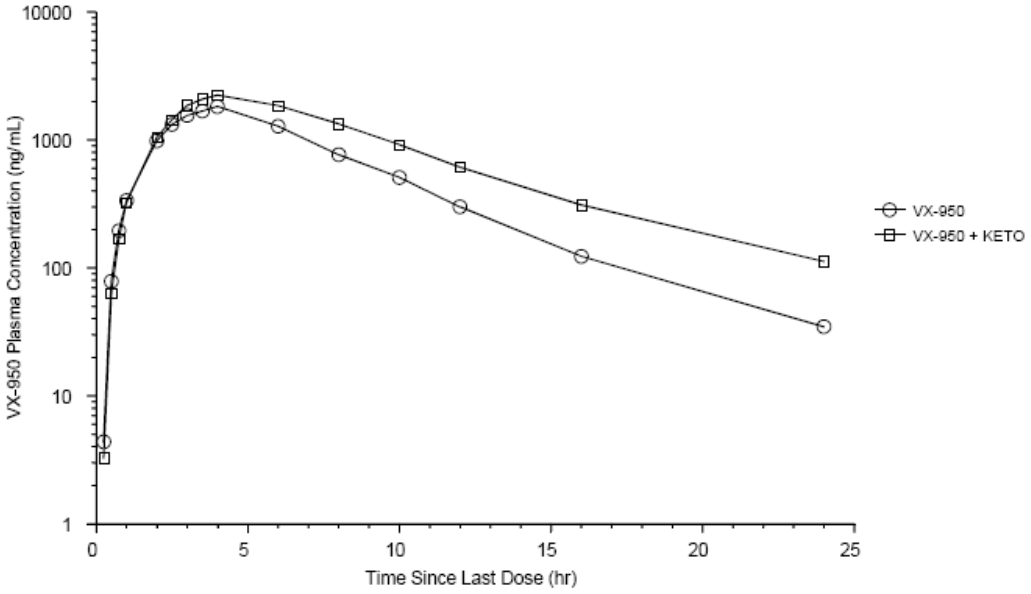



**Table 7 Mean VX-950 PK Parameters for Subjects Administered VX-950 Alone or With KETO**

| VX-950 Pharmacokinetic Parameter | VX-950 Alone | VX-950 With Ketoconazole |
|---|---|---|
| $t_{max}$ (hr)[a] | 4.00 (2.00-6.01) | 4.00 (2.00-6.01) |
| $C_{max}$ (ng/mL) | 2020 (843) | 2430 (786) |
| $t_{1/2}$ (hr) | 3.45 (0.511) | 4.51 (1.01) |
| $AUC_{0-\infty}$ (ng hr/mL) | 12385 (5528) | 19315 (6970) |
| $AUC_{0-24}$ (ng hr/mL) | 12195 (5387) | 18486 (6338) |
| VX-950 $AUC_{0-\infty}$/total $AUC_{0-\infty}$[b] | 0.669 (0.030) | 0.636 (0.022) |
| VX-950 $AUC_{0-24}$/total $AUC_{0-24}$[b] | 0.671 (0.029) | 0.642 (0.018) |

[a] Median (range)
[b] Total equals the sum of respective VX-950 and VRT-127394 AUC values

**Table 8 Mean VRT-127394 PK Parameters for Subjects Administered VX-950 Alone or With KETO**

| VRT-127394 Pharmacokinetic Parameter | VX-950 Alone | VX-950 With Ketoconazole |
|---|---|---|
| $t_{max}$ (hr)[a] | 4.00 (3.00-8.01) | 6.00 (3.00-8.03) |
| $C_{max}$ (ng/mL) | 762 (324) | 1020 (299) |
| $t_{1/2}$ (hr) | 3.71 (0.803) | 4.91 (1.25) |
| $AUC_{0-\infty}$ (ng hr/mL) | 6331 (3210) | 11084 (4151) |
| $AUC_{0-24}$ (ng hr/mL) | 6158 (3078) | 10297 (3536) |

[a] Median (Range)

*Effect of RTV on VX-950 and VRT-127394 PK*

Overall, co-administration with RTV caused an increase in exposure to VX-950 as compared to VX-950 administration alone. Mean VX-950 $AUC_{inf}$ values were 94% higher, mean $AUC_{0-24h}$ values were 75% higher, and mean VX-950 Cmax values were ~30% higher when VX-

950 was administered with RTV (Table 9). Similar to KETO, RTV also significantly increased the half-life of VX-950 (~88% higher in the presence of RTV).

**Figure 3 Mean VX-950 Plasma Concentration-Time Profiles With and Without Co-Administration with RTV**

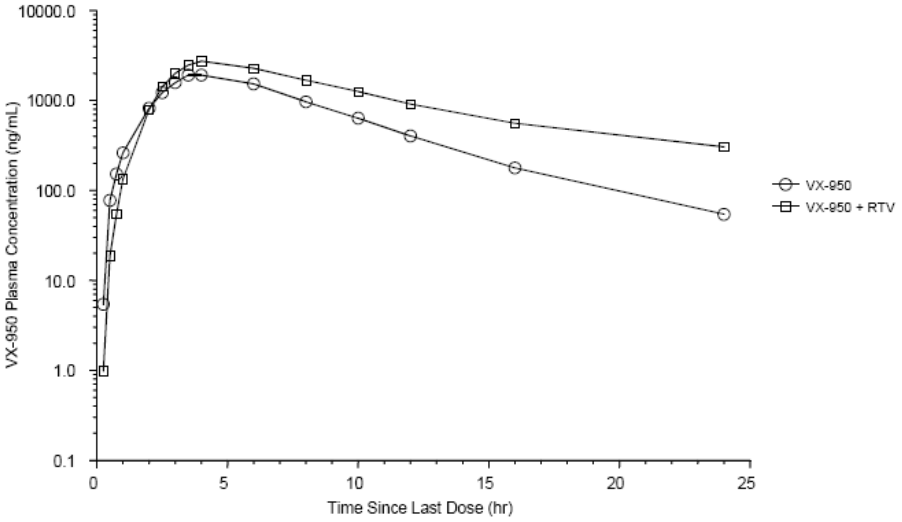



**Table 9 Mean VX-950 PK Parameters for Subjects Administered VX-950 Alone or With RTV**

| VX-950 Pharmacokinetic Parameter | VX-950 Alone | VX-950 With Ritonavir |
|---|---|---|
| $t_{max}$ (hr)[a] | 4.00 (3.00-6.01) | 4.00 (2.51-6.00) |
| $C_{max}$ (ng/mL) | 2180 (679) | 2830 (717) |
| $t_{1/2}$ (hr) | 3.84 (0.765) | 7.20 (1.15) |
| $AUC_{0-\infty}$ (ng hr/mL) | 14369 (6153) | 27867 (8378) |
| $AUC_{0-24}$ (ng hr/mL) | 14037 (5939) | 24541 (6692) |
| VX-950 $AUC_{0-\infty}$/total $AUC_{0-\infty}$[b] | 0.666 (0.024) | 0.605 (0.022) |
| VX-950 $AUC_{0-24}$/total $AUC_{0-24}$[b] | 0.669 (0.023) | 0.620 (0.018) |

[a] Median (range)
[b] Total equals the sum of respective VX-950 and VRT-127394 AUC values

Summary PK parameters for VRT-127394 are listed in Table 10 below. Mean VRT-127394 $AUC_{inf}$ and $AUC_{0-24h}$ values were ~200% higher, and mean VRT-127394 Cmax values were ~55% higher when VX-950 was co-administered with RTV. Although the magnitude of change was larger for VRT-127394, the general PK characteristics for VRT-127394 were similar to those of VX-950 following co-administration with RTV.

**Table 10 Mean VRT-127394 PK Parameters for Subjects Administered VX-950 Alone or With RTV**

| VRT-127394 Pharmacokinetic Parameter | VX-950 Alone | VX-950 With Ritonavir |
|---|---|---|
| $t_{max}$ (hr)[a] | 6.00 (3.00-8.00) | 6.00 (4.00-8.01) |
| $C_{max}$ (ng/mL) | 841 (256) | 1300 (276) |
| $t_{1/2}$ (hr) | 3.98 (0.834) | 7.95 (1.35) |
| $AUC_{0-\infty}$ (ng hr/mL) | 7255 (3196) | 18098 (5090) |
| $AUC_{0-24}$ (ng hr/mL) | 6978 (2991) | 14965 (3672) |

[a] Median (Range)

*Food Effect*

Mean VX-950 plasma concentrations following fasted conditions from part 1 were compared with concentrations following fed conditions in part 2. The mean PK parameters show that when VX-950 is administered with a regular breakfast, mean $AUC_{0\text{-}16h}$, $AUC_{inf}$, and Cmax were approximately 4- to 5-fold higher than when VX-950 is administered without food (Table 11). Mean half-life of VX-950 was lower when VX-950 was administered under fed conditions. Overall, food significantly enhances the bioavailability of VX-950.

**Table 11 Mean VX-950 PK Parameters for Subjects Administered VX-950 While Fasting (N=35) or with a Regular Breakfast (N=32)**

| VX-950 Pharmacokinetic Parameter | VX-950 Alone (Fasted, Part 1) | VX-950 With a Regular Breakfast (Fed, Part 2) |
|---|---|---|
| $t_{max}$ (hr)[a] | 3.50 (2.00-6.00) | 4.00 (2.00-6.01) |
| $C_{max}$ (ng/mL) | 379 (327) | 2091 (763) |
| $t_{1/2}$ (hr) | 5.24 (2.06) | 3.63 (0.662) |
| $AUC_{0\text{-}\infty}$ (ng hr/mL) | 3199 (2357) | 13315 (5821) |
| $AUC_{0\text{-}16}$ (ng hr/mL) | 2779 (2070) | 12374 (5195) |
| VX-950 $AUC_{0\text{-}\infty}$/total $AUC_{0\text{-}\infty}$ [b] | 0.703 (0.028) | 0.668 (0.027) |
| VX-950 $AUC_{0\text{-}16}$/ total $AUC_{0\text{-}16}$ [b] | 0.725 (0.027) | 0.676 (0.024) |

*Reviewer's Comments:*
*-KETO and RTV plasma concentrations were also assessed in this study. However, because there was no comparator group within this study, only one set of mean data are presented and it is not possible to directly assess the effect of VX-950 on KETO or RTV plasma levels, although the Applicant states that the calculated PK parameters for KETO and RTV in this study are comparable to historical values reported in literature.*
*-Since VX-950 demonstrates non-linear pharmacokinetics and is not dose proportional in the therapeutic dose range, a multiple-dose study with VX-950 should have been performed in order to accurately assess any changes in KETO concentrations caused by VX-950. However, the Applicant's proposed wording on limiting the dose of KETO to not more than 200 mg/day in the label is reasonable. Other ritonavir-boosted HIV PI's include the same recommendation when KETO exposures were increased by up to 2- to 3-fold (Prezista, Kaletra, Invirase). It is unlikely that the CYP3A suppression caused by VX-950 would exceed that of ritonavir in combination with a PI.*
*-A multiple-dose study with RTV and VX-950 has been conducted (see review of study VX06-950-009).*

Conclusions

This study demonstrated that the addition of vitamin E TPGS and HPMC, co-administration with CYP3A4 inhibitor KETO, and co-administration with CYP3A4 inhibitor RTV all resulted in increased VX-950 exposures. (b) (4) . The Applicant's proposed wording for the label concerning limiting the dose of ketoconazole is acceptable. The proposed wording for the label is presented below.

**Section 7.4, Table 5**

| Concomitant Drug Class: Drug Name | Effect on concentration of (b) (4) or Concomitant Drug | **Clinical Comment** |
|---|---|---|
| ketoconazole*<br>itraconazole<br>posaconazole<br>voriconazole | ↑ ketoconazole<br>↑ telaprevir<br>↑ itraconazole<br>↑ posaconazole<br>↑ or ↓ voriconazole | Ketoconazole increases the plasma concentrations of telaprevir. Concomitant systemic use of itraconazole or posaconazole with telaprevir may increase plasma concentrations of telaprevir.<br><br>Plasma concentrations of itraconazole, ketoconazole, or posaconazole may be increased in the presence of telaprevir. When co-administration is required, high doses of itraconazole or ketoconazole (> 200 mg/day) are not recommended.<br><br>Caution is warranted and clinical monitoring is recommended for itraconazole, posaconazole and voriconazole.<br>QT interval prolongation and Torsade de Pointes have been reported with voriconazole and posaconazole. QT interval prolongation has been reported with ketoconazole.<br>Due to multiple enzymes involved with voricanazole metabolism, it is difficult to predict the interaction with telaprevir. Voriconazole should not be administered to patients receiving telaprevir unless an assessment of the benefit/risk ratio justifies its use. |

**Section 12.3, Table 6**

| | **Dose and Schedule** | | | | **LS Mean Ratio (90% CI) of Telaprevir PK With/Without Coadministered Drug** | | |
|---|---|---|---|---|---|---|---|
| **Drug** | **Drug** | **Telaprevir** | **N** | **Effect on Telaprevir PK[a]** | **$C_{max}$** | **AUC or $C_{avg,ss}$[b]** | **$C_{min}$** |
| Ketoconazole | Ketoconazole 400 mg single dose | 750 mg single dose | 17 | ↑ | 1.24 (1.10; 1.41) | 1.62 (1.45; 1.81) | NA |

**Individual Study Review—VX06-950-007**

Title (Study VX06-950-007)

"An Open-label Phase 1 Study of VX-950 in Healthy Adult Female Subjects to Examine the Drug-Drug Interaction Between VX-950 and Oral Contraceptives"

Objectives

- To compare the plasma steady-state pharmacokinetics of NE and EE in healthy adult female subjects after repeated once daily (qd) dose of Modicon® (0.5 mg NE + 0.035 mg EE) before and after coadministration of 750 mg VX-950 every 8 hours (q8h) for 28 days
- To assess the activity of Modicon by comparing progesterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) serum levels in healthy adult female subjects after qd dosing of Modicon before and after coadministration of 750 mg VX-950 q8h for 28 days
- To assess the safety of coadministration of 750 mg VX-950 q8h and Modicon qd to healthy adult female subjects for 28 days
- To compare the plasma steady-state pharmacokinetics of VX-950 and VRT-127394 (*R*-diastereomer of VX-950) in healthy adult female subjects after coadministration of 750 mg VX-950 q8h and Modicon qd for 28 days

Study Dates and Location(s):
Study initiation: July 16, 2006 (first subject enrolled)
Study completion: October 16, 2006 (last subject's last follow-up)
Clinical Site: PRA International, Stationsweg 163, 9471 GP Zuidlaren, The Netherlands

Study Design

This was an open-label, single-center, non-randomized study of oral VX-950 in combination with Modicon in healthy adult female subjects of childbearing age already on an oral contraceptive. A total of 24 subjects were enrolled in the study. Subjects discontinued their current oral contraceptive on Day -7. Subjects were treated with Modicon alone as a control from days 1 through 21. The same subjects were then treated with Modicon plus VX-950 from days 29 to 49; therefore each subject served as her own control with and without VX-950. From days 50 to 56, TVR alone was administered. Modicon was chosen as the NE- and EE-containing contraceptive as it was commonly used in the region where the clinical trial was conducted (the Netherlands). All doses of VX-950 were to be administered with food. The protocol and study report do not explicitly state how Modicon was to be administered with respect to food when subjects were not in clinic.

While in the clinic for PK sampling days, study drug was administered between 7 AM and 9 AM, within 60 minutes after completion of a standard breakfast. The two study drugs were given at approximately the same time on each dosing occasion (within a 1-hour window). See table below for the treatment schedule.

**Table 1 Treatment Schedule**

| | Cycle 1 | | Cycle 2 | |
|---|---|---|---|---|
| Study Drug | Study Day 1 to 21 | Study Day 22 to 28[a] | Study Day 29 to 49 | Study Day 50 to 56[a] |
| Modicon (0.5 mg NE and 0.035 mg EE qd) | X | | X | |
| VX-950 (750 mg q8h) | | | X | X |

[a] Per package insert, Modicon treatment consisted of 21 days of tablets qd, followed by 7 days of no tablets.

Study Doses Used and Dose Rationale

The TVR dose used in this study was 750 mg q8h. This regimen was generally safe and well-tolerated in healthy subjects and was being used in ongoing clinical trials, as well as is the dose proposed for approval. The dose used for Modicon (0.5 mg NE + 0.035 mg EE) is an approved and commercially available product in the Netherlands.

*Reviewer's Comments:*
*-Modicon in the Netherlands is the same product as Modicon-28 in the U.S.*
*-It is unknown if there exists a food effect for Modicon. The label is silent on dosing instructions with reference to a meal.*

Formulation(s) Used

The TVR 250-mg (b) (4) tablet was used in this study. The same 250-mg tablet was used in a BE study (VX06-950-010) comparing it to the 375-mg core tablet. That study showed that in the fed state, the 375-mg tablet had ~35% higher bioavailability than the 250-mg tablet.

*Key Inclusion Criteria:*
-Female subjects between 18 and 45 years of age (inclusive) who were premenopausal
-Subjects must have been taking Modicon or an equivalent monophasic OC containing at least 0.02 mg EE combined with progesterone for at least 3 months. Note: Subjects using contraceptive patches or injectable or implanted contraceptives were considered eligible
-Subjects must have had a negative serum pregnancy test at screening
-Subjects' partners must have been vasectomized or subject agreed to use 2 methods of contraception, that are highly effective, one barrier method (condom or diaphragm with spermicidal jelly), during the study and for 24 weeks following the last dose of study drug. The OC taken for study purposes did not count as a contraception method
-Subjects must have had a body mass index (BMI) from 18.0 to 28.0 $kg/m^2$ (inclusive) at screening
-Subjects must have been judged to be in good health on the basis of medical history, physical examination, and routine laboratory measurement results. Medical history and physical examination (including ECG) must have been without major or clinically significant findings
-Subjects must have had hematology and clinical chemistry values of blood and urine within normal range or showed no clinically significant deviations from normal range during the screening period, as judged by the medical investigator

*Key Exclusion Criteria:*
-Subjects who were pregnant or lactating at screening
-Subjects with a smoking habit. Note: Subjects who had stopped smoking ≥6 months prior to screening were considered non-smokers

-Subjects with a history of any illness that, in the opinion of the investigator or the subject's general practitioner, confounded the results of the study or posed an additional risk in administering study drug(s) to the subject
-Regular treatment with prescription medications. Subjects were to have ended any short courses of prescription medications at least 14 days prior to the screening visit. Prescription medications were not to be administered during the study. (Potential subjects were not to stop any chronic, prescribed medication being taken at the direction of a physician, without obtaining agreement from that physician)
-Regular treatment with over-the-counter medications. Subjects were to end over-the-counter medication on the date of the screening visit but no less than 2 days prior to administration of study drug. Occasional use of acetaminophen or ibuprofen was allowed during the study for the treatment of pain (under supervision of the investigator)
-Subjects who consumed herbal medications or dietary medications, dietary supplements (e.g., St. John's Wort, ginkgo biloba, garlic supplements), vitamins, and grapefruit or grapefruit juice within 14 days before administration of study drug (Day 1).
-Subjects who consumed more than 2 units of alcoholic beverages per day or more than 14 units per week.
-Subjects who consumed an average of more than 5 cups of coffee or other caffeinated beverage
-Subjects who had a history of drug or alcohol abuse or addiction within 2 years prior to dosing, or who tested positive for alcohol or drugs of abuse such as cannabis, cocaine, amphetamines or opiates during the screening period
-Subjects who had participated in a clinical study involving administration of either an investigational or a marketed drug within 2 months or 5 half lives (whichever is longer) prior to the screening visit
-Subjects who tested positive for any of the following infectious disease tests: hepatitis B surface antigen (HBsAg), HCV antibody (HCV Ab), human immunodeficiency virus Type 1 antibody (HIV-1 Ab), or human immunodeficiency virus Type 2 antibody (HIV-2 Ab)

Blood Sampling for PK

Blood samples for determination of TVR and VRT-127394 (R-diastereomer of TVR) plasma concentrations were collected at pre-dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, and 8 hours post-dose after the first dose on study days 49 and 56. In addition, pre-dose blood samples were collected before the morning dose on days 29, 35, and 42.

Blood samples for determination of NE and EE concentrations in plasma were collected at pre-dose on Days -1, 7, 14, 28, 35, and 42 and at the following timepoints on days 21 and 49: pre-dose and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post-dose.

Blood samples to assess progesterone, LH, and FSH levels in serum took place at screening and pre-dose on days 7, 21, 35, and 49.

Bioanalytical Results

Plasma samples were analyzed for TVR and VRT-127394 by HPLC with tandem mass spectrometric detection (LC-MS/MS) by (b) (4). Samples were received in frozen condition between September 21, 2006 and October 9, 2006. Samples were analyzed between September 28, 2006 and October 12, 2006. The samples were stored at -70°C. The maximum sample storage until analysis was 21 days, which is within the validated long-term frozen stability duration of 6 months.

The calibration standard concentrations for both TVR and VRT-127394 were 2.0, 4.0, 10.0, 50.0, 200.0, 500, 800, and 1000 ng/mL. The mean accuracy and precision estimates at each TVR and VRT-127394 standard concentration are presented in Tables 2 and 3, respectively, below. All accuracy and precision (%CV) values were within the acceptable range (≤20% from nominal at the LLOQ concentration and ≤15% from nominal at all other concentrations). Quality control concentrations for both analytes were 6.0, 250, and 800 ng/mL. The mean accuracy ranged from 100.2 to 100.6% for TVR and 99 to 100.4% for VRT-127394. The mean precision ranged from 2.6 to 4.4% for TVR and 4.1 to 5.5% for VRT-127394.

Plasma samples were analyzed for EE by HPLC with tandem mass spectrometric detection (LC-MS/MS) by (b) (4). The samples were received between September 21, 2006 and October 9, 2006. Samples were analyzed between October 18, 2006 and October 27, 2006. The samples were stored at -20°C. The maximum sample storage time for any given sample until analysis was 35 days which is within the long-term frozen stability duration of 268 days.

The calibration standard concentrations for EE were 2.0, 4.0, 10.0, 50.0, 200, 500, 800 and 1000 pg/mL. The mean accuracy and precision estimates at each EE standard concentration are presented in Table 4 below. All accuracy and precision (%CV) values were within the acceptable range (≤20% from nominal at the LLOQ concentration and ≤15% from nominal at all other concentrations). Quality control concentrations were 6, 125, and 800 pg/mL. The mean accuracy ranged from 93.4 to 104% and the mean precision ranged from 5.7 to 8.3%.

Plasma samples were analyzed for NE by HPLC with tandem mass spectrometric detection (LC-MS/MS) by (b) (4). The samples were received between September 21, 2006 and October 9, 2006. Samples were analyzed between October 13, 2006 and October 24, 2006. The samples were stored at -20°C. The maximum sample storage time for any given sample until analysis was 3 days, which is within the validated long-term frozen stability duration of 23 days.

The calibration standard concentrations for NE were 0.1, 0.2, 0.5, 2.50, 10.0, 25.0, 40.0 and 50.0 ng/mL. The mean accuracy and precision estimates at each NE standard concentration are presented in Table 5 below. All accuracy and precision (%CV) values were within the acceptable range (≤20% from nominal at the LLOQ concentration and ≤15% from nominal at all other concentrations). Quality control concentrations were 0.3, 5, and 40 ng/mL. The mean accuracy ranged from 97.2 to 102.6% and the mean precision ranged from 3.9 to 4.5%.

**Table 2 Mean Calibration Standard Concentrations and Statistics for TVR**

| Nominal Concentrations (ng/ml) | 2.00 | 4.00 | 10.0 | 50.0 | 200 | 500 | 800 | 1000 |
|---|---|---|---|---|---|---|---|---|
| Mean (ng/ml) | 2.02 | 4.02 | 9.39 | 48.5 | 205 | 504 | 800 | 1045 |
| SD (ng/ml) | 0.1 | 0.1 | 0.4 | 1.5 | 8.3 | 12.1 | 17.7 | 33.6 |
| CV (%) | 3.8 | 3.4 | 3.9 | 3.1 | 4.1 | 2.4 | 2.2 | 3.2 |
| Accuracy (%) | 101.0 | 100.5 | 93.9 | 96.9 | 102.3 | 100.9 | 100.0 | 104.5 |
| n | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 |

**Table 3 Mean Calibration Standard Concentrations and Statistics for VRT-127394**

| Nominal Concentrations (ng/ml) | 2.00 | 4.00 | 10.0 | 50.0 | 200 | 500 | 800 | 1000 |
|---|---|---|---|---|---|---|---|---|
| Mean (ng/ml) | 1.99 | 4.03 | 10.1 | 48.9 | 199 | 495 | 809 | 1017 |
| SD (ng/ml) | 0.1 | 0.3 | 0.5 | 2.1 | 8.8 | 29.3 | 36.8 | 44.8 |
| CV (%) | 6.7 | 6.5 | 5.0 | 4.2 | 4.4 | 5.9 | 4.6 | 4.4 |
| Accuracy (%) | 99.6 | 100.8 | 100.5 | 97.9 | 99.3 | 99.0 | 101.1 | 101.7 |
| n | 18 | 18 | 18 | 18 | 17 | 18 | 18 | 18 |

**Table 4 Mean Calibration Standard Concentrations and Statistics for EE**

| Nominal Concentrations (pg/ml) | 2.00 | 4.00 | 10.0 | 50.0 | 200 | 500 | 800 | 1000 |
|---|---|---|---|---|---|---|---|---|
| Mean (pg/ml) | 1.97 | 4.08 | 10.3 | 49.0 | 210 | 495 | 789 | 958 |
| SD (pg/ml) | 0.1 | 0.2 | 0.4 | 2.1 | 7.7 | 13.5 | 42.6 | 26.8 |
| CV (%) | 2.7 | 4.9 | 3.5 | 4.3 | 3.7 | 2.7 | 5.4 | 2.8 |
| Accuracy (%) | 98.5 | 101.9 | 103.2 | 98.1 | 104.9 | 99.0 | 98.7 | 95.8 |
| n | 12 | 11 | 12 | 12 | 12 | 12 | 12 | 12 |

**Table 5 Mean Calibration Standard Concentrations and Statistics for NE**

| Nominal Concentrations (ng/ml) | 0.100 | 0.200 | 0.500 | 2.50 | 10.0 | 25.0 | 40.0 | 50.0 |
|---|---|---|---|---|---|---|---|---|
| Mean (ng/ml) | 0.101 | 0.200 | 0.482 | 2.54 | 10.1 | 25.2 | 40.3 | 49.6 |
| SD (ng/ml) | 0.0 | 0.0 | 0.0 | 0.1 | 0.2 | 0.6 | 0.8 | 0.8 |
| CV (%) | 3.2 | 6.9 | 2.3 | 2.1 | 1.8 | 2.4 | 1.9 | 1.6 |
| Accuracy (%) | 100.6 | 100.2 | 96.3 | 101.5 | 100.8 | 100.7 | 100.8 | 99.2 |
| n | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

*Reviewer's Comments:*
*-The bioanalytical results for this study are acceptable.*

Results

All 24 of the enrolled subjects completed the study. See table below for the demographics data on the study subjects.

*Demographics*

| | |
|---|---|
| **Number of Subjects Dosed** | 24 |
| **Race (n [%])** | |
| Caucasian | 19 (79) |
| Black | 2 (8) |
| Asian | 3 (13) |
| **Age (years)** | |
| Mean (SD) | 23.8 (5.8) |
| Median | 22.0 |
| Min, Max | 19, 45 |
| **Height (cm)** | |
| Mean (SD) | 171.0 (6.4) |
| Median | 171.5 |
| Min, Max | 161, 185 |
| **Weight (kg)** | |
| Mean (SD) | 61.4 (6.3) |
| Median | 59.6 |
| Min, Max | 50.1, 78.4 |
| **Body Mass Index (kg/m$^2$)** | |
| Mean (SD) | 21.0 (2.2) |
| Median | 20.7 |
| Min, Max | 17.2, 26.3 |

*Safety*

There were no SAEs and no adverse events that led to study drug interruption, discontinuation, or death. The incidence of adverse events was similar in both treatment groups. The number of adverse events and drug-related adverse events was higher after co-administration of Modicon and TVR as compared with administration of Modicon alone. The most frequent adverse events were irregular menstruation (67%), nausea (54%), and headache (50%). During administration of Modicon alone, the most frequent adverse events considered to be related to study drug were irregular menstruation (33%) and headache (25%). During co-administration of Modicon and TVR, the most frequent adverse events considered to be related to study drug were irregular menstruation (58%), headache (46%), and nausea (42%). There were no pregnancies.

*EE Pharmacokinetics*

The co-administration of TVR with Modicon for 21 days resulted in a decrease in EE plasma concentrations as compared with Modicon administration for 21 days alone (Figure 1). Mean EE Cmax, Cmin, and AUCss were decreased by 26%, 32%, and 27%, respectively. In addition, the pattern of decrease was consistent across all subjects studied (Figure 2). The 90% CI for the LSMeans ratio of each EE PK parameter did not fit within the no-effect limits (80-125%) (Table 6).

**Figure 1 Mean EE Plasma Concentration Versus Time Profiles After Administration of Modicon Alone (Day 21) and With TVR (Day 49)**

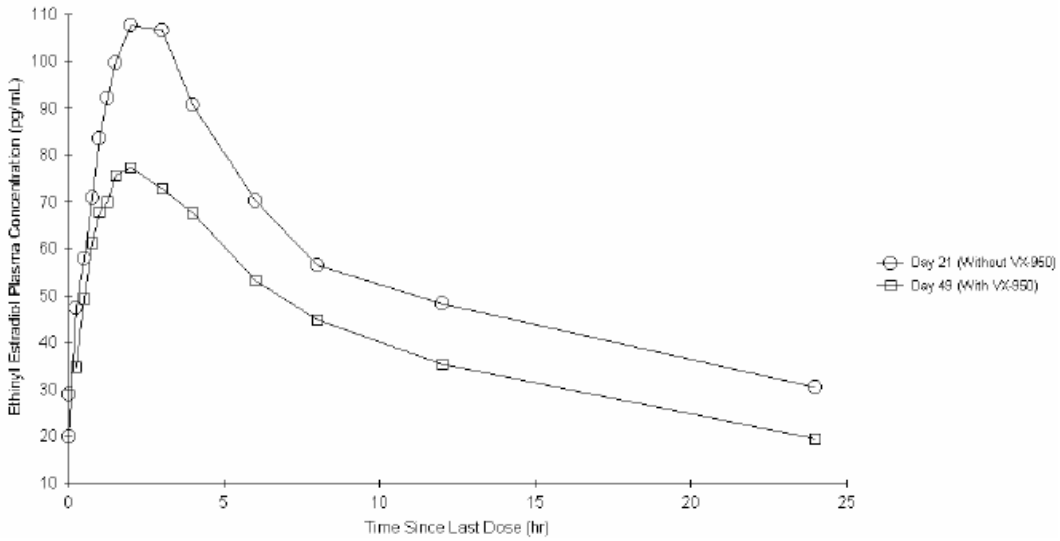



**Figure 2 Mean and Individual EE $AUC_{ss}$ Values**

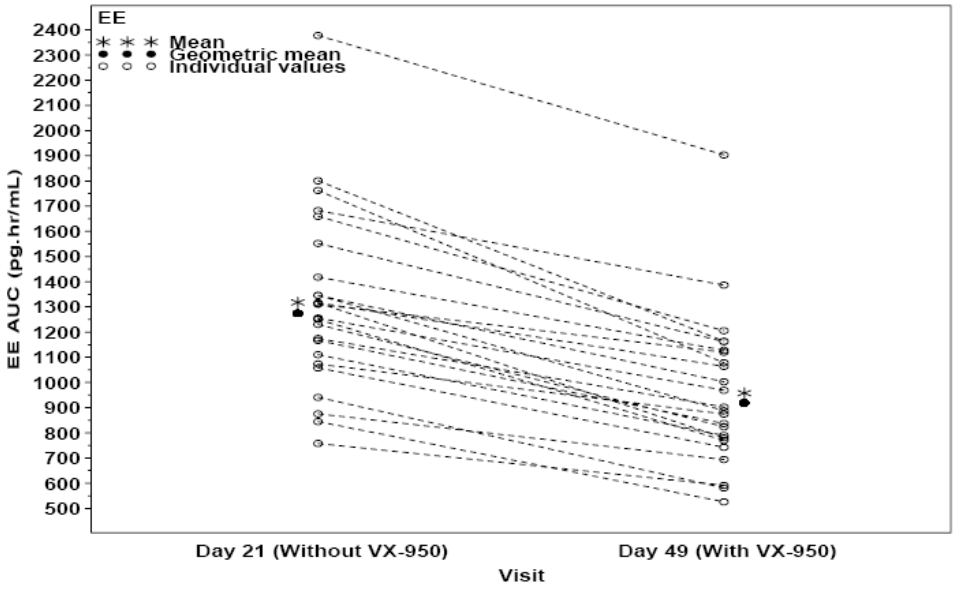



**Table 6 Arithmetic Mean (95%CI) and Statistical Analyses of EE PK Parameters After Administration of Modicon Alone and With Telaprevir**

| Pharmacokinetic Parameter | Day 21: Modicon | Day 49: Modicon + VX-950 |
|---|---|---|
| $AUC_{ss}$ (pg.hr/mL) | 1317.7 (1165.82, 1469.58) | 957.61 (832.26, 1082.97) |
| $C_{max}$ (pg/mL) | 120.87 (107.48, 134.26) | 89.97 (78.16, 101.78) |
| $C_{min}$ (pg/mL) | 27.55 (22.89, 32.2) | 18.72 (14.95, 22.5) |
| $t_{max}$ (hr)[a] | 2.01 (1, 4.02) | 1.75 (0.75, 6) |

| Parameter | Point Estimate (%) | 90% Confidence Interval |
|---|---|---|
| $C_{max}$ Ratio | 73.5 | 67.8, 79.6 |
| $C_{min}$ Ratio | 66.6 | 62.8, 70.7 |
| $AUC_{ss}$ Ratio | 72.1 | 69.3, 74.9 |

*NE Pharmacokinetics*

The co-administration of TVR with Modicon for 21 days resulted in a decrease in NE plasma concentrations as compared with Modicon administration for 21 days alone (Figure 3). Mean NE Cmax, Cmin, and $AUC_{ss}$ were decreased by 16%, 7%, and 10%, respectively. With the exception of approximately 4 subjects, the pattern of decrease was generally consistent across all subjects studied (Figure 4). The largest decrease observed was a 29% decrease in AUC in one subject. The 90% CI for the LSMeans ratio of each NE PK parameter still fit within the no-effect limits (80-125%), indicating that the interaction is not likely to be clinically significant (Table 7).

**Figure 3 Mean NE Plasma Concentration Versus Time Profiles After Administration of Modicon Alone (Day 21) and With TVR (Day 49)**

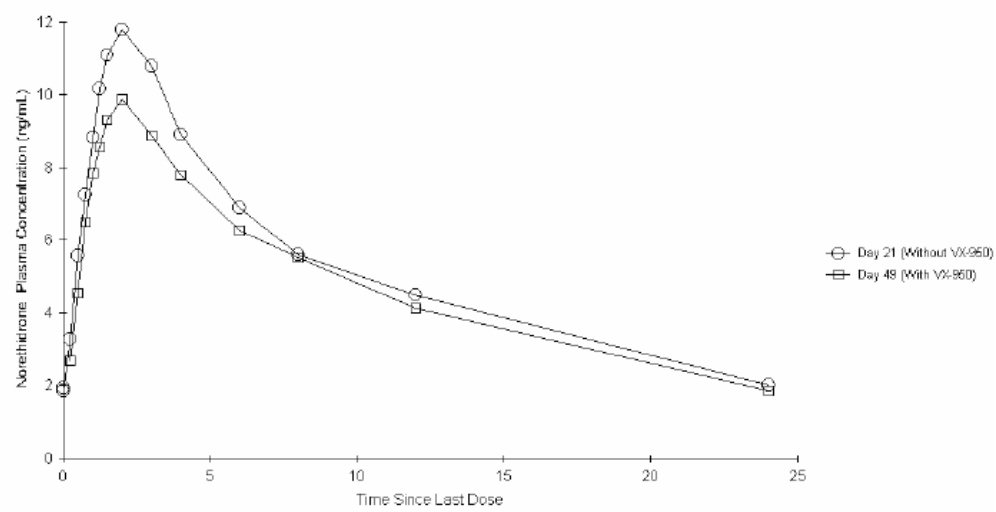



**Figure 4 Mean and Individual NE $AUC_{ss}$ Values**

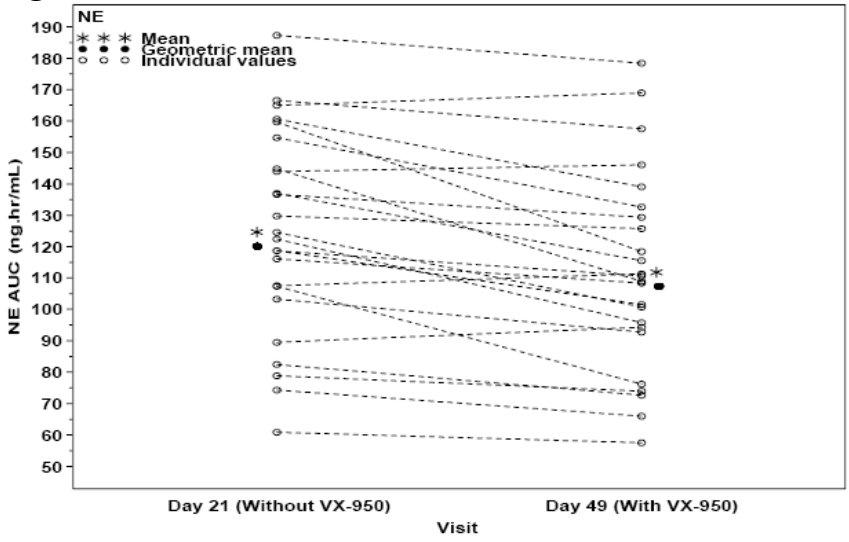


**Table 7 Arithmetic Mean (95%CI) and Statistical Analyses of NE PK Parameters After Administration of Modicon Alone and With Telaprevir**

| Pharmacokinetic Parameter | Day 21: Modicon Alone | Day 49: Modicon + VX-950 |
|---|---|---|
| $AUC_{ss}$ (ng.hr/mL) | 124.63 (110.77, 138.48) | 111.79 (98.39, 125.19) |
| $C_{max}$ (ng/mL) | 12.92 (11.7, 14.15) | 10.91 (9.88, 11.95) |
| $C_{min}$ (ng/mL) | 1.82 (1.48, 2.15) | 1.69 (1.38, 2.01) |
| $t_{max}$ (hr)[a] | 1.76 (0.5, 3) | 2 (0.75, 4.03) |

| Parameter | Point Estimate (%) | 90% Confidence Interval |
|---|---|---|
| $C_{max}$ Ratio | 84.6 | 80.6, 88.8 |
| $C_{min}$ Ratio | 93.6 | 86.7, 101 |
| $AUC_{ss}$ Ratio | 89.4 | 86.1, 92.8 |

*TVR Pharmacokinetics*

Mean TVR plasma concentrations were not significantly affected by the co-administration of Modicon. Mean TVR Cmax, Cmin, and $AUC_{ss}$ were only slightly increased by between 1 and 2%. Although mean TVR PK parameters were not significantly affected, the pattern of effect was not consistent across all subjects studied (Figure 6). Eleven out of the 23 evaluable subjects experienced a decrease in TVR $AUC_{ss}$ while 12/23 experienced and increase. However, the 90% CI for the LSMeans ratio of each TVR PK parameter were within the no-effect limits (80-125%) (Table 8).

**Figure 5 Mean TVR Plasma Concentration Versus Time Profiles After Administration of Modicon+TVR (Day 49) and With TVR alone (Day 56)**

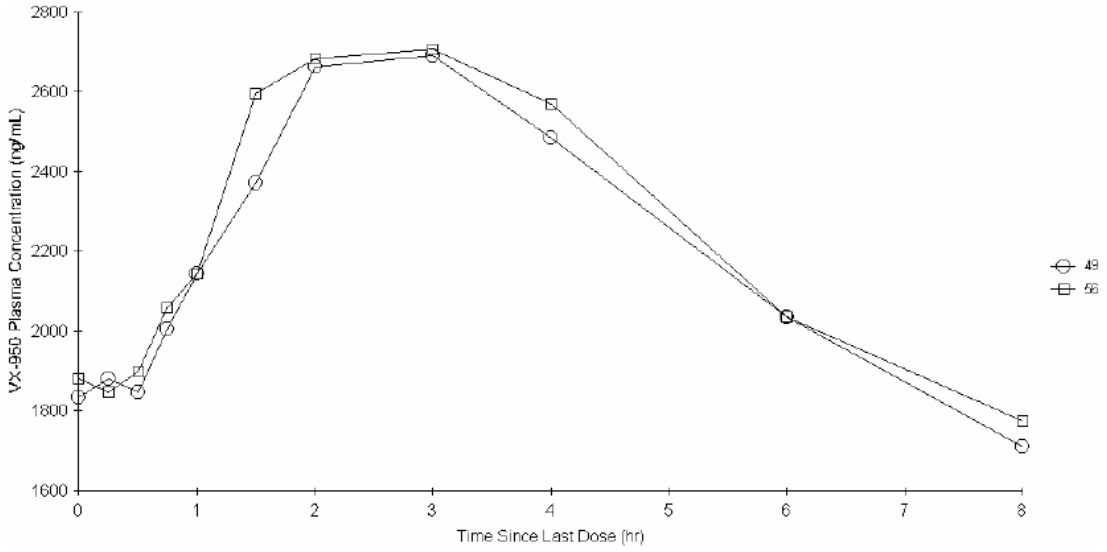


**Figure 6 Mean and Individual TVR $AUC_{ss}$ Values**

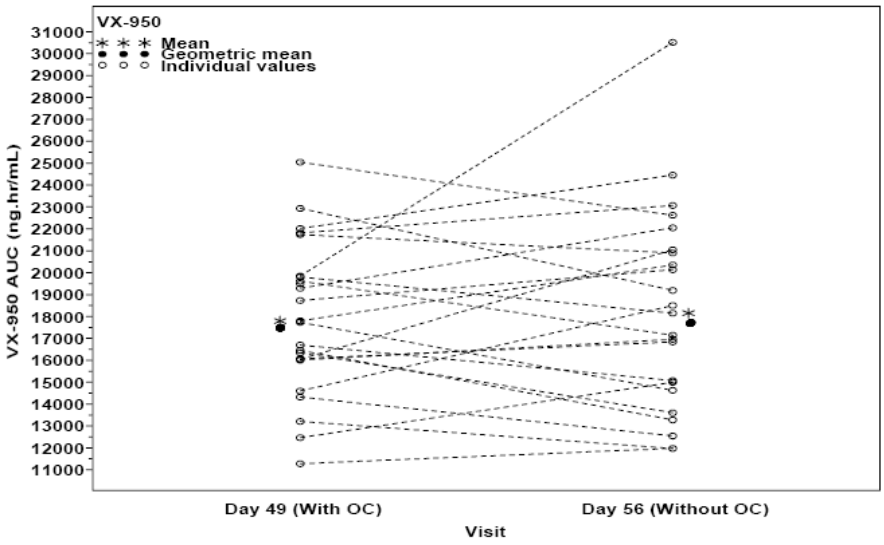



**Table 8 Arithmetic Mean (95%CI) and Statistical Analyses of TVR PK Parameters After Administration of Modicon and With TVR Alone**

| Pharmacokinetic Parameter | Day 49: VX-950 + Modicon | Day 56: VX-950 Alone |
|---|---|---|
| $AUC_{ss}$ (ng.hr/mL) | 17787.01 (16333.2, 19240.82) | 18157.2 (16174.17, 20140.24) |
| $C_{max}$ (ng/mL) | 2914.71 (2659.07, 3170.34) | 2968.57 (2582.43, 3354.7) |
| $C_{min}$ (ng/mL) | 1595.29 (1445.4, 1745.18) | 1608.43 (1427.17, 1789.7) |
| $t_{max}$ (hr)[a] | 3 (0.75, 6.03) | 3 (1.02, 4.02) |

| Parameter | Point Estimate (%) | 90% Confidence Interval |
|---|---|---|
| $C_{max}$ Ratio | 99.7 | 93.3, 106.5 |
| $C_{min}$ Ratio | 100.0 | 92.8, 107.7 |
| $AUC_{ss}$ Ratio | 98.6 | 92.8, 104.8 |

*VRT-127394 Pharmacokinetics*

Similar to TVR PK, mean VRT-127394 plasma concentrations were not significantly affected by the co-administration of Modicon. Mean VRT-127394 Cmax, Cmin, and $AUC_{ss}$ were only slightly increased by between 1 and 2%. The 90% CI for the LSMeans ratio of each VRT-127394 PK parameter were within the no-effect limits (80-125%), indicating that the interaction is not statistically significant and not likely to be clinically significant (Table 9).

**Figure 7 Mean VRT-127394 Plasma Concentration Versus Time Profiles After Administration of Modicon+TVR (Day 49) and With TVR alone (Day 56)**

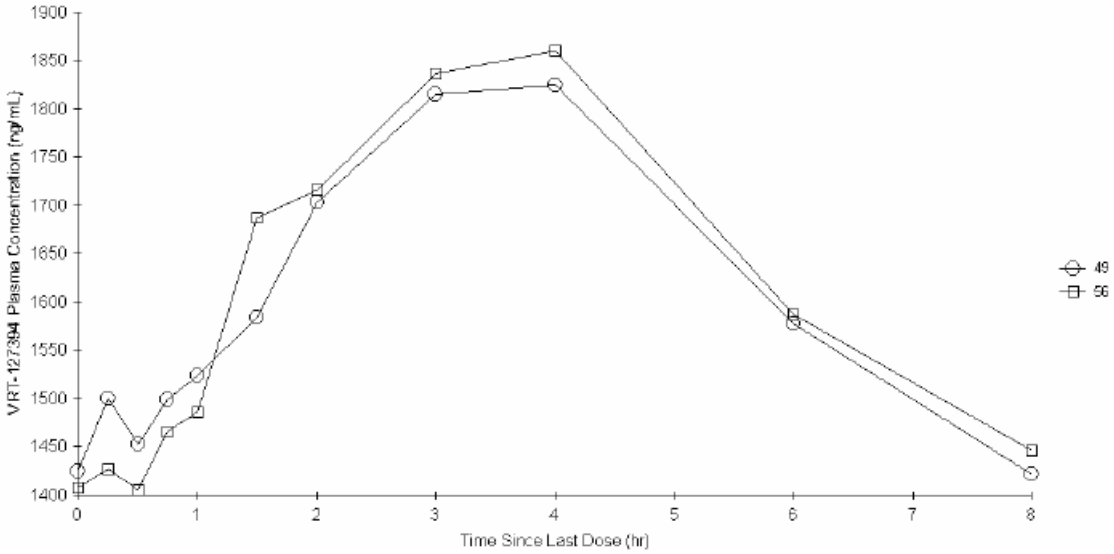



**Table 9 Arithmetic Mean (95%CI) and Statistical Analyses of VRT-127394 PK Parameters After Administration of Modicon Alone and With TVR**

| Pharmacokinetic Parameter | Day 49: VX-950 Plus Modicon | Day 56: VX-950 Alone |
|---|---|---|
| $AUC_{ss}$ (ng.hr/mL) | 13014.12 (11921.44, 14106.8) | 13162.64 (11749.56, 14575.72) |
| $C_{max}$ (ng/mL) | 1984.63 (1818.89, 2150.36) | 1974.13 (1749.83, 2198.43) |
| $C_{min}$ (ng/mL) | 1260.25 (1119.96, 1400.54) | 1256.39 (1112.87, 1399.91) |
| $t_{max}$ (hr)[a] | 3.51 (0.5, 6.03) | 3(1.5, 6.02) |

| Parameter | Point Estimate (%) | 90% Confidence Interval |
|---|---|---|
| $C_{max}$ Ratio | 101.9 | 95.2, 109 |
| $C_{min}$ Ratio | 101.0 | 93.4, 109.3 |
| $AUC_{ss}$ Ratio | 99.9 | 93.7, 106.6 |

*Pharmacodynamic Results-LH and FSH Levels*

Plasma samples were analyzed for LH, FSH, and progesterone concentrations at screening, days 7 and 21 in cycle 1 (Modicon alone), and days 35 and 49 in cycle 2 (Modicon plus TVR). As expected with oral contraceptives, mean values of both LH and FSH declined from day 7 to day 21 in both cycles (Tables 10 and 12). However, the magnitude of decrease in LH and FSH levels were not as great when TVR was co-administered, resulting in higher LH and FSH levels on day 49 in cycle 2 (Modicon+TVR) compared to day 21 in cycle 1 (Modicon alone). Statistical summaries show that the difference is significant for both hormone levels between days 49 and 21 and for FSH between days 35 and 7 (Tables 11 and 13).

**Table 10 Arithmetic Mean (SD) of LH Concentrations (U/L) After Administration of Modicon Alone and Modicon With TVR**

| | | Modicon | | Modicon and VX-950 | |
|---|---|---|---|---|---|
| Parameter | Screening | Day 7 | Day 21 | Day 35 | Day 49 |
| N | 24 | 24 | 24 | 23 | 24 |
| NAQL[a] | 9 | 18 | 5 | 19 | 7 |
| Mean | 0.72 | 3.21 | 0.6 | 3.23 | 1.35 |
| SD | 0.93 | 2.76 | 1.29 | 3.12 | 2.51 |
| Minimum | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| Median | 0.2 | 2.9 | 0.2 | 2.4 | 0.2 |
| Maximum | 3.9 | 9.9 | 6.4 | 10.7 | 9.2 |

[a] Number of samples above the quantifiable limit

**Table 11 Statistical Analysis Summary of LH Concentrations Comparing Modicon With TVR and Without TVR (Day 35 vs. 7 and Day 49 vs. 21)**

| Comparison | Point Estimate (%) | 90% Confidence Interval | *P* value (signed rank test) |
|---|---|---|---|
| Day 35 versus Day 7 | 103.1 | 75.9, 140.1 | 0.9759 |
| Day 49 versus Day 21 | 148.3 | 114.8, 191.6 | 0.0156 |

**Table 12 Arithmetic Mean (SD) of FSH Concentrations (U/L) After Administration of Modicon Alone and Modicon With TVR**

| | | Modicon | | Modicon and VX-950 | |
|---|---|---|---|---|---|
| Parameter | Screening | Day 7 | Day 21 | Day 35 | Day 49 |
| N | 24 | 24 | 24 | 23 | 24 |
| NAQL[a] | 17 | 21 | 14 | 22 | 12 |
| Mean | 1.8 | 2.51 | 0.76 | 3.17 | 1.41 |
| SD | 2.77 | 1.8 | 1.05 | 2.17 | 1.85 |
| Minimum | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| Median | 0.85 | 2.25 | 0.4 | 3.1 | 0.45 |
| Maximum | 13.4 | 6.4 | 4.9 | 7.5 | 6.3 |

[a] Number of samples above the quantifiable limit

**Table 13 Statistical Analysis Summary of FSH Concentrations Comparing Modicon With and Without TVR (Day 35 vs. 7 and Day 49 vs. 21)**

| Comparison | Point Estimate (%) | 90% Confidence Interval | *P* value (signed-ranked test) |
|---|---|---|---|
| Day 35 versus Day 7 | 131.6 | 112.2, 154.3 | 0.0010 |
| Day 49 versus Day 21 | 137.6 | 111.2, 170.2 | 0.0034 |

*Pharmacodynamic Results-Progesterone Levels*

Mean progesterone concentrations decreased from day 7 to 21 while subjects were on Modicon alone (Table 14). Similarly, a decrease was observed from day 35 to day 49

(Modicon+TVR); however, the magnitude of the decrease was not as great. Most subjects had similar progesterone levels on day 7 and day 35 with the exception of 2 outliers (subjects 1004 and 1009). Subject 1004 had a very high level of progesterone at screening (18.8 ng/mL) and at day 7 (10.4 ng/mL) that decreased to 1.2 ng/mL at day 21 in cycle 1. Subject 1009 had a concentration of 1.1 ng/mL at screening, 11 ng/mL at day 7 and 1.6 ng/mL at day 21 in cycle 1. Progesterone levels were lower for most subjects on day 49 compared to day 21. Statistical analysis for progesterone levels show that concentrations were statistically lower when TVR is co-administered with Modicon as compared with Modicon administration alone, irrespective of the cycle day (Table 15).

**Table 14 Arithmetic Mean (SD) of Progesterone Concentrations (ng/mL) After Administration of Modicon Alone and Modicon With TVR**

| | | Modicon | | Modicon and VX-950 | |
|---|---|---|---|---|---|
| ID | Screening | Day 7 | Day 21 | Day 35 | Day 49 |
| N | 24 | 24 | 24 | 23 | 24 |
| NAQL | 24 | 24 | 24 | 23 | 24 |
| Mean | 1.84 | 2.08 | 1.27 | 1.29 | 1.06 |
| SD | 3.62 | 2.67 | 0.27 | 0.23 | 0.33 |
| Minimum | 0.82 | 0.96 | 0.97 | 0.86 | 0.68 |
| Median | 1.1 | 1.3 | 1.25 | 1.3 | 0.99 |
| Maximum | 18.8 | 11 | 1.9 | 1.8 | 2.3 |

**Table 15 Statistical Analysis Summary of Progesterone Concentrations Comparing Modicon With and Without TVR (Day 35 vs. 7 and Day 49 vs. 21)**

| Comparison | Point Estimate (%) | 90% Confidence Interval | *P* value (signed-rank test) |
|---|---|---|---|
| Day 35 versus Day 7 | 83.3 | 63.2, 109.8 | 0.7894 |
| Day 49 versus Day 21 | 82.2 | 75.8, 89.0 | 0.0008 |

*Reviewer's Comments:*
*-Of note, the screening sample for all hormone levels was taken without regard to what day of each subject's cycle they were in. Thus, the relative concentration of hormones in relation to each individual subject's cycle was unknown.*
*-The reproductive/urologic teams within OCP and OND were consulted in order to aid in interpretation of the data and determine whether the decreases in LH, FSH, and progesterone levels as a result of concomitant TVR dosing would be clinically significant and how it would impact the Applicant's proposed labeling statements.*

Conclusions

Although the addition of Modicon to TVR did not alter the PK of TVR and VRT-127394, co-administration with TVR decreased exposure to EE as compared with Modicon administration alone by approximately 25-30%. TVR did not significantly affect exposure to NE following administration with Modicon. Surrogates for the PD effectiveness of Modicon, as measured by decreases in progesterone, FSH, and LH levels, were diminished by co-administration with TVR. The 90% CIs for the geometric mean ratios (Modicon+TVR : Modicon alone) did not fall within the accepted limits for lack of interaction (80-125%).

Upon consultation with the reproductive/urologic teams in both OCP and OND regarding the issue of decreased EE concentrations observed in this study, it was decided that alternative methods (e.g., IUDs or double barrier methods of contraception) should be used when patients are taking TVR. Generally speaking, contraceptive efficacy is more closely related to progestin dose than to estrogen dose. Although there could theoretically be a decrease in efficacy, it is difficult to speculate based on clinical pharmacology results alone because efficacy is affected by the relative proportions of the estrogen and progestin components and their effects on cervical mucus, ovulation and endometrial lining changes. It is unknown whether recommending a minimum ethinyl estradiol dose may ameliorate the concern and the Division of Reproductive and Urologic Products (DRUP) would not favor making such a recommendation. DRUP recommends that alternative methods (e.g., IUDs or double barrier methods of contraception) should be used when patients are taking TVR.

The Applicant's proposed wording for the label is as follows (reviewer's changes in red):

**Highlights**
**WARNINGS AND PRECAUTIONS**

- Patients must have a negative pregnancy test prior to therapy, use at least 2 non-hormonal forms of contraception, and undergo monthly pregnancy tests. (5.3)

(b) (4)

[redacted]

**Section 7, Table 5**

| *HORMONAL CONTRACEPTIVES/ESTROGEN* | | |
|---|---|---|
| ***ethinyl estradiol**** <br> ***norethindrone*** | ↓ ethinyl estradiol <br> ↔ norethindrone | (b) (4) [redacted] <br> ***Patients using estrogens as hormone replacement therapy should be clinically monitored for signs of estrogen deficiency. Refer also to* Contraindications (4), Warnings and Precautions (5.3), Use in Specific Populations (8.1), *and* Patient Counseling Information (17.2).** |

**Section 12.3, Table 6**

| Drug | Dose and Schedule: Drug | Dose and Schedule: Telaprevir | N | Effect on Telaprevir PK[a] | LS Mean Ratio (90% CI) of Telaprevir PK With/Without Coadministered Drug: $C_{max}$ | AUC or $C_{avg,ss}$[b] | $C_{min}$ |
|---|---|---|---|---|---|---|---|
| Oral Contraceptive | Norethindrone/ ethinyl estradiol 0.5 mg/0.035 mg qd for 21 days | 750 mg q8h for 21 days | 23 | ↔ | 1.00 (0.93; 1.07) | 0.99 (0.93; 1.05) | 1.00 (0.93; 1.08) |

**Section 12.3, Table 7**

| Drug | Dose and Schedule: Drug | Dose and Schedule: Telaprevir | N | Effect on Drug PK[a] | LS Mean Ratio (90% CI) of Drug PK With/Without Telaprevir[b]: $C_{max}$ | AUC | $C_{min}$ |
|---|---|---|---|---|---|---|---|
| Ethinyl estradiol (EE), coadministered with norethindrone (NE) | 0.035 mg qd EE/ 0.5 mg qd NE for 21 days | 750 mg q8h for 21 days | 24 | ↓ | 0.74 (0.68; 0.80) | 0.72 (0.69; 0.75) | 0.67 (0.63; 0.71) |

**Section 17.2**
**Pregnancy**

(b) (4)

**Individual Study Review—VX-950-TiDP24-C123**

Title (Study VX-950-TiDP24-C123)

"A Phase I, open-label, randomized, 3-way crossover trial in 18 healthy subjects to investigate the pharmacokinetic interaction between telaprevir and tenofovir disoproxil fumarate at steady-state."

Objectives

- To determine the effect of steady-state concentrations of telaprevir 750 mg q8h on the steady-state pharmacokinetics of tenofovir after administration of TDF 300 mg q.d. in healthy subjects
- To determine the effect of steady-state TDF 300 mg q.d. on the steady-state pharmacokinetics of telaprevir and VRT-127394 after administration of telaprevir 750 mg q8h in healthy subjects
- To determine the short-term safety and tolerability of telaprevir administered alone and in combination with TDF in healthy subjects, after 7 days of dosing.

Study Dates and Location(s):
Study initiation: November 22, 2007
Study completion: March 9, 2008
Clinical Sites: PAREXEL International GmbH, Berlin, Germany

Study Design

This was a phase 1, open-label, randomized, 3-treatment, 3-period, 6-sequence, crossover trial in 18 healthy subjects. In 3 sessions, subjects received treatments A, B, and C in a randomized crossover design. In treatment A, 750 mg telaprevir (TVR) q8h was administered for 6 days with an additional 750-mg morning dose on Day 7. In treatment B, 300 mg TDF QD was administered for 7 days. In treatment C, 750 mg TVR q8h and 300 mg TDF QD were co-administered for 7 days. There was a washout period of at least 7 days between subsequent sessions. All treatments were administered under fed conditions. Telaprevir was taken within 30 minutes after the start of a meal or snack. TDF was taken within 30 minutes after the start of a standard breakfast (555 kcal). When TVR and TDF were co-administered (treatment C), TDF had to be administered within 5 minutes after the morning dose of TVR. A schematic overview of the study design is presented in Figure 1 below.

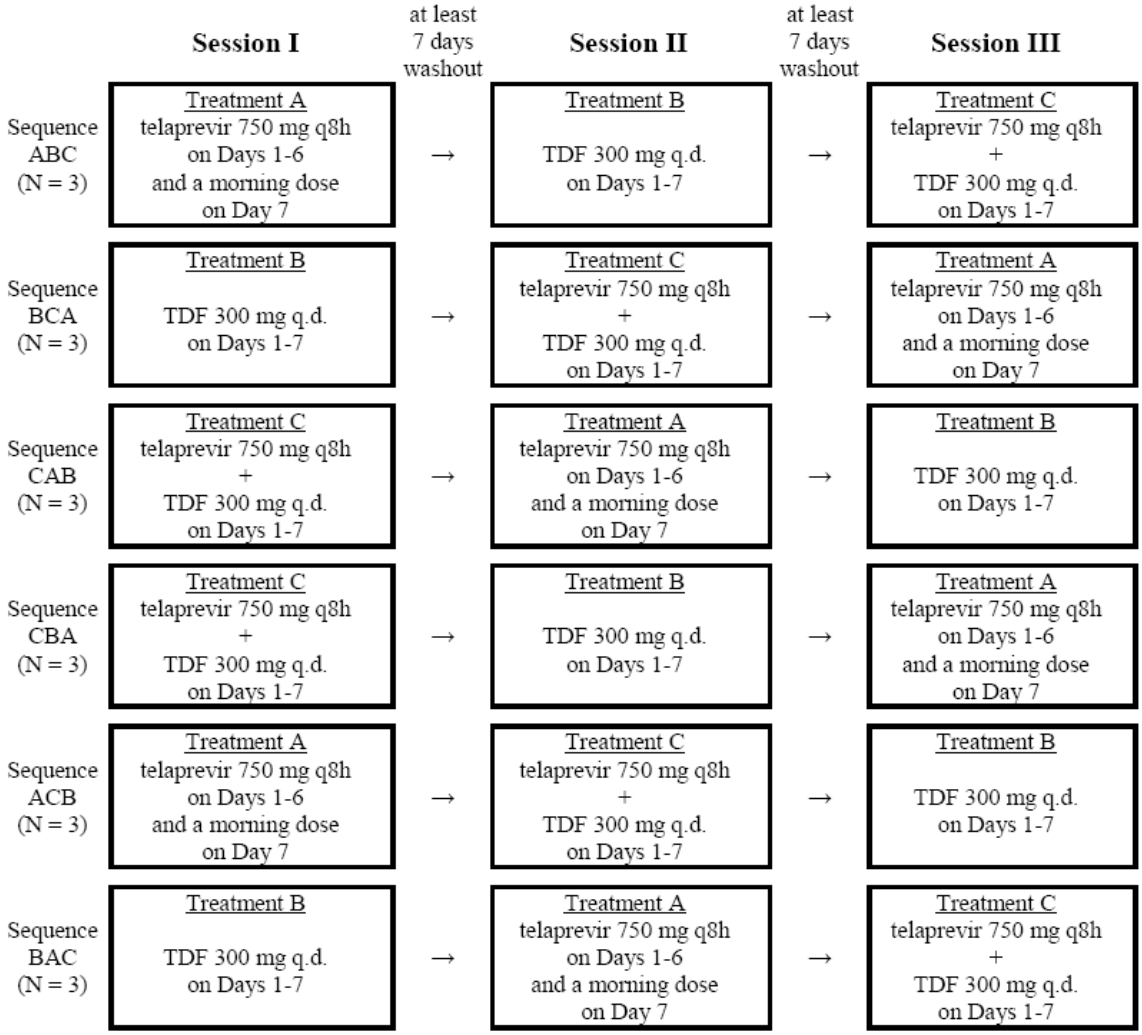
Study Doses Used and Dose Rationale

TVR was administered at a dose of 750 mg q8h, the dose proposed for approval. This dose regimen was generally safe and well-tolerated in healthy subjects and was being used in ongoing clinical trials. The dose used for TDF is the approved dosing regimen of 300 mg QD without regard to food.

Formulation(s) Used

TVR was provided as the 375-mg core (uncoated) tablet. According to the Applicant's Summary of Biopharmaceutics Studies and Associated Analytical Methods document, it is the same formulation as was used in the phase 3 studies. TDF was provided as the commercially available Viread® 300 mg tablets.

**Figure 1 Study Design**




*Key Inclusion Criteria:*
-Male or female, aged between 18 and 55 years of age, extremes included
-Females had to be postmenopausal for at least 2 years, or had to have had a hysterectomy or tubal ligation (without reversal operation)
-Being nonsmoking or smoking no more than 10 cigarettes, or 2 cigars, or 2 pipes per day for at least 3 months before screening
-Having a normal weight as defined by a body mass index (BMI) between 18 and 30 $kg/m^2$ extremes included, at screening
-Being healthy on the basis of a medical evaluation that revealed the absence of any clinically relevant abnormality and included a physical examination, medical history, electrocardiogram (ECG), vital signs, blood biochemistry and hematology tests, and a urinalysis carried out at screening

*Key Exclusion Criteria:*
-Having a history of any illness that, in the opinion of the investigator, could confound the results of the trial or pose an additional risk in administering study medication to the subject
-Having any history of renal disease

-Having a serum creatinine abnormality grade 1 or higher (≥1.1 x upper limit of laboratory normal range [ULN])
-Currently using prescription medication
-Being regularly treated with over-the-counter medications
-Consuming herbal medications or dietary supplements (e.g., St. John's wort, ginkgo biloba, garlic supplements), vitamins, and grapefruit or grapefruit juice, apple juice, or orange juice within 14 days before the first administration of study medication
-Consuming more than 2 units of alcoholic beverages per day, or more than 14 units per week
-Consuming an average of more than 5 240-mL servings of coffee or other caffeinated beverage (e.g., tea, cola) per day
-Consuming an average of more than 5 240-mL servings of coffee or other caffeinated beverage (e.g., tea, cola) per day
-Having a hemoglobin value of < 12 g/dL
-Having a positive test result for any of the following infectious disease tests: hepatitis A infection (confirmed by hepatitis A antibody immunoglobulin M [IgM]), hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCVAb), HIV-1 antibody (HIV1Ab), or HIV-2 antibody (HIV2Ab)
-Male subjects having female partners who were pregnant, breastfeeding, or planning to become pregnant during the trial or within 90 days of the last dose of study medication
-Having previously participated in a trial (single or multiple dose) with telaprevir
-Breastfeeding women

Blood Sampling for PK

**Treatment A:** Blood samples for determination of TVR and VRT-127394 (R-diastereomer of TVR) plasma concentrations were collected at pre-dose on days 5 and 6 and at the following times on day 7: pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, and 8 hours post-dose. A blood sample for determination of TNF concentrations was collected on day -1 (pre-dose).

**Treatment B:** A blood sample for determination of TVR and VRT-127394 plasma concentrations was collected on day -1 (pre-dose). Blood samples for determination of tenofovir plasma concentrations were collected at pre-dose on days -1, 5, and 6 and at the following times on day 7: pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 hours post-dose.

**Treatment C:** Blood samples for determination of TVR and VRT-127394 plasma concentrations were collected at pre-dose on days -1, 5, and 6 and at the following times on day 7: pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 16, and 24 hours post-dose. Blood samples for determination of tenofovir plasma concentrations were collected at pre-dose on days -1, 5, and 6 and at the following times on day 7: pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 16, and 24 hours post-dose.

Urine Sampling for Urinary Excretion and Creatinine Clearance Measurements

For all treatments (A, B, and C), serial 24-hour urine samples were obtained following the last dose of study drug on day 7.

Bioanalytical Results

Plasma samples were analyzed for TVR and VRT-127394 by HPLC with tandem mass spectrometric detection (LC-MS/MS) by (b) (4). Samples were received in frozen condition between January 22, 2008 and January 31, 2008. The samples were stored at -70°C. The samples were analyzed between January 29, 2008 and February 4, 2008.

The maximum sample storage time until analysis was 74 days, which is within the validated long-term frozen stability duration of 6 months.

The calibration standard concentrations for both TVR and VRT-127394 were 2.0, 4.0, 10.0, 50.0, 200.0, 500, 800, and 1000 ng/mL. The mean accuracy and precision estimates at each TVR and VRT-127394 standard concentration are presented in Tables 2 and 3, respectively, below. All accuracy and precision (%CV) values were within the acceptable range (≤20% from nominal at the LLOQ concentration and ≤15% from nominal at all other concentrations). Quality control concentrations for TVR and VRT-127394 were 6.0, 250, and 800 ng/mL. The mean accuracy ranged from 92.8 to 100.8% for TVR and 95.4 to 100.0% for VRT-127394. The mean precision ranged from 2.6 to 9.5% for TVR and 5.0 to 6.6% for VRT-127394.

Plasma samples were analyzed for tenofovir by HPLC with tandem mass spectrometric detection (LC-MS/MS) by (b) (4). Samples were received in frozen condition between January 22, 2008 and January 31, 2008. The samples were stored at -20°C. The samples were analyzed between January 31, 2008 and February 11, 2008. The maximum sample storage time until analysis was 81 days, which is outside the validated long-term frozen stability duration of 88 days.

The calibration standard concentrations for tenofovir were 4, 8, 20, 50, 100, 250, 400, and 500 ng/mL. The mean accuracy and precision estimates at each tenofovir standard concentration are presented in Table 4 below. All accuracy and precision (%CV) values were within the acceptable range (≤20% from nominal at the LLOQ concentration and ≤15% from nominal at all other concentrations). Quality control concentrations for tenofovir were 12, 75, and 400 ng/mL. The mean accuracy in the QC samples ranged from 102.2 to 104.4%. The mean precision ranged from 8.2 to 10.7%.

Urine samples were analyzed for tenofovir by HPLC with tandem mass spectrometric detection (LC-MS/MS) by (b) (4). Samples were received in frozen condition between January 22, 2008 and January 29, 2008. The samples were stored at -20°C. The samples were analyzed between February 14, 2008 and February 15, 2008. The maximum sample storage time until analysis was 74 days, which is within the validated long-term frozen stability duration of 88 days.

The calibration standard concentrations for tenofovir in urine were 20, 40, 100, 500, 1000, 2500, 4000, and 5000 ng/mL. The mean accuracy and precision estimates at each tenofovir standard concentration are presented in Table 5 below. Quality control concentrations for tenofovir were 60, 750, 4000, and 40000 ng/mL. The mean accuracy in the QC samples ranged from 88% to 105.3%. The mean precision ranged from 3.9 to 23%.

**Table 2 Mean Calibration Standard Concentrations and Statistics for TVR**

| | VX-950, ng/ml | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Analytical batch | 2.00 | 4.00 | 10.0 | 50.0 | 200 | 500 | 800 | 1000 |
| n | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| mean | 2.00 | 4.05 | 9.66 | 48.6 | 207 | 517 | 833 | 940 |
| std. dev. | 0.1 | 0.2 | 0.3 | 1.2 | 6.6 | 10.7 | 22.8 | 25.9 |
| %CV | 5.1 | 4.4 | 3.4 | 2.6 | 3.2 | 2.1 | 2.7 | 2.8 |
| % accuracy | 100.2 | 101.2 | 96.6 | 97.2 | 103.4 | 103.4 | 104.1 | 94.0 |

**Table 3 Mean Calibration Standard Concentrations and Statistics for VRT-127394**

| | VX-950, ng/ml | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Analytical batch | 2.00 | 4.00 | 10.0 | 50.0 | 200 | 500 | 800 | 1000 |
| n | 12 | 11 | 12 | 12 | 12 | 12 | 12 | 12 |
| mean | 1.99 | 4.02 | 10.1 | 51.0 | 198 | 504 | 815 | 956 |
| std. dev. | 0.2 | 0.2 | 0.8 | 2.7 | 10.2 | 24.5 | 39.9 | 39.9 |
| %CV | 8.1 | 5.8 | 7.7 | 5.3 | 5.2 | 4.9 | 4.9 | 4.2 |
| % accuracy | 99.6 | 100.5 | 100.8 | 102.0 | 98.8 | 100.8 | 101.9 | 95.6 |

**Table 4 Mean Calibration Standard Concentrations and Statistics for Tenofovir in Plasma**

| | Tenofovir, ng/ml | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Analytical batch | 4.00 | 8.00 | 20.0 | 50.0 | 100 | 250 | 400 | 500 |
| n | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 5 |
| mean | 4.02 | 7.84 | 20.2 | 51.4 | 101 | 247 | 390 | 503 |
| std. dev. | 0.1 | 0.5 | 1.0 | 2.7 | 5.7 | 9.5 | 13.3 | 17.8 |
| %CV | 3.3 | 6.9 | 4.7 | 5.2 | 5.6 | 3.8 | 3.4 | 3.5 |
| % accuracy | 100.6 | 98.0 | 101.1 | 102.8 | 100.7 | 98.9 | 97.4 | 100.6 |

**Table 5 Mean Calibration Standard Concentrations and Statistics for Tenofovir in Urine**

| | Tenofovir, ng/ml | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Analytical batch | 20.0 | 40.0 | 100 | 500 | 1000 | 2500 | 4000 | 5000 |
| AQ12-001 | 21.2 | 36.4 | 92.6 | 483 | 1070 | 2560 | 4170 | 5010 |
| AQ12-002 | 20.3 | (31.7) [1)] | 92.4 | 517 | 902 | 2720 | 3930 | 5270 |
| n | 2 | 1 | 2 | 2 | 2 | 2 | 2 | 2 |
| mean | 20.7 | 36.4 | 92.5 | 500 | 986 | 2640 | 4050 | 5140 |
| std. dev. | 0.6 | | 0.2 | 23.8 | 118.0 | 113.8 | 168.3 | 184.1 |
| %CV | 3.0 | | 0.2 | 4.8 | 12.0 | 4.3 | 4.2 | 3.6 |
| % accuracy | 103.7 | 91.1 | 92.5 | 100.1 | 98.6 | 105.6 | 101.2 | 102.8 |

[1)] Value outside the acceptance limits, not included in summary statistics.

*Reviewer's Comments:*
*-One precision (%CV) value for tenofovir in urine was not within the acceptable range (inter-batch precision was 23% at the LLOQ). However, most sample concentrations were well above the LLOQ and thus ranged between the middle, high, and very high QC concentrations.*

Results

A total of 39 subjects were screened and 18 were randomized to start treatment. One subject discontinued the trial due to an AE (right hand fracture) and one subject withdrew consent. The remaining 16 subjects completed the trial.

*Demographics*

| Parameter | Sequence ABC N = 3 | Sequence BCA N = 3 | Sequence CAB N = 3 | Sequence CBA N = 3 | Sequence ACB N = 3 | Sequence BAC N = 3 | All Subjects N = 18 |
|---|---|---|---|---|---|---|---|
| Age, years | 44.0 | 48.0 | 47.0 | 36.0 | 48.0 | 46.0 | 45.0 |
| Median (range) | (43-53) | (30-51) | (44-54) | (30-37) | (21-53) | (35-51) | (21-54) |
| Height, cm | 171.0 | 174.0 | 184.0 | 186.0 | 182.0 | 176.0 | 179.0 |
| Median (range) | (168-177) | (164-191) | (156-189) | (173-196) | (182-192) | (166-181) | (156-196) |
| Weight, kg | 81.0 | 88.0 | 89.0 | 85.0 | 95.0 | 79.0 | 83.0 |
| Median (range) | (75-96) | (71-108) | (63-96) | (69-107) | (74-109) | (70-81) | (63-109) |
| BMI, $kg/m^2$ | 28.70 | 29.10 | 25.90 | 27.90 | 28.70 | 25.40 | 27.15 |
| Median (range) | (25.6-30.6) | (26.4-29.6) | (24.9-28.4) | (19.9-28.4) | (22.3-29.6) | (24.7-25.5) | (19.9-30.6) |
| Sex, n (%) | | | | | | | |
| Female | 1 (33.3) | 1 (33.3) | 1 (33.3) | 0 | 0 | 0 | 3 (16.7) |
| Male | 2 (66.7) | 2 (66.7) | 2 (66.7) | 3 (100.0) | 3 (100.0) | 3 (100.0) | 15 (83.3) |
| Ethnic Origin, n (%) | | | | | | | |
| Caucasian/White | 3 (100.0) | 3 (100.0) | 3 (100.0) | 3 (100.0) | 2 (66.7) | 3 (100.0) | 17 (94.4) |
| Other | 0 | 0 | 0 | 0 | 1 (33.3) | 0 | 1 (5.6) |
| Type of Smoker, n (%) | | | | | | | |
| Light | 2 (66.7) | 1 (33.3) | 2 (66.7) | 3 (100.0) | 1 (33.3) | 3 (100.0) | 12 (66.7) |
| Nonsmoker | 1 (33.3) | 2 (66.7) | 1 (33.3) | 0 | 2 (66.7) | 0 | 6 (33.3) |

N = number of subjects; n = number of observations
Treatment A: telaprevir 750 mg q8h on Days 1-6; 750-mg morning dose on Day 7;
Treatment B: TDF 300 mg q.d. on Days 1-7;
Treatment C: telaprevir 750 mg q8h on Days 1-7; TDF 300 mg q.d. on Days 1-7.

*Safety*

Overall, 14 (77.8%) subjects experienced at least one AE during the whole trial. One or more AEs were reported in 11 (64.7%) subjects during administration of TVR alone, in 10 (62.5%) subjects during administration of TDF alone, and in 7 (41.2%) subjects during co-administration of TVR and TDF. One (5.9%) subject experienced an SAE (hand fracture) during treatment with TVR alone in the first session that was judged as not related to the study medication by the investigator. In addition, no AEs with severity grade 3 were reported during this trial.

The most frequent AEs were related to the nervous system disorders and gastrointestinal disorders (AEs in both system organ classes were reported in 11 [61.1%] subjects). The most frequently reported AEs (reported in more than 3 subjects in this trial) were headache (in 9 [50%] subjects), anal discomfort (in 7 [38.9%] subjects), and somnolence (in 4 [22.2%] subjects).

*TVR Pharmacokinetics*

When examining the individual concentration-time profiles for TVR, plasma concentrations between TVR treatment and TVR+TDF treatment appear similar at each timepoint (mean profile Figure 2). In addition, the inter-subject variability is not significantly different between treatments. TVR alone or in the presence of TDF resulted in comparable mean values of $C_{0h}$, Cmin, Cmax, and $AUC_{8h}$ for TVR (Table 5). The %CV for Cmin, Cmax, and $AUC_{8h}$ ranged from 23% to 32%. Tmax was also not affected by the co-administration of TDF (~3 hours for both treatment groups).

*Reviewer's Comments:*
*-There is an initial decline in TVR concentrations that is present in the concentration-time profiles of both treatment groups. The Applicant has not provided an explanation for this occurrence but it does not appear to be related to the concomitant treatment with TDF since it occurs irrespective of TDF treatment.*

**Figure 2 Mean Plasma Concentration-Time Profiles for TVR**

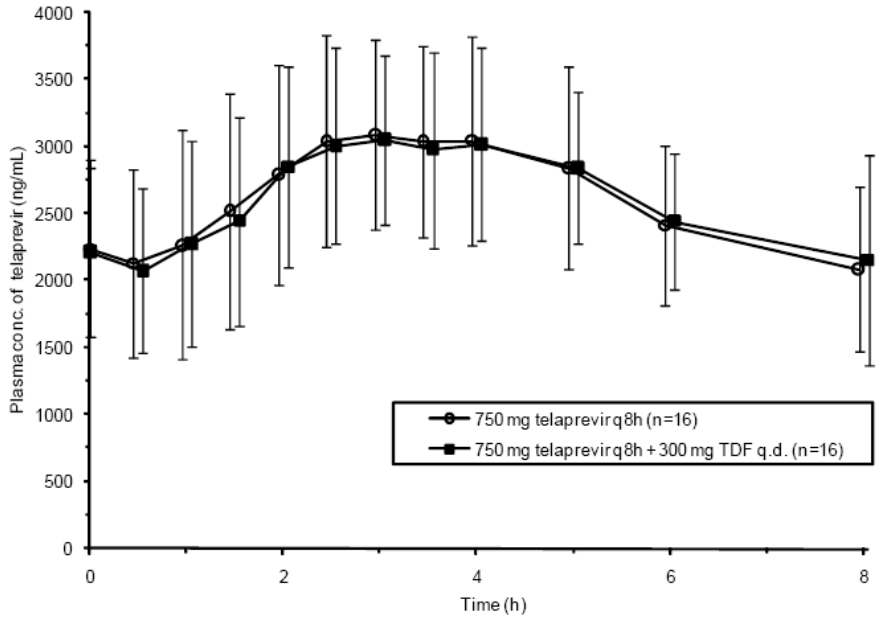
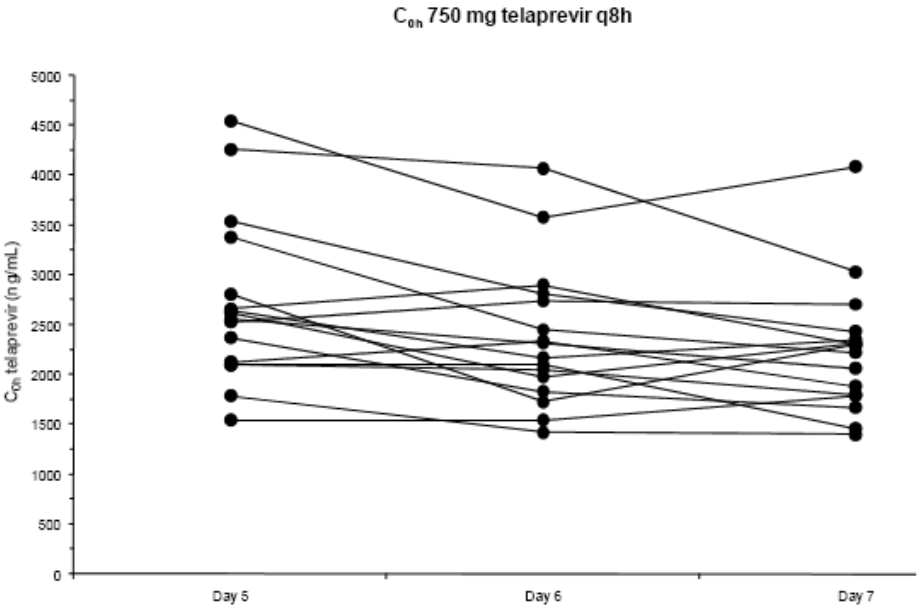



**Figure 3 Pre-dose Plots of TVR ($C_{0h}$ on Days 5, 6, 7)**




Based on the plots of individual C0h concentrations on days 5, 6, and 7, most subjects appeared to reach steady-state by day 7 (Figure 3).

**Table 5 Summary TVR PK Parameters Following Administration of TVR Alone and in Combination with TDF**

| *Pharmacokinetics of telaprevir* (mean ± SD, $t_{max}$: median [range]) | 750 mg telaprevir q8h | 750 mg telaprevir q8h + 300 mg TDF q.d. |
|---|---|---|
| n | 16 | 16 |
| $C_{0h}$, ng/mL | 2238 ± 659.6 | 2215 ± 628.1 |
| $C_{min}$, ng/mL | 1903 ± 617.9 | 1941 ± 575.2 |
| $C_{max}$, ng/mL | 3338 ± 765.5 | 3362 ± 812.3 |
| $t_{max}$, h | 3.0 (1.5 - 5.0) | 3.0 (2.0 - 8.0) |
| $AUC_{8h}$, ng.h/mL | 20810 ± 5230 | 20790 ± 4788 |
| $C_{ss, av}$, ng/mL | 2602 ± 653.8 | 2599 ± 598.5 |
| FI, % | 56.95 ± 19.59 | 55.44 ± 14.73 |

**Table 6 Summary Statistics of TVR PK Parameters**

| *Parameter* | LSmeans[a] | | LSmeans ratio, % | 90% CI,%[b] | p-value | |
|---|---|---|---|---|---|---|
| | 750 mg telaprevir q8h (reference) | 750 mg telaprevir q8h + 300 mg TDF q.d. (test) | | | Period | Sequence |
| $C_{min}$, ng/mL | 1805 | 1856 | 102.9 | 92.95 - 113.8 | 0.7730 | 0.2121 |
| $C_{max}$, ng/mL | 3223 | 3239 | 100.5 | 95.75 - 105.4 | 0.2162 | 0.3413 |
| $AUC_{8h}$, ng.h/mL | 20120 | 20140 | 100.1 | 93.55 - 107.2 | 0.5845 | 0.3104 |
| | Median[a] | | | | p-value | |
| *Parameter* | 750 mg telaprevir q8h (reference) | 750 mg telaprevir q8h + 300 mg TDF q.d. (test) | Treatment difference median | 90% CI,%[b] | Period | Sequence |
| $t_{max}$, h | 3.0 | 3.0 | 0.125 | (-0.25) - (0.75) | 0.8286 | 0.0727* |

[a] n=16 for reference and n=16 for test
[b] 90% confidence intervals
* Statistically significant difference

Summary statistics for TVR PK parameters reveal that the 90% confidence intervals for Cmin, Cmax, and $AUC_{8h}$ all fall within the standard no-effect range of 80-125% (Table 6). Thus, co-administration of TDF does not affect the PK of TVR.

*VRT-127394 Pharmacokinetics*

Similar to TVR, VRT-127394 also demonstrated similar plasma concentrations across the entire dosing interval between TVR alone and TVR+TDF treatments (Figure 4). Inter-subject variability (%CV) of Cmin, Cmax, and $AUC_{8h}$ was comparable between both treatments, with values ranging from 24% to 33%. No significant differences were detected for any of the PK parameters evaluated. Again, the 90% confidence intervals for Cmin, Cmax, and $AUC_{8h}$ fell within the no-effect range, indicating that there is no significant effect of TDF on VRT-127394 (Table 7).

**Figure 4 Mean Plasma Concentration-Time Profiles for VRT-127394**

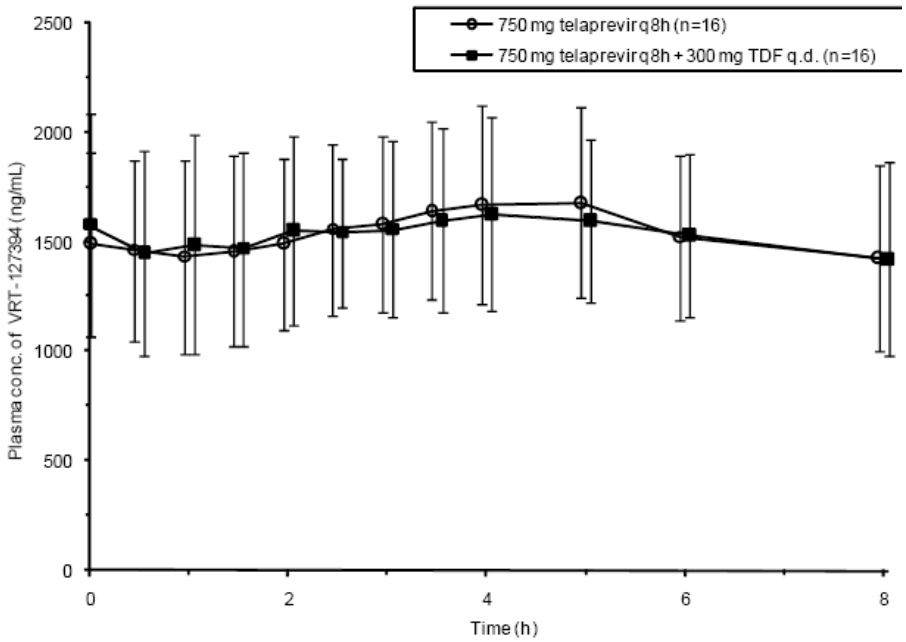



**Table 7 Summary VRT-127394 PK Parameters Following Administration of TVR Alone and in Combination with TDF**

| ***Pharmacokinetics of VRT-127394*** (mean ± SD, $t_{max}$: median [range]) | **750 mg telaprevir q8h** | **750 mg telaprevir q8h + 300 mg TDF q.d.** |
|---|---|---|
| n | 16 | 16 |
| $C_{0h}$, ng/mL | 1493 ± 420.6 | 1579 ± 507.8 |
| $C_{min}$, ng/mL | 1303 ± 423.7 | 1263 ± 339.9 |
| $C_{max}$, ng/mL | 1804 ± 431.9 | 1794 ± 498.5 |
| $t_{max}$, h | 3.75 (0.0-6.0) | 3.0 (0.0-8.0) |
| $AUC_{8h}$, ng.h/mL | 12320 ± 3145 | 12250 ± 3138 |
| $C_{ss, av}$, ng/mL | 1540 ± 393.1 | 1531 ± 392.2 |
| FI, % | 34.42 ± 14.55 | 33.57 ± 13.89 |

*Reviewer's Comments:*
*-A similar dip in plasma concentrations occurred with VRT-127394 following treatment with TVR alone as well as TVR+TDF as was observed with TVR plasma concentrations. However, for VRT-127394, the decrease was slightly more pronounced in the TVR+TDF treatment group.*

*Tenofovir Pharmacokinetics*

As shown in Figure 4, mean plasma concentrations of tenofovir were higher throughout the entire dosing period when TVR was co-administered. Mean Cmax and $AUC_{24h}$ were approximately 28% and 30% higher, respectively, with TVR+TDF treatment as compared with TDF treatment alone (Table 8). Despite these differences, the shape of the curve remained the same between treatments and Tmax was nearly identical. The upper range of the 90% confidence intervals for Cmin, Cmax, and $AUC_{24h}$ all exceeded the no-effect boundary, thus indicating a significant interaction between TVR and TDF (Table 9).

**Figure 4 Mean Plasma Concentration-Time Profile for Tenofovir**

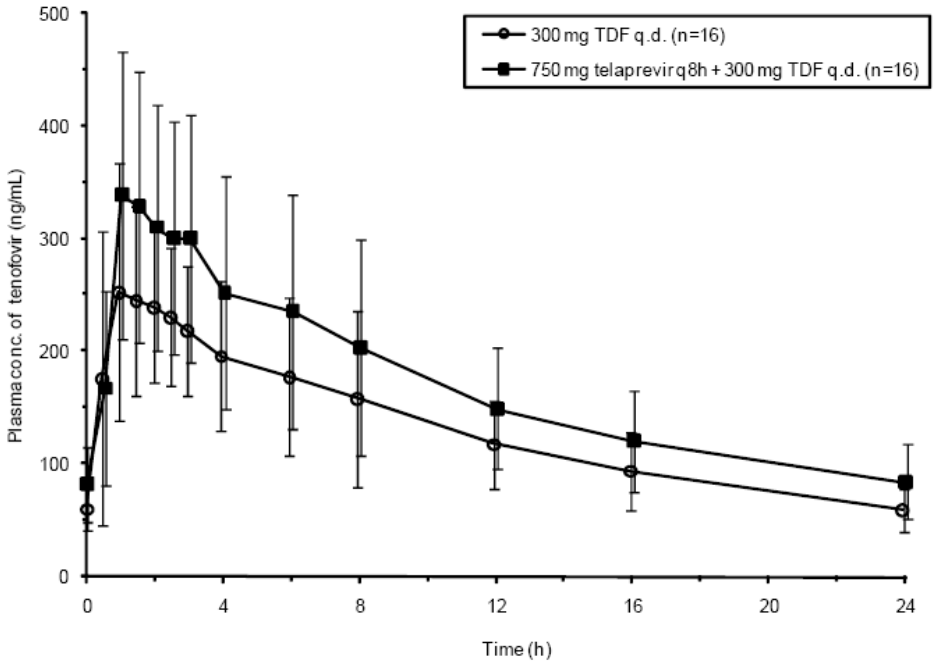



**Table 8 Summary Tenofovir PK Parameters Following Administration of TVR Alone and in Combination with TDF**

| ***Pharmacokinetics of tenofovir*** (mean ± SD, $t_{max}$: median [range]) | **300 mg TDF q.d.** | **300 mg TDF q.d. + 750 mg telaprevir q8h** |
|---|---|---|
| n | 16 | 16 |
| $C_{0h}$, ng/mL | 60.31 ± 19.54 | 82.10 ± 33.63 |
| $C_{min}$, ng/mL | 56.31 ± 17.72 | 80.58 ± 33.52 |
| $C_{max}$, ng/mL | 324.1 ± 81.09 | 414.8 ± 96.42 |
| $t_{max}$, h | 1.25 (0.5 - 8.0) | 1.25 (1.0 - 4.0) |
| $AUC_{24h}$, ng.h/mL | 3120 ± 935.9 | 4059 ± 1405 |
| $C_{ss, av}$, ng/mL | 130.0 ± 39.00 | 169.1 ± 58.54 |
| FI, % | 214.5 ± 53.46 | 210.7 ± 58.23 |

**Table 9 Summary Statistics of Tenofovir PK Parameters**

| ***Parameter*** | LSmeans[a] | | LSmeans ratio, % | 90% CI,%[b] | p-value | |
|---|---|---|---|---|---|---|
| | 300 mg TDF q.d. (reference) | 300 mg TDF q.d. + 750 mg telaprevir q8h (test) | | | Period | Sequence |
| $C_{min}$, ng/mL | 52.77 | 74.56 | 141.3 | 129.4 - 154.3 | 0.2033 | 0.8629 |
| $C_{max}$, ng/mL | 312.1 | 404.3 | 129.6 | 116.2 - 144.5 | 0.3859 | 0.6572 |
| $AUC_{24h}$, ng.h/mL | 2952 | 3835 | 129.9 | 121.6 - 138.8 | 0.2058 | 0.8113 |
| | Median[a] | | | | p-value | |
| ***Parameter*** | 300 mg TDF q.d. (reference) | 300 mg TDF q.d. + 750 mg telaprevir q8h (test) | Treatment difference median | 90% CI,%[b] | Period | Sequence |
| $t_{max}$, h | 1.25 | 1.25 | 0.25 | (-0.75) - (0.50) | 0.8302 | 0.1338 |

[a] n=16 for reference and n=16 for test
[b] 90% confidence intervals

*Tenofovir Urinary Excretion and Creatinine Clearance*

Following treatment with TDF either alone or in the presence of TVR, the amount of tenofovir excreted in the urine was comparable (Table 10). The mean percentage of the dose excreted in urine at steady-state was 23-26% for both treatments. Mean renal clearance ($Cl_R$) of tenofovir was lower when TDF was taken in combination with TVR compared to TDF administered alone. Based on the ratios of the LS means, $Cl_R$ of tenofovir was decreased by 36% when TDF was co-administered with TVR as compared to TDF administered alone (Table 11). Mean $Cl_{cr}$ was only slightly lower when TDF was taken in combination with TVR compared to TDF alone. Based on the ratios of the LSmeans, $Cl_{cr}$ was decreased by only 8% and the 90% CI was contained within the 80-125% no-effect limits.

**Table 10 Urinary Tenofovir Excretion and Creatinine Clearance Results**

| *Pharmacokinetics of tenofovir and $Cl_{cr}$* (mean ± SD) | **300 mg TDF q.d.** | **300 mg TDF q.d. + 750 mg telaprevir q8h** |
|---|---|---|
| n | 16 | 16 |
| $Ae_{total}$, mg | 35.25 ± 8.703 | 31.51 ± 11.63 |
| $D_{urine,total}$, % | 25.92 ± 6.399 | 23.17 ± 8.549 |
| $Cl_R$, mL/min | 199.0 ± 59.31 | 134.7 ± 49.87 |
| $Cl_{cr}$, mL/min | 128.5 ± 30.51 | 119.6 ± 31.05 |

$Ae_{total}$: Total amount of drug excreted in urine (0-24 hrs) post-dose
$D_{urine,total}$: % of dose excreted in the urine 0-24 hrs post-dose (100 x $Ae_{total}$/Dose)
$Cl_R$: $Ae_{total}/AUC_{24h}$

**Table 11 Summary Statistical Analysis of Tenofovir Urine Excretion Parameters and Creatinine Clearance**

| *Parameter* | LSmeans[a] | | LSmeans ratio, % | 90% CI,%[b] | p-value | |
|---|---|---|---|---|---|---|
| | 300 mg TDF q.d. (reference) | 300 mg TDF q.d. + 750 mg telaprevir q8h (test) | | | Period | Sequence |
| $D_{urine,total}$, % | 25.02 | 20.88 | 83.44 | 63.60 - 109.5 | 0.7204 | 0.7631 |
| $Cl_R$, mL/min | 192.1 | 123.4 | 64.23 | 50.28 - 82.04 | 0.5798 | 0.6640 |
| $Cl_{cr}$, mL/min | 125.8 | 116.1 | 92.31 | 89.92 - 94.76 | 0.0325* | 0.8141 |

[a] n=16 for reference and n=16 for test
[b] 90% confidence intervals
* Statistically significant difference

*Reviewer's Comments:*
*-Although tenofovir is mainly renally eliminated, it is not uncommon for this effect to be observed with protease inhibitors. Co-administration with ATZ/RTV, LPV/RTV, DRV/RTV, and SQV/RTV all resulted in similar increases in tenofovir Cmin, Cmax, and AUC.*
*-The main tenofovir parameter affected by concomitant TVR treatment was Cmax, which indicates that TVR somehow increased the extent of absorption of TDF. In addition, the half-life of tenofovir was not significantly affected by TVR. One published study (Tong et al, 2007) shows that TDF is subject to P-gp mediated transport across intestinal membranes and the inhibition of P-gp by several RTV-boosted PI's may be the reason behind the increased absorption of TDF, thus leading to increased plasma concentrations of tenofovir. (TDF is rapidly converted to tenofovir <u>after</u> absorption.)*

*-Renal clearance of tenofovir (amount of tenofovir excreted in urine over 24 hours [$Ae_{total}$]/$AUC_{24h}$) decreased in the presence of TVR as compared with TDF administration alone, without a decrease in $Ae_{total}$. This could indicate that while absorption of tenofovir is increased by TVR, active tubular secretion of tenofovir could not compensate for the increased amount of tenofovir in plasma or that TVR was competing with tenofovir for renal function. Although tenofovir is a substrate for the renal uptake tranpsorters, hOAT1 and hOAT3, it is unlikely that TVR is inhibiting these transporters since tenofovir $A_e$ did not change significantly.*

Conclusions

Co-administration of TDF with TVR did not appear to affect the PK of TVR or VRT-127394. However, the combination of TDF and TVR increased exposures to tenofovir by approximately 30-40%. The magnitude of interaction between TDF and TVR is likely not great enough to warrant a dose adjustment of TDF in the case of co-administration with TVR (no dose adjustment is recommended for TDF when given in combination with Kaletra®, which resulted in a ~32-51% increase in tenofovir exposures). However, increased monitoring is warranted. The Applicant's proposed statement in section 7 is acceptable with the addition of a statement regarding discontinuing use of TDF (in line with the Viread® label) (b) (4) The Applicant's proposed wording for the label are presented below (reviewer-proposed changes in red):

(b) (4)

**Section 12.3, Table 6**

| Drug | Dose and Schedule | | N | Effect on Drug PK[a] | LS Mean Ratio (90% CI) of Telaprevir PK With/Without Coadministered Drug | | |
|---|---|---|---|---|---|---|---|
| | Drug | Telaprevir | | | $C_{max}$ | AUC | $C_{min}$ |
| Tenofovir disoproxil fumarate (TDF) | 300 mg qd TDF for 7days | 750 mg q8h for 7 days | 16 | ↔ | 1.01 (0.96; 1.05) | 1.00 (0.94; 1.07) | 1.03 (0.93; 1.14) |

**Section 12.3, Table 7**

| Drug | Dose and Schedule | | N | Effect on Drug PK[a] | LS Mean Ratio (90% CI) of Drug PK With/Without Telaprevir [b] | | |
|---|---|---|---|---|---|---|---|
| | Drug | Telaprevir | | | $C_{max}$ | AUC | $C_{min}$ |
| Tenofovir disoproxil fumarate | 300 mg qd for 7 days | 750 mg q8h for 7 days | 16 | ↑ | 1.30 (1.16; 1.45) | 1.30 (1.22; 1.39) | 1.41 (1.29;1.54) |

**Individual Study Review—VX-950-TiDP24-C124**

Title (Study VX-950-TiDP24-C124)

"A Phase I, open-label, randomized, 2-way crossover trial in 40 healthy subjects to investigate the potential pharmacokinetic interactions between telaprevir and darunavir/ritonavir and between telaprevir and fosamprenavir/ritonavir at steady-state"

Objectives

- To determine the effect of steady-state DRV/RTV 600/100 mg BID on the steady-state pharmacokinetics of telaprevir 750 mg q8h and 1125 mg q12h and vice versa
- To determine the effect at steady-state of fAPV/RTV 700/100 mg BID on the steady-state pharmacokinetics of telaprevir 750 mg q8h and 1125 mg q12h and vice versa
- To determine the steady-state pharmacokinetics of telaprevir 750 mg q8h versus telaprevir 1125 mg q12h, alone and during coadministration of either steady-state DRV/RTV 600/100 mg BID or fAPV/RTV 700/100 mg BID
- To determine the short-term safety and tolerability of coadministration of telaprevir and DRV/RTV, and telaprevir and fAPV/RTV

Study Dates and Location(s):
Study initiation: June 2, 2008
Study completion: October 4, 2008
Clinical Site: Clinical Pharmacology Unit, Kendle, Bolognalaan 40, 3584 CJ Utrecht, The Netherlands

Study Design

This was a Phase I, open-label, randomized, 2-way crossover trial in healthy subjects to investigate the effect of steady-state DRV/RTV 600/100 mg BID or fAPV/RTV 700/100 mg BID on the steady-state pharmacokinetics of telaprevir 750 mg q8h and 1125 mg q12h, and vice versa. A total of 40 subjects were planned for the study. This study consisted of 2 panels (see Figure 1 below for study design schematic). Treatment sessions within each panel were separated by a washout period of at least 13 days.

In treatments A and C, TVR 750 mg q8h was administered from day 1 to day 10 and TVR 1125 mg q12h was administered from Day 11 to Day 13, with an additional morning dose on day 14. In treatment B, DRV/RTV 600/100 mg BID was administered for 23 days with an additional morning dose on day 24. TVR 750 mg q8h was co-administered from day 11 to day 20 and TVR 1125 mg q12h was co-administered from day 21 to day 23, with an additional morning dose on day 24. In Treatment D, fAPV/RTV 700/100 mg BID was administered for 23 days with an additional morning dose on day 24. TVR 750 mg q8h was co-administered from day 11 to day 20 and TVR 1125 mg q12h was co-administered from day 21 to day 23, with an additional morning dose on day 24. All study medication was given under fed conditions.

Study Doses Used and Dose Rationale

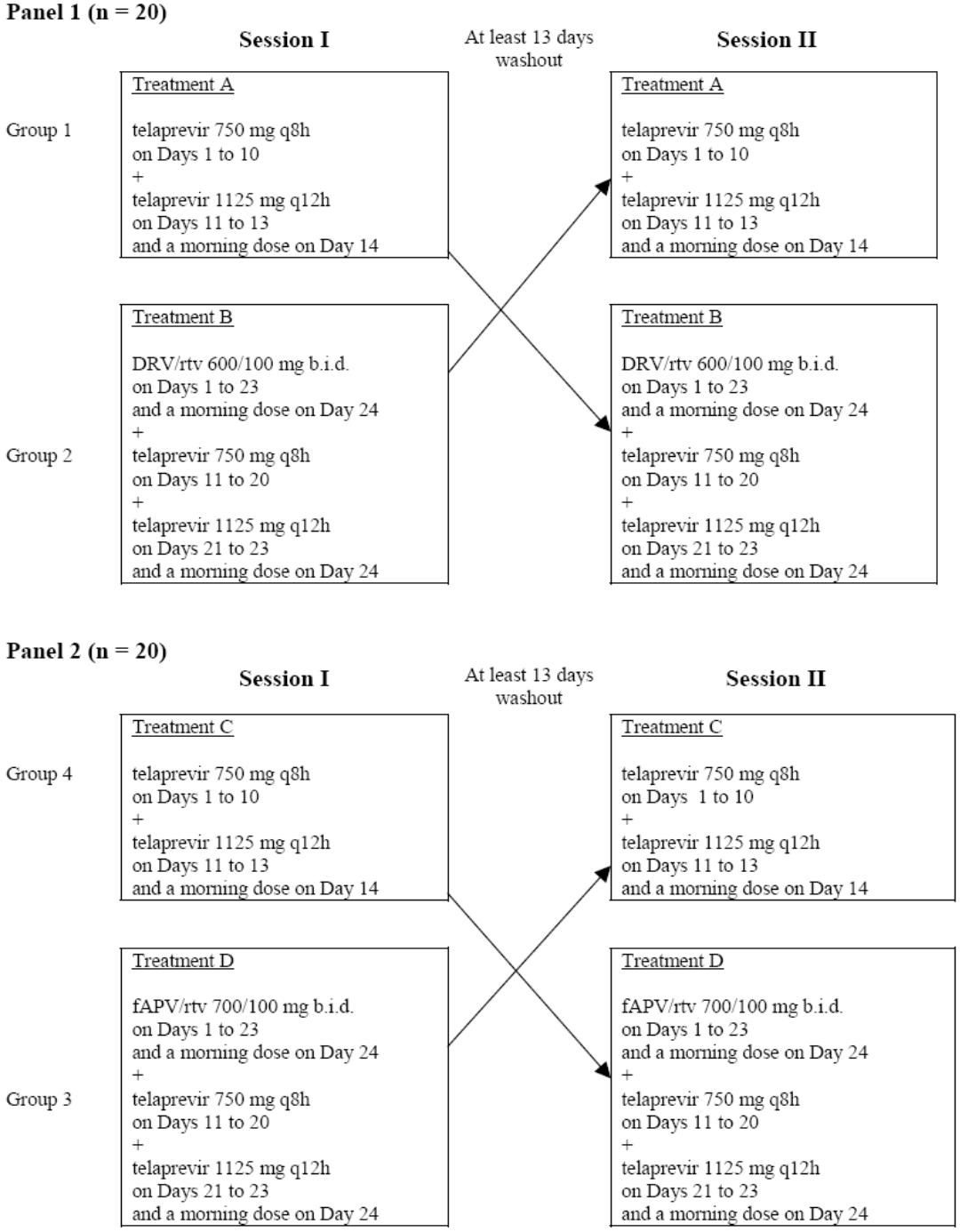
The dosage of 750 mg q8h was being used in the ongoing clinical trials at the time of this trial. The dose regimen of 1125 mg q12h was included in the current trial to explore the possibility of a reduced dosing frequency of TVR, which could enhance subject compliance.

DRV/RTV and fAPV/RTV were both administered at the current recommended dose for HIV-infected patients.

Formulation(s) Used

The TVR 375-mg core tablet was used in this study. According to the Applicant's Summary of Biopharmaceutics Studies and Associated Analytical Methods document, it is the same formulation as was used in the phase 3 studies.

**Figure 1 Study Design Schematic**



*Key Inclusion Criteria:*
-Being male or female, aged between 18 and 55 years, extremes included
-Females were to be amenorrheal for at least 3 years, or were to have had a post-hysterectomy or post-tubal ligation (without reversal operation)
-Being nonsmoking or smoking no more than 10 cigarettes, or 2 cigars, or 2 pipes per day in the 3 months prior to screening
-Having a normal weight at screening as defined by a body mass index (BMI) of 18 to 30 $kg/m^2$, extremes included
Having a normal 12-lead electrocardiogram (ECG) at screening including:
- normal sinus rhythm (heart rate [HR] between 50 and 120 beats per minute [bpm]);
- QTc interval ≤ 450 ms
- 50 ms < QRS interval < 120 ms;
- PR interval < 210 ms

-Being healthy on the basis of a medical evaluation that revealed the absence of any clinically relevant abnormality and included a physical examination, medical history, ECG, vital signs, blood biochemistry, blood coagulation and hematology tests, and urinalysis carried out at screening

*Key Exclusion Criteria:*
-Subjects with a history of any illness that, in the opinion of the investigator or the subject's general practitioner, confounded the results of the study or posed an additional risk in administering study drug(s) to the subject
-Regular treatment with prescription medications. Subjects were to have ended any short courses of prescription medications at least 14 days prior to the screening visit. Prescription medications were not to be administered during the study. (Potential subjects were not to stop any chronic, prescribed medication being taken at the direction of a physician, without obtaining agreement from that physician)
-Regular treatment with over-the-counter medications. Subjects were to end over-the-counter medication on the date of the screening visit but no less than 2 days prior to administration of study drug. Occasional use of acetaminophen or ibuprofen was allowed during the study for the treatment of pain (under supervision of the investigator)
-Subjects who consumed herbal medications or dietary medications, dietary supplements (e.g., St. John's Wort, ginkgo biloba, garlic supplements), vitamins, and grapefruit or grapefruit juice within 14 days before administration of study drug (Day 1).
-Subjects who consumed more than 2 units of alcoholic beverages per day or more than 14 units per week.
-Subjects who consumed an average of more than 5 cups of coffee or other caffeinated beverage
-Subjects who had a history of drug or alcohol abuse or addiction within 2 years prior to dosing, or who tested positive for alcohol or drugs of abuse such as cannabis, cocaine, amphetamines or opiates during the screening period
-Subjects who had participated in a clinical study involving administration of either an investigational or a marketed drug within 2 months or 5 half lives (whichever is longer) prior to the screening visit
-Subjects with a hemoglobin of <12.0 g/dL

-Subjects who tested positive for any of the following infectious disease tests: hepatitis B antigen (HBsAg), hepatitis C virus antibody (HCVAb), human immunodeficiency virus 1 antibody (HIV1Ab), or human immunodeficiency virus 2 antibody (HIV2Ab)
-Subjects who had a female partner who was pregnant, nursing, or planning to become pregnant during the study or within 90 days of the TVR dose
-Having previously participated in a trial with TVR

Blood Sampling for PK

*For treatments A and C (TVR alone):* Blood samples for determination of TVR and VRT-127394 (R-diastereomer of TVR) plasma concentrations were collected at pre-dose on days 1, 5, 8, 9, 12, and 13. Intensive PK sampling took place on days 10 and 14 at the following timepoints: pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, and 16 hours post-dose (the last timepoint was at 12 hours for the day 14 blood collection).

*For treatments B and D (TVR+PI/RTV):* Blood samples for determination of TVR and VRT-127394 (R-diastereomer of TVR) plasma concentrations were collected at pre-dose on days 1, 15, 18, 19, 22, and 23. Intensive PK sampling took place on days 20 and 24 at the following timepoints: pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, and 8 hours post-dose. Blood samples for determination of the relevant PI/RTV (depending on the panel) were collected pre-dose on days 1, 5, 8, 9, 15, 18, 19, 22, and 23. Intensive PK sampling took place on days 10, 20, and 24 at the following timepoints: pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hours post-dose.

Bioanalytical Results

Plasma samples were analyzed for TVR and VRT-127394 by HPLC with tandem mass spectrometric detection (LC-MS/MS) by (b) (4) . Samples were received in frozen condition between July 14, 2008 and September 2, 2008. The samples were stored at -70°C. Samples were analyzed between August 7, 2008 and September 17, 2008. The maximum sample storage time until end of analysis was 65 days, which is within the validated long-term frozen stability duration of 6 months.

The calibration standard concentrations for both TVR and VRT-127394 were 2.0, 4.0, 10.0, 50.0, 200.0, 500, 800, and 1000 ng/mL. The mean accuracy and precision estimates at each TVR and VRT-127394 standard concentration are presented in Tables 1 and 2, respectively, below. All accuracy and precision (%CV) values were within the acceptable range (≤20% from nominal at the LLOQ concentration and ≤15% from nominal at all other concentrations). Quality control concentrations for both analytes were 6.0, 250, and 800 ng/mL. The mean accuracy ranged from 98.9 to 100.4% for TVR and 98 to 100% for VRT-127394. The mean precision ranged from 4.1 to 5.5% for TVR and 6.8 to 11.7% for VRT-127394.

**Table 1 Mean Calibration Standard Concentrations and Statistics for TVR**

| | VX-950, ng/ml | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Analytical batch | 2.00 | 4.00 | 10.0 | 50.0 | 200 | 500 | 800 | 1000 |
| n | 60 | 59 | 58 | 59 | 58 | 59 | 58 | 59 |
| mean | 2.00 | 4.01 | 9.79 | 50.7 | 202 | 504 | 796 | 990 |
| std. dev. | 0.0774 | 0.169 | 0.335 | 1.58 | 7.58 | 18.7 | 35.9 | 32.3 |
| %CV | 3.9 | 4.2 | 3.4 | 3.1 | 3.8 | 3.7 | 4.5 | 3.3 |
| % accuracy | 100.0 | 100.3 | 97.9 | 101.4 | 101.0 | 100.8 | 99.5 | 99.0 |

**Table 2 Mean Calibration Standard Concentrations and Statistics for VRT-127394**

| | VRT-127394, ng/ml | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Analytical batch | 2.00 | 4.00 | 10.0 | 50.0 | 200 | 500 | 800 | 1000 |
| n | 60 | 57 | 56 | 56 | 58 | 54 | 53 | 56 |
| mean | 2.01 | 3.97 | 9.88 | 51.0 | 202 | 495 | 804 | 987 |
| std. dev. | 0.116 | 0.247 | 0.532 | 2.54 | 10.4 | 22.3 | 44.1 | 65.4 |
| %CV | 5.8 | 6.2 | 5.4 | 5.0 | 5.1 | 4.5 | 5.5 | 6.6 |
| % accuracy | 100.5 | 99.2 | 98.8 | 102.0 | 101.0 | 99.0 | 100.5 | 98.7 |

Plasma samples were analyzed for DRV and RTV by HPLC with tandem mass spectrometric detection (LC-MS/MS) by (b) (4). Samples were received in frozen condition between July 28, 2008 and September 2, 2008. The samples were stored at -70°C. Samples were analyzed between August 26, 2008 and September 2, 2008. The maximum sample storage time until end of analysis was 37 days, which is within the validated long-term frozen stability duration of 1064 days for both DRV and RTV.

The calibration standard concentrations for both DRV and RTV were 5.0, 10., 20, 50, 100, 200, 500, 1000, 2000, 5000, and 10,000 ng/mL. The mean accuracy and precision estimates at each DRV and RTV standard concentration are presented in Tables 3 and 4, respectively, below. All accuracy and precision (%CV) values were within the acceptable range (≤20% from nominal at the LLOQ concentration and ≤15% from nominal at all other concentrations). Quality control concentrations for DRV and RTV were 13.6, 240, and 7680 ng/mL. The mean accuracy ranged from 96.7 to 98.5% for DRV and from 97% to 100.7% for RTV. The mean precision ranged from 2.7 to 5.6% for DRV and from 3.6 to 6.2% for RTV.

**Table 3 Mean Calibration Standard Concentrations and Statistics for DRV**

| Assay Date | Run ID | 5.00 | 10.0 | 20.0 | 50.0 | 100 | 200 | 500 | 1000 | 2000 | 5000 | 10000 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 26-Aug-2008 | 1 | 5.17 | 10.2 | 19.7 | 49.0 | 97.2 | 193 | 501 | 1020 | 2080 | 5090 | 9750 |
| 28-Aug-2008 | 2 | 4.91 | 10.2 | 20.0 | 49.3 | 96.6 | 203 | 519 | 999 | 2050 | 5110 | 9470 |
| 29-Aug-2008 | 3 | 5.01 | 9.98 | 19.3 | 49.0 | 99.7 | 208 | 514 | 1040 | 2020 | 5000 | 9470 |
| 01-Sep-2008 | 4 | 5.22 | 10.4 | 19.1 | 48.3 | 99.8 | 188 | 480 | 1060 | 2100 | 4980 | 9930 |
| Mean | | 5.08 | 10.2 | 19.5 | 48.9 | 98.3 | 198 | 504 | 1030 | 2060 | 5050 | 9660 |
| S.D. | | 0.143 | 0.172 | 0.403 | 0.424 | 1.66 | 9.13 | 17.4 | 26.2 | 35.0 | 64.5 | 226 |
| %C.V. | | 2.8 | 1.7 | 2.1 | 0.9 | 1.7 | 4.6 | 3.5 | 2.5 | 1.7 | 1.3 | 2.3 |
| %Bias | | 1.6 | 2.0 | -2.5 | -2.2 | -1.7 | -1.0 | 0.8 | 3.0 | 3.0 | 1.0 | -3.4 |
| n | | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

**Table 4 Mean Calibration Standard Concentrations and Statistics for RTV**

| Assay Date | Run ID | 5.00 | 10.0 | 20.0 | 50.0 | 100 | 200 | 500 | 1000 | 2000 | 5000 | 10000 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 26-Aug-2008 | 1 | 4.81 | 9.94 | 20.5 | 49.4 | 101 | 198 | 526 | 1020 | 2070 | 5000 | 9360 |
| 28-Aug-2008 | 2 | 4.69 | 10.1 | 20.4 | 51.8 | 100 | 203 | 523 | 955 | 2010 | 5060 | 9680 |
| 29-Aug-2008 | 3 | 4.80 | 10.5 | 19.6 | 52.0 | 97.4 | 199 | 499 | 992 | 2060 | 4980 | 9880 |
| 01-Sep-2008 | 4 | 5.10 | 10.0 | 19.5 | 49.7 | 101 | 198 | 496 | 1010 | 2020 | 4990 | 10000 |
| Mean | | 4.85 | 10.1 | 20.0 | 50.7 | 99.9 | 200 | 511 | 994 | 2040 | 5010 | 9730 |
| S.D. | | 0.175 | 0.252 | 0.523 | 1.36 | 1.70 | 2.38 | 15.7 | 28.6 | 29.4 | 35.9 | 280 |
| %C.V. | | 3.6 | 2.5 | 2.6 | 2.7 | 1.7 | 1.2 | 3.1 | 2.9 | 1.4 | 0.7 | 2.9 |
| %Bias | | -3.0 | 1.0 | 0.0 | 1.4 | -0.1 | 0.0 | 2.2 | -0.6 | 2.0 | 0.2 | -2.7 |
| n | | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

Plasma samples were analyzed for APV and RTV by HPLC with tandem mass spectrometric detection (LC-MS/MS) by (b) (4).

Samples were received in frozen condition between July 28, 2008 and September 2, 2008. The samples were stored at -70°C. Samples were analyzed between September 9, 2008 and September 16, 2008. The maximum sample storage time until end of analysis was 50 days, which is within the validated long-term frozen stability duration of 223 for RTV. However, the storage time slightly exceeded the time that APV was demonstrated to be stable in frozen condition (35 days).

The calibration standard concentrations for APV and RTV were 5.0, 10., 20, 50, 100, 200, 500, 1000, 2000, 5000, and 10,000 ng/mL. The mean accuracy and precision estimates at each APV and RTV standard concentration are presented in Tables 5 and 6, respectively, below. All accuracy and precision (%CV) values were within the acceptable range (≤20% from nominal at the LLOQ concentration and ≤15% from nominal at all other concentrations). Quality control concentrations for APV and RTV were 13.7, 190, and 7600 ng/mL. The mean accuracy ranged from 96.2to 101.5% for APV and from 103.5% to 105.6% for RTV. The mean precision ranged from 2.7 to 6% for APV and from 3.5% to 5.6% for RTV.

**Table 5 Mean Calibration Standard Concentrations and Statistics for APV**

| Assay Date | Run ID | 5.00 | 10.0 | 20.0 | 50.0 | 100 | 200 | 500 | 1000 | 2000 | 5000 | 10000 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 09-Sep-2008 | 6 | 5.04 | 9.23 | 20.6 | 50.9 | 98.9 | 206 | 514 | 989 | 2110 | 4990 | 9380 |
| 11-Sep-2008 | 7 | 4.82 | 10.2 | 20.0 | 49.8 | 101 | 199 | 510 | 989 | 2120 | 4840 | 9780 |
| 12-Sep-2008 | 8 | 4.93 | 10.1 | 19.8 | 51.6 | 98.0 | 200 | 496 | 1000 | 2040 | 5030 | 9810 |
| 15-Sep-2008 | 9 | 5.33 | 8.58 | 22.1 | 53.8 | 91.3 | 203 | 495 | 973 | 2000 | 5120 | 10100 |
| Mean | | 5.03 | 9.53 | 20.6 | 51.5 | 97.3 | 202 | 504 | 988 | 2070 | 5000 | 9770 |
| S.D. | | 0.219 | 0.767 | 1.04 | 1.69 | 4.19 | 3.16 | 9.67 | 11.1 | 57.4 | 117 | 296 |
| %C.V. | | 4.4 | 8.0 | 5.0 | 3.3 | 4.3 | 1.6 | 1.9 | 1.1 | 2.8 | 2.3 | 3.0 |
| %Bias | | 0.6 | -4.7 | 3.0 | 3.0 | -2.7 | 1.0 | 0.8 | -1.2 | 3.5 | 0.0 | -2.3 |
| n | | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

**Table 6 Mean Calibration Standard Concentrations and Statistics for RTV**

| Assay Date | Run ID | 5.00 | 10.0 | 20.0 | 50.0 | 100 | 200 | 500 | 1000 | 2000 | 5000 | 10000 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 09-Sep-2008 | 6 | 4.92 | 9.51 | 20.9 | 51.6 | 95.0 | 205 | 523 | 992 | 2080 | 4930 | 9550 |
| 11-Sep-2008 | 7 | 4.98 | 9.67 | 20.8 | 50.5 | 98.3 | 198 | 501 | 1010 | 2060 | 5000 | 9720 |
| 12-Sep-2008 | 8 | 4.96 | 9.90 | 20.6 | 50.3 | 98.1 | 194 | 508 | 1010 | 2070 | 5030 | 9680 |
| 15-Sep-2008 | 9 | 4.60 | 9.37 | 22.3 | 54.0 | 100 | 197 | 493 | 1000 | 2070 | 5000 | 9480 |
| Mean | | 4.87 | 9.61 | 21.2 | 51.6 | 97.9 | 199 | 506 | 1000 | 2070 | 4990 | 9610 |
| S.D. | | 0.178 | 0.228 | 0.777 | 1.70 | 2.08 | 4.65 | 12.7 | 8.72 | 8.16 | 42.4 | 112 |
| %C.V. | | 3.7 | 2.4 | 3.7 | 3.3 | 2.1 | 2.3 | 2.5 | 0.9 | 0.4 | 0.8 | 1.2 |
| %Bias | | -2.6 | -3.9 | 6.0 | 3.2 | -2.1 | -0.5 | 1.2 | 0.0 | 3.5 | -0.2 | -3.9 |
| n | | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

*Reviewer's Comments:*
*-The bioanalytical results are acceptable.*

Results

A total of 53 subjects were randomized but only 40 subjects received treatment (10 were reserve subjects and the remaining 3 either withdrew consent, did not show up for admission or reported an AE during screening). In each of the 2 panels, 20 subjects were randomized to a treatment sequence (A/B or B/A in Panel 1 and C/D or D/C in Panel 2). A total of 32 subjects completed the trial. Six (30.0%) subjects in Panel 1 and 2 (10.0%) subjects in Panel 2 prematurely discontinued study medication. In Panel 1, 4 subjects discontinued study medication

during administration of telaprevir alone (all due to an AE) and 2 subjects during administration of DRV/RTV alone (1 subject due to an AE and 1 subject due to noncompliance). In Panel 2, 2 subjects discontinued study medication during co-administration of fAPV/RTV and TVR (both due to an AE).

*Demographics*

| Parameter | Panel 1 | | | Panel 2 | | |
|---|---|---|---|---|---|---|
| | Treatment A/B N = 10 | Treatment B/A N = 10 | All Subjects N = 20 | Treatment C/D N = 10 | Treatment D/C N = 10 | All Subjects N = 20 |
| Age, years Median (range) | 40.0 (19-53) | 46.5 (21-54) | 42.0 (19-54) | 26.5 (21-55) | 27.0 (20-44) | 26.5 (20-55) |
| Height, cm Median (range) | 182.0 (166-193) | 180.5 (156-190) | 181.5 (156-193) | 179.0 (167-189) | 180.5 (174-198) | 179.0 (167-198) |
| Weight, kg Median (range) | 78.0 (60-88) | 77.5 (57-95) | 78.0 (57-95) | 77.5 (66-93) | 79.5 (64-111) | 78.5 (64-111) |
| BMI, $kg/m^2$ Median (range) | 22.8 (19-25) | 23.9 (22-28) | 23.4 (19-28) | 24.4 (20-29) | 23.8 (20-28) | 24.1 (20-29) |
| Sex, n (%) | | | | | | |
| Male | 9 (90.0) | 7 (70.0) | 16 (80.0) | 9 (90.0) | 10 (100.0) | 19 (95.0) |
| Female | 1 (10.0) | 3 (30.0) | 4 (20.0) | 1 (10.0) | 0 | 1 (5.0) |
| Race, n (%) | | | | | | |
| White | 10 (100.0) | 10 (100.0) | 20 (100.0) | 9 (90.0) | 9 (90.0) | 18 (90.0) |
| Asian | 0 | 0 | 0 | 1 (10.0) | 0 | 1 (5.0) |
| Black | 0 | 0 | 0 | 0 | 1 (10.0) | 1 (5.0) |
| Ethnicity, n (%) | | | | | | |
| Hispanic or Latino | 0 | 0 | 0 | 2 (20.0) | 0 | 2 (10.0) |
| Not Hispanic or Latino | 10 (100.0) | 10 (100.0) | 20 (100.0) | 8 (80.0) | 10 (100.0) | 18 (90.0) |
| Smoker, n (%) | | | | | | |
| No | 10 (100.0) | 10 (100.0) | 20 (100.0) | 10 (100.0) | 10 (100.0) | 20 (100.0) |

N = total number of subjects with data; n = number of subjects with that observation
Treatment A and C: telaprevir 750 mg q8h on Days 1-10; 1125 mg q12h on Days 11-13, 1125-mg morning dose on Day 14;
Treatment B: DRV/rtv 600/100 mg b.i.d. on Days 1-23; 600/100-mg morning dose on Day 24 + telaprevir 750 mg q8h on Days 11-20; 1125 mg q12h on Days 21-23, 1125-mg morning dose on Day 24;
Treatment D: fAPV/rtv 700/100 mg b.i.d. on Days 1-23; 700/100-mg morning dose on Day 24 + telaprevir 750 mg q8h on Days 11-20; 1125 mg q12h on Days 21-23, 1125-mg morning dose on Day 24.

*Safety*

Overall, 7 (17.5%) subjects permanently discontinued study medication due to an AE, i.e., 5 subjects in Panel 1 and 2 subjects in Panel 2. In Panel 1, 4 subjects discontinued study medication due to an AE during administration of TVR alone and 1 subject during administration of DRV/RTV alone. In Panel 2, 2 subjects discontinued study medication due to an AE during co-administration of fAPV/RTV and TVR. In Panel 1, the most frequently reported AEs by system organ class were related to gastrointestinal disorders (15 [75.0%] subjects), skin and subcutaneous tissue disorders (14 [70.0%] subjects), general disorders and administration site conditions (13 [65.0%] subjects), and nervous system disorders (11 [55.0%] subjects). In Panel 2, the most frequently reported AEs were related to gastrointestinal disorders (14 [70.0%] subjects), skin and subcutaneous tissue disorders (13 [65.0%] subjects), and nervous system disorders (12 [60.0%] subjects). Please refer to the medical officer's review for further details.

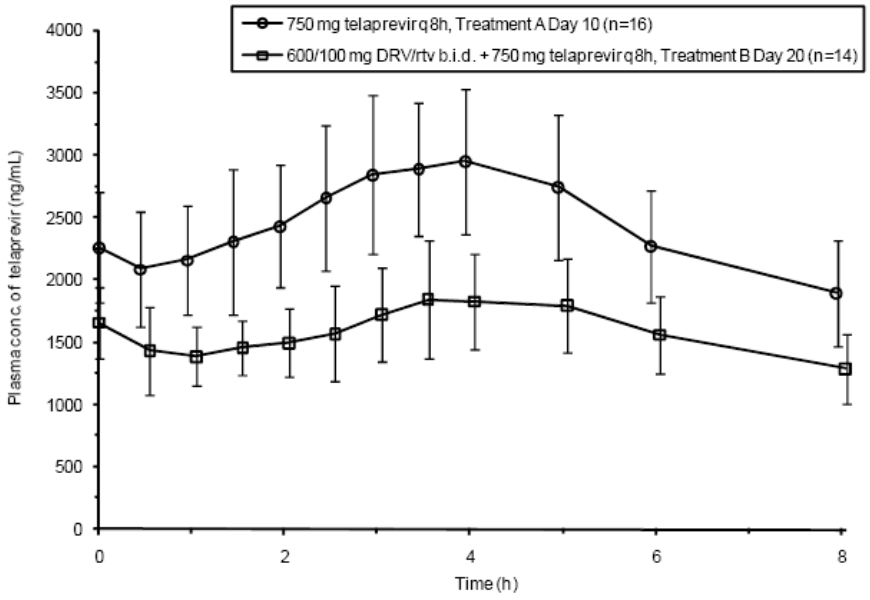
*Effect of DRV/RTV on TVR Pharmacokinetics*

The co-administration of DRV/RTV resulted in a significant decrease in steady-state TVR exposures as compared with TVR alone, irrespective of the concomitant TVR regimen (750 mg q8h or 1125 mg q12h). However, based on the concentration-time profiles, the shape of the curve remained the same for both treatments (Figure 2). In both treatments and for both dosing regimens, a decrease in mean plasma concentrations was observed immediately after intake (similar to what has occurred in other studies for both TVR and VRT-127394). This effect is

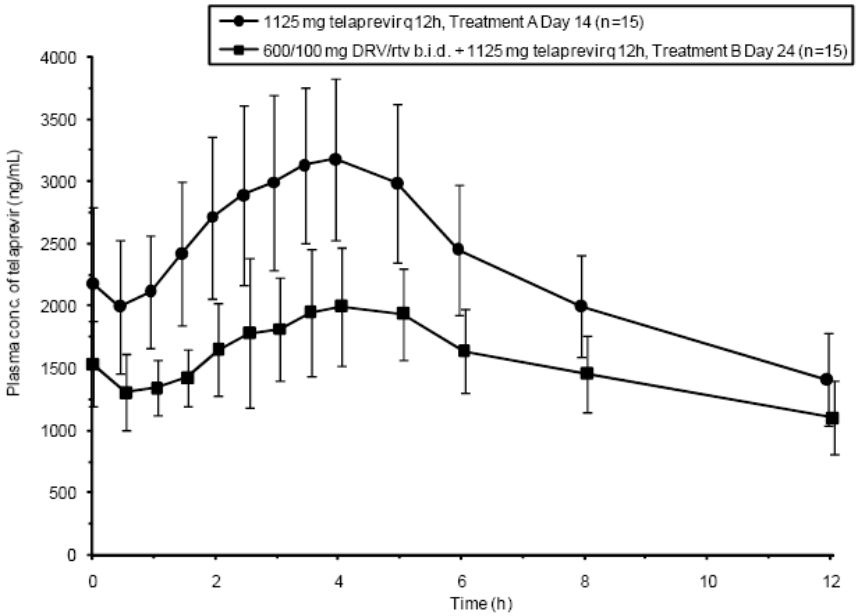
likely due to delayed absorption of TVR and is more readily apparent with subjects already at steady-state with TVR.

**Figure 2 Mean Plasma Concentration-Time Curves of TVR Following Administration of TVR Alone at 750 mg q8h for 10 Days (panel A below), Followed by 1125 mg q12h for 3 Days (panel B below) and in the Presence of Steady-State DRV/RTV 600/100 mg BID (treatment B, days 20 and 24)**

**A. TVR PK (750 mg q8h)**




**B. TVR PK (1125 mg q12h)**



On average, steady-state TVR $AUC_\tau$, Cmax, and Cmin were approximately 36%, 35%, and 33% lower when DRV/RTV was added to a TVR regimen of 750 mg q8h (Table 7). When DRV/RTV was added to a TVR 1125 mg q12h regimen, mean $AUC_\tau$, Cmax, and Cmin were approximately 33%, 36%, and 25% lower as compared with TVR treatment alone. Of note, TVR $AUC_\tau$ was not significantly different between the TVR 750 mg q8h alone treatment and the TVR 1125 mg q12h + DRV/RTV treatment. However, the Cmin and Cmax were ~42% and ~28% lower, respectively, when TVR 1125 mg q12h + DRV/RTV was administered. When comparing the TVR 750 mg q8h and TVR 1125 mg q12h (alone) treatments, Cmax is higher and the Cmin is lower for the 1125 mg regimen (as expected). The $AUC_\tau$ appears higher for the 1125 mg regimen; however, when corrected for total daily AUC, the two values are not significantly different (58,440 vs. 54,920 ng*h/mL). Based on the Applicant's statistical analysis of $AUC_\tau$, Cmin, and Cmax, the decrease in TVR concentrations was statistically significant and the 90% confidence intervals did not fall within the no-effect limits (Table 8).

**Table 7 Summary TVR PK Parameters After Administration of TVR Alone at 750 mg q8h for 10 Days, Followed by 1125 mg q12h for 3 Days and in the Presence of Steady State DRV/RTV 600/100 mg BID (treatment B, days 20 and 24)**

| *Pharmacokinetics of telaprevir* (mean ± SD, $t_{max}$: median [range]) | telaprevir q8h, Day 10 (reference 1) | telaprevir q12h, Day 14 (reference 2) |
|---|---|---|
| n | 16 | 15 |
| $C_{0h}$, ng/mL | 2261 ± 446.1 | 2183 ± 617.6 |
| $C_{min}$, ng/mL | 1835 ± 380.9 | 1410 ± 372.5 |
| $C_{max}$, ng/mL | 3061 ± 580.3 | 3429 ± 633.5 |
| $t_{max}$, h | 4.0 (2.0-5.0) | 3.5 (1.5-5.0) |
| $AUC_\tau$, ng.h/mL[b] | 19480 ± 3734 | 27460 ± 5375 |
| $C_{ss,av}$, ng/mL | 2436 ± 466.8 | 2289 ± 447.9 |
| FI, % | 50.63 ± 8.192 | 89.66 ± 23.44 |
| | **telaprevir q8h + DRV/rtv, Day 20 (test 1)** | **telaprevir q12h + DRV/rtv, Day 24 (test 2)** |
| n | 11[a] | 15 |
| $C_{0h}$, ng/mL | 1657 ± 284.5 | 1536 ± 343.9 |
| $C_{min}$, ng/mL | 1237 ± 207.3 | 1063 ± 240.8 |
| $C_{max}$, ng/mL | 2000 ± 399.0 | 2193 ± 491.0 |
| $t_{max}$, h | 3.75 (0.0-5.0) | 4.0 (2.0-5.0) |
| $AUC_\tau$, ng.h/mL[b] | 12560 ± 1909 | 18430 ± 3550 |
| $C_{ss,av}$, ng/mL | 1570 ± 238.6 | 1536 ± 295.8 |
| FI, % | 47.67 ± 11.44 | 73.52 ± 15.74 |

[a] n = 14 for $C_{max}$ and $t_{max}$
[b] τ=8h for reference 1 and test 1, τ=12h for reference 2 and test 2

**Table 8 Summary Statistics of TVR PK Parameters**

**A. Following TVR 750 mg q8h**

| *Parameter* | LSmeans[a] | | LSmeans ratio, % | 90% CI, % | p-value | |
|---|---|---|---|---|---|---|
| | 750 mg telaprevir q8h (reference 1) | 600/100 mg DRV/rtv b.i.d. + 750 mg telaprevir q8h (test 1) | | | Period | Sequence |
| $C_{min}$, ng/mL | 1803 | 1223 | 67.86 | 62.54 - 73.63 | 0.2970 | 0.8069 |
| $C_{max}$, ng/mL[b] | 3050 | 1959 | 64.24 | 61.20 - 67.43 | 0.7172 | 0.5299 |
| $AUC_{8h}$, ng.h/mL | 19290 | 12520 | 64.91 | 61.23 - 68.82 | 0.3560 | 0.5627 |
| | Median[c] | | Treatment difference median | 90% CI, h | p-value | |
| *Parameter* | 750 mg telaprevir q8h (reference 1) | 600/100 mg DRV/rtv b.i.d. + 750 mg telaprevir q8h (test 1) | | | Period | Sequence |
| $t_{max}$, h | 4.0 | 4.0 | -0.125 | (-0.75 - 0.50) | 0.5127 | 0.8280 |

[a] n=16 for reference 1 and n=11 for test 1
[b] n=14 for test 1
[c] n= 13 for reference 1 and test 1

**B. Following TVR 1125 mg q12h**

| *Parameter* | LSmeans[a] | | LSmeans ratio, % | 90% CI,% | p-value | |
|---|---|---|---|---|---|---|
| | 1125 mg telaprevir q12h (reference 2) | 600/100 mg DRV/rtv b.i.d. + 1125 mg telaprevir q12h (test 2) | | | Period | Sequence |
| $C_{min}$, ng/mL | 1335 | 1049 | 78.58 | 71.50 - 86.37 | 0.3569 | 0.2431 |
| $C_{max}$, ng/mL | 3329 | 2164 | 64.99 | 59.14 - 71.42 | 0.9813 | 0.0566* |
| $AUC_{12h}$, ng.h/mL | 26540 | 18310 | 68.98 | 64.08 - 74.24 | 0.5240 | 0.1176 |
| | Median[b] | | Treatment difference median | 90% CI, h | p-value | |
| *Parameter* | 1125 mg telaprevir q12h (reference 2) | 600/100 mg DRV/rtv b.i.d. + 1125 mg telaprevir q12h (test 2) | | | Period | Sequence |
| $t_{max}$, h | 3.5 | 3.75 | 0.25 | (0.00 - 0.50) | 0.8929 | 0.2438 |

[a] n=15 for reference 2 and test 2
[b] n= 14 for reference 2 and test 2
*Statistically significant effect

*Effect of DRV/RTV on VRT-127394 Pharmacokinetics*

Similar to TVR PK characteristics, VRT-127394 exposure was reduced when DRV/RTV was co-administered with TVR across the dose range for both the TVR q8h and q12h dosing regimens. Again, the shape of the curves was similar for both treatments. A similar pattern and magnitude of decreases were observed for VRT-127394 PK parameters as for TVR (Table 9). However, VRT-127394 Cmin and Cmax values were more comparable between the two TVR regimens than TVR concentrations were.

**Table 9 Summary VRT-127394 PK Parameters After Administration of TVR Alone and in the Presence of Steady State DRV/RTV 600/100 mg BID (treatment B, days 20 and 24)**

| *Pharmacokinetics of VRT-127394* (mean ± SD, $t_{max}$: median [range]) | telaprevir q8h, Day 10 (reference 1) | telaprevir q12h, Day 14 (reference 2) |
|---|---|---|
| n | 16 | 15 |
| $C_{0h}$, ng/mL | 1857 ± 460.5 | 1704 ± 530.6 |
| $C_{min}$, ng/mL | 1463 ± 314.9 | 1218 ± 356.8 |
| $C_{max}$, ng/mL | 2088 ± 456.1 | 2091 ± 579.0 |
| $t_{max}$, h | 4.0 (0.0-5.0) | 4.0 (0.0-5.0) |
| $AUC_{\tau}$, ng.h/mL[b] | 13960 ± 2929 | 19310 ± 4517 |
| $C_{ss,av}$, ng/mL | 1747 ± 366.4 | 1609 ± 376.4 |
| FI, % | 35.63 ± 12.02 | 54.89 ± 17.67 |
| | **telaprevir q8h + DRV/rtv, Day 20 (test 1)** | **telaprevir q12h + DRV/rtv, Day 24 (test 2)** |
| n | 11[a] | 15 |
| $C_{0h}$, ng/mL | 1395 ± 228.4 | 1275 ± 277.7 |
| $C_{min}$, ng/mL | 972.4 ± 168.9 | 942.5 ± 203.1 |
| $C_{max}$, ng/mL | 1502 ± 248.3 | 1512 ± 390.4 |
| $t_{max}$, h | 3.75 (0.0-6.0) | 3.5 (0.0-8.0) |
| $AUC_{\tau}$, ng.h/mL[b] | 9923 ± 1152 | 14440 ± 3145 |
| $C_{ss,av}$, ng/mL | 1240 ± 144.1 | 1203 ± 262.1 |
| FI, % | 43.58 ± 14.99 | 46.35 ± 15.11 |

[a] n = 14 for $C_{max}$ and $t_{max}$
[b] τ=8h for reference 1 and test 1, τ=12h for reference 2 and test 2

*Effect of TVR on DRV Pharmacokinetics*

DRV concentrations were decreased in the presence of TVR. The direction and approximate magnitude of the observed effect was irrespective of TVR's dosing regimen. DRV $AUC_{12h}$, Cmin, and Cmax decreased by 38-48%, 39-53%, and 39-44%, respectively, across both TVR regimens when compared with DRV/RTV administration alone (Table 10). Based on the Applicant's statistical analysis of these PK parameters, the decrease in DRV concentrations was statistically significant and the 90% confidence intervals did not fall within the no-effect limits (results not shown).

**Figure 3 Mean Plasma Concentration-Time Curves of DRV After Administration of DRV/RTV at 600/100 mg BID for 23 Days, Co-Administered with TVR at 750 mg q8h from Day 11 to 20 and at 1125 mg q12h from Day 21 to 23 (treatment B, day 10, 20, and 24)**

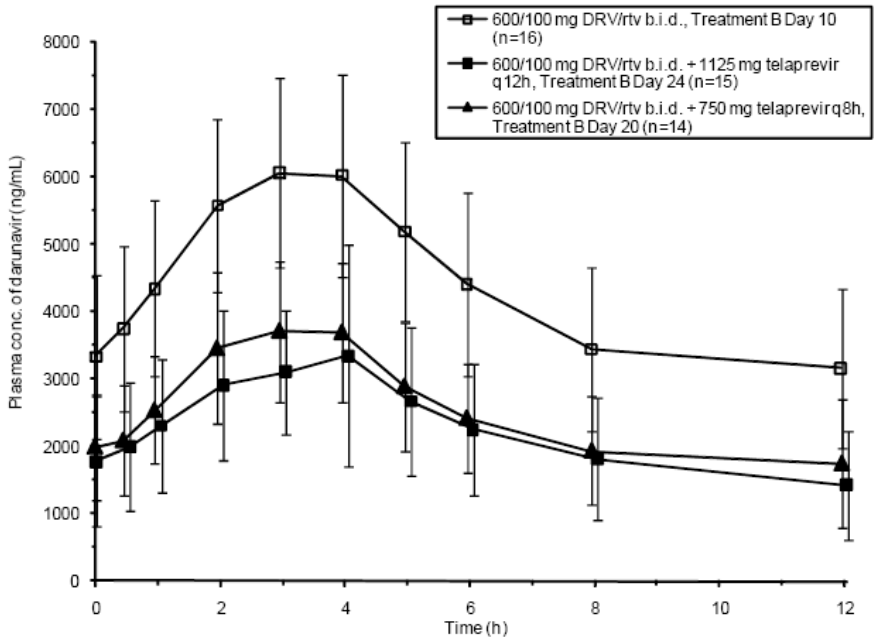



**Table 10 Summary DRV PK Parameters After Administration of DRV/RTV at 600/100 mg BID for 23 Days, Co-Administered with TVR at 750 mg q8h from Day 11 to 20 and at 1125 mg q12h from Day 21 to 23 (treatment B, day 10, 20, and 24)**

| *Pharmacokinetics of darunavir* (mean ± SD, $t_{max}$: median [range]) | DRV/rtv, Day 10 (reference) | telaprevir q8h + DRV/rtv, Day 20 (test 1) | telaprevir q12h + DRV/rtv, Day 24 (test 2) |
|---|---|---|---|
| n | 16 | 11[a] | 15 |
| $C_{0h}$, ng/mL | 3329 ± 1213 | 1995 ± 783.9 | 1777 ± 964.0 |
| $C_{min}$, ng/mL | 2964 ± 1122 | 1794 ± 868.5 | 1392 ± 804.9 |
| $C_{max}$, ng/mL | 6522 ± 1280 | 3984 ± 1061 | 3657 ± 1569 |
| $t_{max}$, h | 3.0 (1.0-4.0) | 3.0 (2.0-4.0) | 3.0 (1.0-4.0) |
| $AUC_{12h}$, ng.h/mL | 51940 ± 14290 | 32120 ± 9713 | 26780 ± 11110 |
| $C_{ss,av}$, ng/mL | 4329 ± 1191 | 2677 ± 809.4 | 2232 ± 925.9 |
| FI, % | 87.62 ± 27.35 | 97.13 ± 29.37 | 107.5 ± 27.48 |

[a] n=14 for $C_{max}$ and $t_{max}$

*Effect of TVR on RTV Pharmacokinetics (as part of DRV/RTV regimen)*

Contrary to the results from the effect of TVR on DRV PK, RTV exposure appears to be slightly increased in the presence of TVR, indicating that a change in RTV concentrations is likely not responsible for the effect of TVR on DRV. Again, the concentration-time profiles have the same general shape (Figure 4). The difference in $AUC_{12h}$, Cmin, and Cmax were slightly greater with the TVR 750-mg q8h regimen than with the TVR 1125 mg q12h regimen (Table 11). However, based on the Applicant's statistical analysis of these PK parameters, the 90%

confidence intervals did not fall within the no-effect limits for either TVR regimen (results not shown).

**Figure 4 Mean Plasma Concentration-Time Curves of RTV After Administration of DRV/RTV at 600/100 mg BID for 23 Days, Co-Administered with TVR at 750 mg q8h from Day 11 to 20 and at 1125 mg q12h from Day 21 to 23 (treatment B, day 10, 20, and 24)**

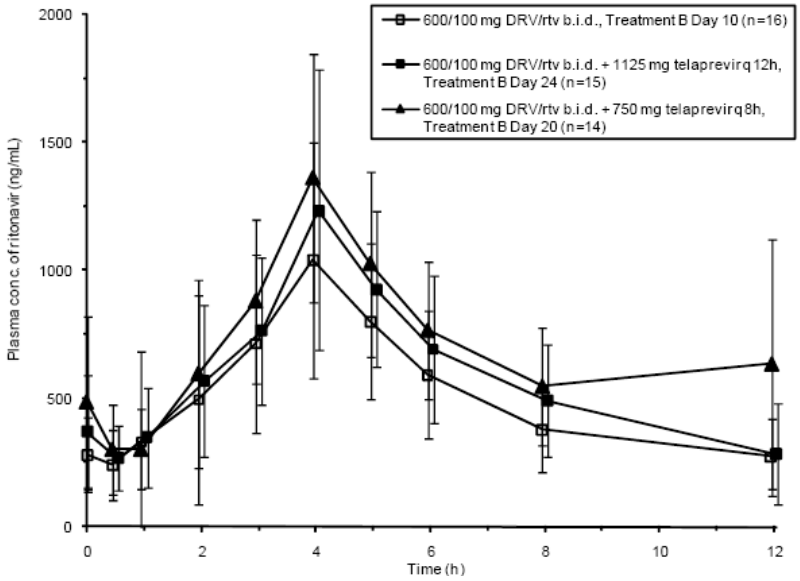



**Table 11 Summary RTV PK Parameters After Administration of DRV/RTV at 600/100 mg BID for 23 Days, Co-Administered with TVR at 750 mg q8h from Day 11 to 20 and at 1125 mg q12h from Day 21 to 23 (treatment B, day 10, 20, and 24)**

| *Pharmacokinetics of ritonavir* (mean ± SD, $t_{max}$: median [range]) | DRV/rtv, Day 10 (reference) | telaprevir q8h + DRV/rtv, Day 20 (test 1) | telaprevir q12h + DRV/rtv, Day 24 (test 2) |
|---|---|---|---|
| n | 16 | 11[a] | 15 |
| $C_{0h}$, ng/mL | 281.2 ± 143.2 | 485.9 ± 336.8 | 371.0 ± 217.5 |
| $C_{min}$, ng/mL | 199.9 ± 97.11 | 281.8 ± 153.3 | 230.3 ± 122.0 |
| $C_{max}$, ng/mL | 1080 ± 467.3 | 1407 ± 485.4 | 1268 ± 536.5 |
| $t_{max}$, h | 4.0 (2.0-5.0) | 4.0 (2.0-12.0) | 4.0 (4.0-5.0) |
| $AUC_{12h}$, ng.h/mL | 6012 ± 2411 | 8662 ± 3137 | 6972 ± 2241 |
| $C_{ss,av}$, ng/mL | 501.0 ± 200.9 | 721.9 ± 261.4 | 581.0 ± 186.7 |
| FI, % | 176.2 ± 43.28 | 161.2 ± 37.07 | 183.5 ± 71.04 |

[a] n=14 for $C_{max}$ and $t_{max}$

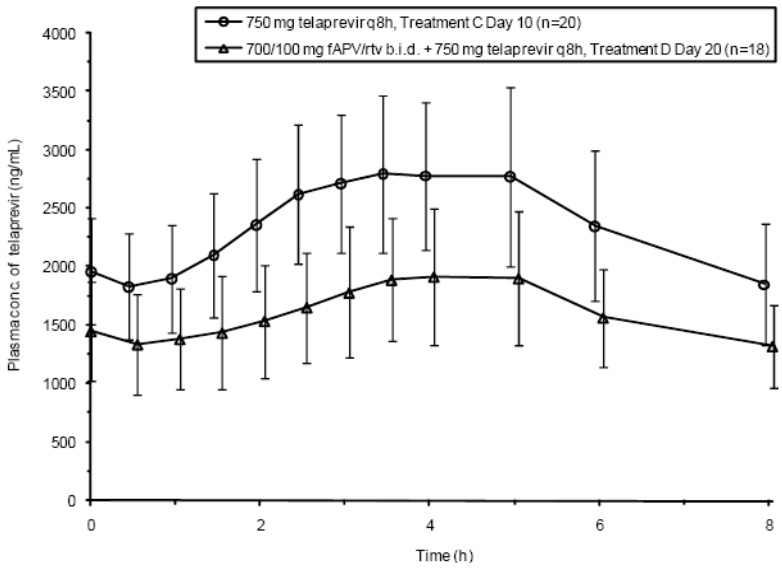
*Effect of APV on TVR Pharmacokinetics*

For both the q8h and q12h TVR regimens, mean plasma concentrations of TVR were lower in the presence of fAPV/RTV across the entire dosing interval, compared to TVR alone. When comparing the PK parameters of the two TVR regimens (TVR alone vs. TVR+fAPV/RTV), TVR $AUC_t$, Cmin, and Cmax were approximately 30-32%, 28-29%, and 31-32% lower with the addition of fAPV/RTV (Table 12). Additionally, the 1125 mg q12h regimen

given in combination with fAPV/RTV did not appear to compensate for the lowering effect on TVR PK. The total daily AUC, Cmax and Cmin were 36%, 25%, and 47% lower, respectively, for the TVR 1125 mg+fAPV/RTV combination than for TVR 750 mg alone. The summary statistics for TVR show that there is a significant interaction effect of fAPV/RTV on TVR PK for both the 750 mg q8h and the 1125 mg q12h regimens (Table 13).

**Figure 5 Mean Plasma Concentration-Time Curves of TVR After Administration of TVR Alone at 750 mg q8h for 10 Days, Followed by 1125 mg q12h for 3 Days and in the Presence of Steady-State fAPV/RTV 700/100 mg BID (treatment D, days 20 and 24)**

**A. TVR PK (TVR 750 mg q8h)**




**B. TVR PK (TVR 1125 mg q12h)**

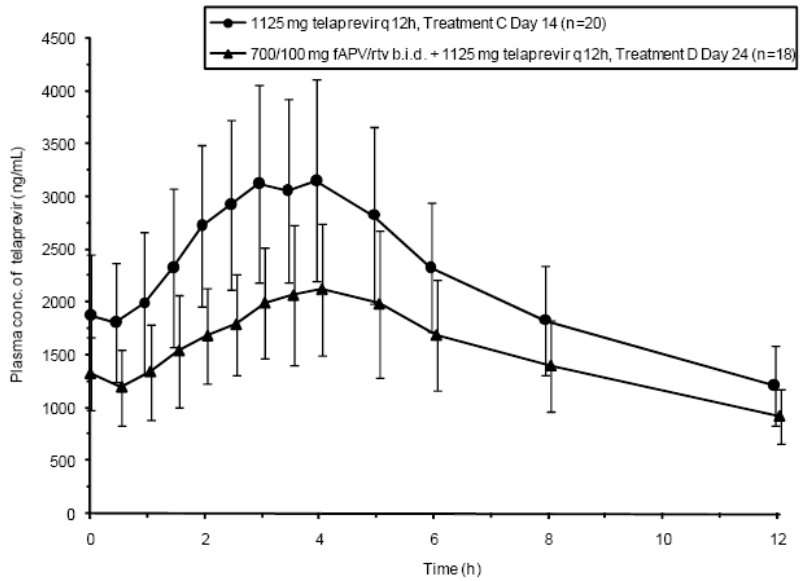


**Table 12 Summary TVR PK Parameters After Administration of TVR Alone at 750 mg q8h for 10 Days, Followed by 1125 mg q12h for 3 Days and in the Presence of Steady State fAPV/RTV 700/100 mg BID (treatment D, days 20 and 24)**

| *Pharmacokinetics of telaprevir* (mean ± SD, $t_{max}$: median [range]) | telaprevir q8h, Day 10 (reference 1) | telaprevir q12h, Day 14 (reference 2) |
|---|---|---|
| n | 20 | 20 |
| $C_{0h}$, ng/mL | 1964 ± 455.1 | 1876 ± 576.7 |
| $C_{min}$, ng/mL | 1658 ± 334.7 | 1214 ± 376.2 |
| $C_{max}$, ng/mL | 3104 ± 752.0 | 3359 ± 898.4 |
| $t_{max}$, h | 3.5 (2.0-5.0) | 3.5 (2.0-5.0) |
| $AUC_{\tau}$, ng.h/mL[b] | 18850 ± 4091 | 25940 ± 7066 |
| $C_{ss,av}$, ng/mL | 2356 ± 511.3 | 2162 ± 588.8 |
| FI, % | 60.40 ± 12.26 | 100.1 ± 21.22 |
| | **telaprevir q8h + fAPV/rtv, Day 20 (test 1)** | **telaprevir q12h + fAPV/rtv, Day 24 (test 2)** |
| n | 18 | 17[a] |
| $C_{0h}$, ng/mL | 1450 ± 422.7 | 1325 ± 347.2 |
| $C_{min}$, ng/mL | 1185 ± 381.4 | 880.7 ± 225.3 |
| $C_{max}$, ng/mL | 2099 ± 534.5 | 2323 ± 629.8 |
| $t_{max}$, h | 4.0 (2.0-5.0) | 4.0 (1.5-8.0) |
| $AUC_{\tau}$, ng.h/mL[b] | 12870 ± 3442 | 18050 ± 4449 |
| $C_{ss,av}$, ng/mL | 1609 ± 430.2 | 1504 ± 370.8 |
| FI, % | 58.04 ± 17.01 | 97.21 ± 23.78 |

[a] n = 18 for $C_{0h}$ and $C_{min}$
[b] τ=8h for reference 1 and test 1, τ=12h for reference 2 and test 2

**Table 13 Summary Statistics of TVR PK Parameters**

**A. Following TVR 750 mg q8h**

| *Parameter* | LSmeans[a] | | LSmeans ratio, % | 90% CI,% | p-value | |
|---|---|---|---|---|---|---|
| | 750 mg telaprevir q8h (reference 1) | 700/100 mg fAPV/rtv b.i.d. + 750 mg telaprevir q8h (test 1) | | | Period | Sequence |
| $C_{min}$, ng/mL | 1624 | 1140 | 70.24 | 63.82 - 77.30 | 0.7095 | 0.4924 |
| $C_{max}$, ng/mL | 3018 | 2022 | 67.00 | 63.01 - 71.25 | 0.7958 | 0.4851 |
| $AUC_{8h}$, ng.h/mL | 18410 | 12440 | 67.55 | 63.42 - 71.95 | 0.9004 | 0.3516 |
| | Median[b] | | | | p-value | |
| *Parameter* | 750 mg telaprevir q8h (reference 1) | 700/100 mg fAPV/rtv b.i.d. + 750 mg telaprevir q8h (test 1) | Treatment difference median | 90% CI, h | Period | Sequence |
| $t_{max}$, h | 3.5 | 4.0 | 0.25 | (-0.25 - 1.00) | 0.0665 | 0.2605 |

[a] n=20 for reference 1 and n=18 for test 1
[b] n=18 for reference 1 and test 1

**B. Following TVR 1125 mg q12h**

| *Parameter* | LSmeans[a] | | LSmeans ratio, % | 90% CI,% | p-value | |
|---|---|---|---|---|---|---|
| | 1125 mg telaprevir q12h (reference 2) | 700/100 mg fAPV/rtv b.i.d. + 1125 mg telaprevir q12h (test 2) | | | Period | Sequence |
| $C_{min}$, ng/mL[b] | 1158 | 869.5 | 75.07 | 70.14 - 80.34 | 0.0256* | 0.7659 |
| $C_{max}$, ng/mL | 3243 | 2214 | 68.27 | 62.11 - 75.03 | 0.4172 | 0.8764 |
| $AUC_{12h}$, ng.h/mL | 25040 | 17500 | 69.89 | 65.07 - 75.07 | 0.7977 | 0.6836 |
| | Median[c] | | Treatment difference median | 90% CI, h | p-value | |
| *Parameter* | 1125 mg telaprevir q12h (reference 2) | 700/100 mg fAPV/rtv b.i.d. + 1125 mg telaprevir q12h (test 2) | | | Period | Sequence |
| $t_{max}$, h | 3.0 | 4.0 | 0.50 | (-0.25 - 1.00) | 0.2480 | 0.2369 |

[a] n=20 for reference 2 and n=17 test 2
[b] n=18 for test 2
[c] n=17 for reference 2 and test 2
* Statistically significant effect

*Effect of APV on VRT-127394 Pharmacokinetics*

Similar to TVR PK characteristics, VRT-127394 exposure was reduced when fAPV/RTV was co-administered with TVR across the dose range for both the TVR q8h and q12h dosing regimens. Again, the shape of the curves was similar for both treatments. A similar pattern and magnitude of decreases were observed for VRT-127394 PK parameters as for TVR (Table 14). However, VRT-127394 PK parameter values were more comparable between the two TVR regimens than TVR parameter values were.

**Table 14 Summary VRT-127394 PK Parameters After Administration of TVR Alone and in the Presence of Steady-State fAPV/RTV 700/100 mg BID**

| ***Pharmacokinetics of VRT-127394*** (mean ± SD, $t_{max}$: median [range]) | **telaprevir q8h, Day 10 (reference 1)** | **telaprevir q12h, Day 14 (reference 2)** |
|---|---|---|
| n | 20 | 20 |
| $C_{0h}$, ng/mL | 1643 ± 387.5 | 1642 ± 377.0 |
| $C_{min}$, ng/mL | 1372 ± 280.4 | 1097 ± 289.3 |
| $C_{max}$, ng/mL | 2033 ± 419.8 | 2119 ± 476.6 |
| $t_{max}$, h | 4.0 (2.0-6.0) | 4.0 (3.0-6.0) |
| $AUC_{\tau}$, ng.h/mL[b] | 13660 ± 2598 | 19550 ± 4442 |
| $C_{ss,av}$, ng/mL | 1708 ± 324.7 | 1629 ± 370.1 |
| FI, % | 38.26 ± 14.73 | 63.49 ± 15.86 |
| | **telaprevir q8h + fAPV/rtv, Day 20 (test 1)** | **telaprevir q12h + fAPV/rtv, Day 24 (test 2)** |
| n | 18 | 17[a] |
| $C_{0h}$, ng/mL | 1317 ± 287.9 | 1199 ± 246.3 |
| $C_{min}$, ng/mL | 1023 ± 266.7 | 821.4 ± 188.1 |
| $C_{max}$, ng/mL | 1544 ± 311.2 | 1573 ± 326.1 |
| $t_{max}$, h | 3.75 (0.0-8.0) | 5.0 (0.0-8.0) |
| $AUC_{\tau}$, ng.h/mL[b] | 10180 ± 2156 | 14150 ± 2672 |
| $C_{ss,av}$, ng/mL | 1272 ± 269.6 | 1179 ± 222.6 |
| FI, % | 42.00 ± 16.60 | 65.04 ± 24.24 |

[a] n = 18 for $C_{0h}$ and $C_{min}$
[b] τ=8h for reference 1 and test 1, τ=12h for reference 2 and test 2

*Effect of TVR on APV Pharmacokinetics*

APV concentrations were decreased in the presence of TVR. The direction and approximate magnitude of the observed effect was irrespective of TVR's dosing regimen. APV $AUC_{12h}$, Cmin, and Cmax decreased by ~50%, 57-59%, and 37-40%, respectively, across both TVR regimens when compared with fAPV/RTV administration alone (Table 15). Based on the Applicant's statistical analysis of these PK parameters, the decrease in DRV concentrations was statistically significant and the 90% confidence intervals did not fall within the no-effect limits (results not shown).

**Figure 6 Mean Plasma Concentration-Time Curves of APV After Administration of fAPV/RTV at 700/100 mg BID for 23 Days, Co-Administered with TVR at 750 mg q8h from Day 11 to 20 and at 1125 mg q12h from Day 21 to 23**

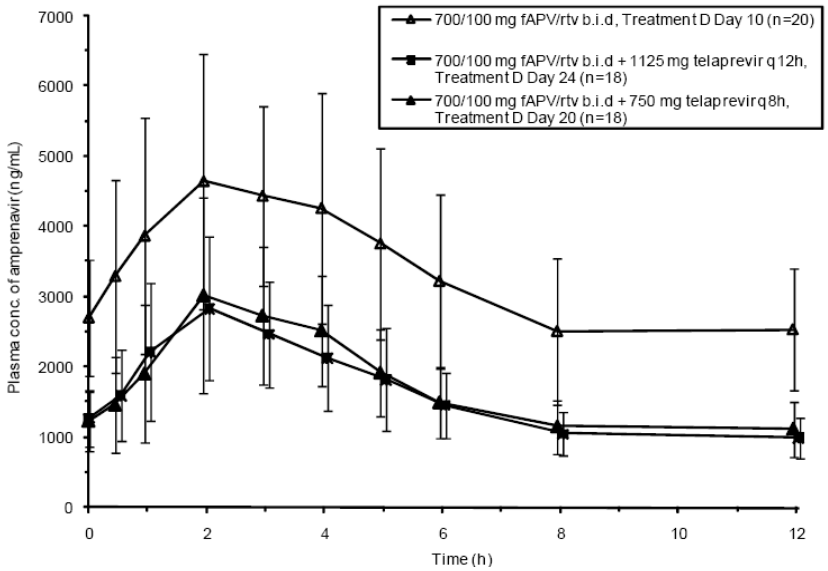



**Table 15 Summary APV PK Parameters After Administration of fAPV/RTV at 700/100 mg BID for 23 Days, Co-Administered with TVR at 750 mg q8h from Day 11 to 20 and at 1125 mg q12h from Day 21 to 23 (treatment D, days 10, 20, and 24)**

| ***Pharmacokinetics of amprenavir*** (mean ± SD, $t_{max}$: median [range]) | **fAPV/rtv, Day 10 (reference)** | **telaprevir q8h + fAPV/rtv, Day 20 (test 1)** | **telaprevir q12h + fAPV/rtv, Day 24 (test 2)** |
|---|---|---|---|
| n | 20 | 18 | 17[a] |
| $C_{0h}$, ng/mL | 2705 ± 835.7 | 1232 ± 425.9 | 1274 ± 407.8 |
| $C_{min}$, ng/mL | 2276 ± 804.5 | 981.9 ± 301.1 | 927.7 ± 294.5 |
| $C_{max}$, ng/mL | 5695 ± 1741 | 3609 ± 1017 | 3389 ± 795.1 |
| $t_{max}$, h | 2.5 (0.5-5.0) | 3.0 (1.0-4.0) | 2.0 (1.0-5.0) |
| $AUC_{12h}$, ng.h/mL | 39670 ± 12100 | 20530 ± 5353 | 19560 ± 4120 |
| $C_{ss,av}$, ng/mL | 3306 ± 1008 | 1711 ± 446.1 | 1630 ± 343.4 |
| FI, % | 105.9 ± 34.41 | 155.7 ± 42.66 | 151.9 ± 42.24 |

[a] n=18 for $C_{0h}$ and $C_{min}$

*Effect of TVR on RTV Pharmacokinetics (as part of fAPV/RTV regimen)*

Contrary to the results from the effect of TVR on DRV PK, RTV exposure is increased in the presence of TVR, indicating that a change in RTV concentrations is likely not responsible for the effect of TVR on lowering DRV plasma concentrations. Again, the concentration-time

profiles have the same general shape (Figure 7). The difference in $AUC_{12h}$, Cmin, and Cmax were slightly greater with the TVR 750-mg q8h regimen than with the TVR 1125 mg q12h regimen (Table 16). However, based on the Applicant's statistical analysis of these PK parameters, the 90% C.I. for the LSmeans ratios between fAPV/RTV alone treatment and fAPV/RTV+TVR treatment did not fall within the no-effect limits for either TVR regimen (results not shown).

**Figure 7 Mean Plasma Concentration-Time Curves of RTV After Administration of fAPV/RTV at 700/100 mg BID for 23 Days, Co-Administered with TVR at 750 mg q8h from Day 11 to 20 and at 1125 mg q12h from Day 21 to 23 (treatment D, days 10, 20, and 24)**

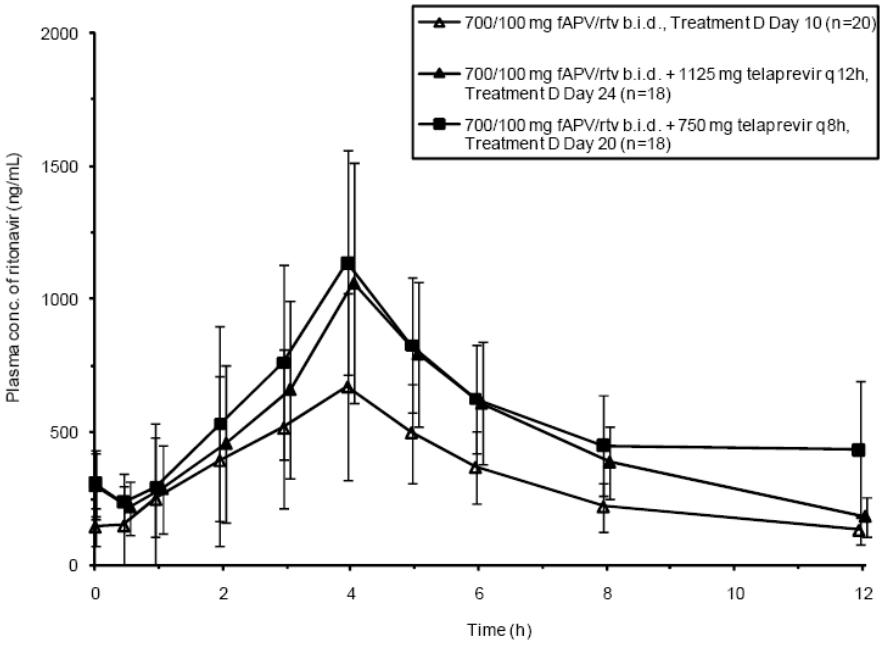



**Table 16 Summary RTV PK Parameters After Administration of fAPV/RTV at 700/100 mg BID for 23 Days, Co-Administered with TVR at 750 mg q8h from Day 11 to 20 and at 1125 mg q12h from Day 21 to 23 (treatment D, days 10, 20, and 24)**

| *Pharmacokinetics of ritonavir* (mean ± SD, $t_{max}$: median [range]) | fAPV/rtv, Day 10 (reference) | telaprevir q8h + fAPV/rtv, Day 20 (test 1) | telaprevir q12h + fAPV/rtv, Day 24 (test 2) |
|---|---|---|---|
| n | 20 | 18 | 17[a] |
| $C_{0h}$, ng/mL | 144.3 ± 70.95 | 307.5 ± 123.2 | 297.1 ± 123.2 |
| $C_{min}$, ng/mL | 105.6 ± 46.58 | 212.8 ± 82.68 | 167.6 ± 70.19 |
| $C_{max}$, ng/mL | 779.3 ± 328.9 | 1167 ± 408.0 | 1125 ± 429.8 |
| $t_{max}$, h | 4.0 (1.0-5.0) | 4.0 (2.0-5.0) | 4.0 (2.0-5.0) |
| $AUC_{12h}$, ng.h/mL | 3798 ± 1511 | 6794 ± 2244 | 5816 ± 1905 |
| $C_{ss,av}$, ng/mL | 316.5 ± 126.0 | 566.2 ± 187.0 | 484.7 ± 158.8 |
| FI, % | 213.8 ± 50.87 | 168.9 ± 33.98 | 197.2 ± 52.78 |

[a] n=18 for $C_{0h}$ and $C_{min}$

*Reviewer's Comments:*
*-Since TVR is a CYP3A4 inhibitor, the decreases in DRV and APV plasma concentrations observed in this study were unexpected. However, it is noted that saquinavir (without RTV) when co-administered with DRV/RTV also decreased DRV exposures (by ~26% in AUC and ~17% in Cmax).*
*-The decrease in TVR exposures when co-administered with either RTV-boosted PI was also not anticipated. Since both RTV-boosted PIs were administered for 10 days prior to introduction of TVR dosing, RTV should have reached steady-state and the inductive effect on CYP3A4 would have been overtaken by its potent inhibitory effect. It is possible that there exists a complex interaction that involves P-gp at the level of absorption and mixed effects on CYP3A4 metabolism by both RTV and TVR. Other uncharacterized transporters in the gut or liver (e.g. BCRP, OATP1B1/3) may also contribute to the complexity of the observed interactions.*

Conclusions

This study demonstrated that when TVR is co-administered with the RTV-boosted protease inhibitors (PIs) DRV and fAPV, exposure to TVR and the PIs are reduced. The magnitude of the effect is similar for both regimens of TVR (750 mg q8h and 1125 mg q12h). These changes were not expected given that TVR is both a substrate for and inhibitor of CYP3A4 (similar to the HIV protease inhibitors). However, TVR appeared to increase exposure to RTV both when it was given in combination with DRV and fAPV. The Applicant's proposed wording for the label concerning these interactions are acceptable and are presented below:

**Section 7.4, Table 5**

| | | |
|---|---|---|
| darunavir/ritonavir* | ↓ telaprevir<br>↓darunavir | (b) (4) It is not recommended to co-administer darunavir/ritonavir and telaprevir. |
| fosamprenavir/ ritonavir* | ↓ telaprevir<br>↓fosamprenavir | (b) (4) It is not recommended to co-administer fosamprenavir/ritonavir and telaprevir. |

*These interactions have been studied. See Clinical Pharmacology (12.3), Tables 6 and 7.

**Section 12.3, Table 6**

| | Dose and Schedule | | | Effect on Telaprevir PK[a] | LS Mean Ratio (90% CI) of Telaprevir PK With/Without Coadministered Drug | | |
|---|---|---|---|---|---|---|---|
| Drug | Drug | Telaprevir | N | | $C_{max}$ | AUC or $C_{avg,ss}$[b] | $C_{min}$ |
| Darunavir (DRV)/ritonavir (rtv) | 600 mg DRV/ 100 mg rtv bid for 20 days | 750 mg q8h for 10 days | 11 (N=14 for $C_{max}$) | ↓ | 0.64 (0.61; 0.67) | 0.65 (0.61; 0.69) | 0.68 (0.63; 0.74) |

| Drug | Dose and Schedule: Drug | Dose and Schedule: Telaprevir | N | Effect on Telaprevir PK[a] | LS Mean Ratio (90% CI) of Telaprevir PK With/Without Coadministered Drug: $C_{max}$ | AUC or $C_{avg,ss}$[b] | $C_{min}$ |
|---|---|---|---|---|---|---|---|
| Fosamprenavir (fAPV)/ ritonavir (rtv) | 700 mg fAPV/ 100 mg rtv bid for 20 days | 750 mg q8h for 10 days | 18 | ↓ | 0.67 (0.63; 0.71) | 0.68 (0.63; 0.72) | 0.70 (0.64; 0.77) |

[a] The direction of the arrow (↑ = *increase,* ↓ = *decrease,* ↔ = *no change*) indicates the direction of the change in PK

**Section 12.3, Table 7**

| Drug | Dose and Schedule: Drug | Dose and Schedule: Telaprevir | N | Effect on Drug PK[a] | LS Mean Ratio (90% CI) of Drug PK With/Without Telaprevir: $C_{max}$ | AUC or $C_{avg,ss}$[b] | $C_{min}$ |
|---|---|---|---|---|---|---|---|
| Darunavir (DRV), boosted with ritonavir (rtv) | 600 mg DRV/ 100 mg rtv bid for 20 days | 750 mg q8h for 10 days | 11 (N=14 for $C_{max}$) | ↓ | 0.60 (0.56; 0.64) | 0.60 (0.57; 0.63) | 0.58 (0.52; 0.64) |
| | 600 mg DRV/ 100 mg rtv bid for 24 days | 1125 mg q12h for 4 days | 15 | ↓ | 0.53 (0.47; 0.59) | 0.49 (0.43; 0.55) | 0.42 (0.35; 0.51) |
| Fosamprenavir (fAPV), boosted with ritonavir (rtv) | 700 mg fAPV/ 100 mg bid rtv for 20 days | 750 mg q8h for 10 days | 18 | ↓ | 0.65 (0.59; 0.70) | 0.53 (0.49; 0.58) | 0.44 (0.40; 0.50) |
| | 700 mg fAPV/ 100 mg bid rtv for 24 days | 1125 mg q12h for 4 days | 17 (N=18 for $C_{min}$) | ↓ | 0.60 (0.55; 0.67) | 0.51 (0.47; 0.55) | 0.42 (0.37; 0.47) |

[a] The direction of the arrow (↑ = *increase,* ↓ = *decrease,* ↔ = *no change*) indicates the direction of the change in PK

**Individual Study Review—VX-950-TiDP24-C130**

Title (Study VX-950-TiDP24-C130)

"A Phase I, open-label, randomized crossover trial in 24 healthy subjects to investigate the effect of steady-state esomeprazole on the pharmacokinetics of a single dose of telaprevir."

Objectives

- To investigate the effect of steady-state esomeprazole on the single-dose pharmacokinetics of telaprevir (TVR) and VRT-127394 (*R*-diastereomer of telaprevir)
- To determine the short-term safety and tolerability of co-administration of telaprevir and esomeprazole

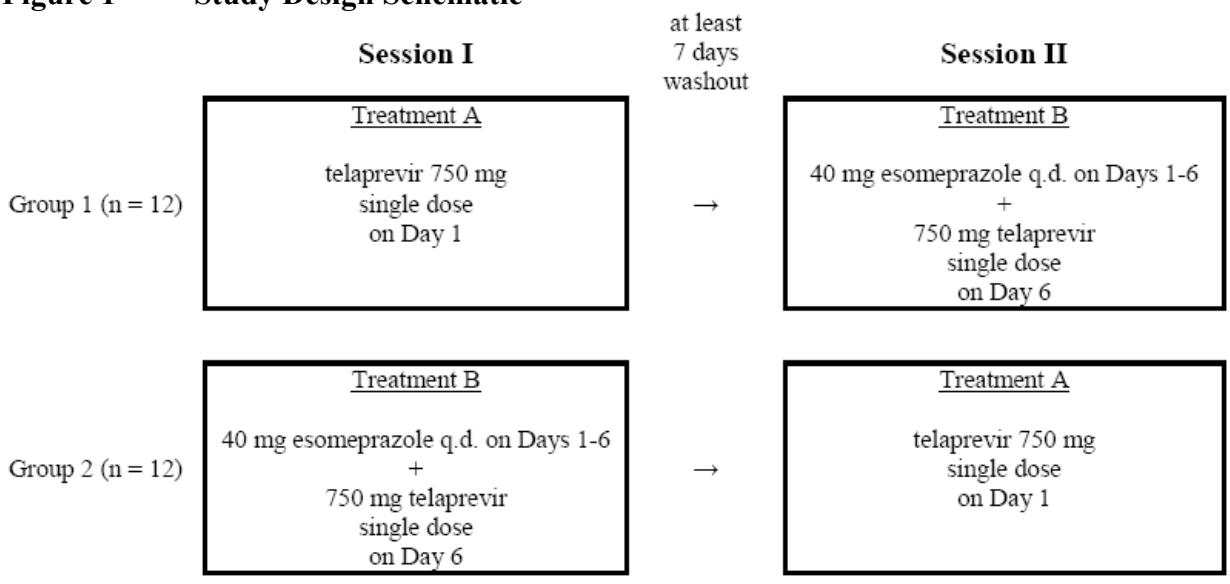
Study Dates and Location(s):

Study initiation: March 7, 2008
Study completion: June 3, 2008
Clinical Site: Medisch Laboratorium Noord, Damsterdiep 191, 9713 EC Groningen, The Netherlands

Study Design

This was a phase 1, open-label, randomized crossover trial in 24 healthy subjects to investigate the effect of steady-state esomeprazole on the pharmacokinetics of a single dose of TVR. Subjects were randomized (1:1) to receive treatment A and treatment B in 2 separate sessions. In treatment A, a single dose of 750 mg telaprevir was administered. In treatment B, 40 mg esomeprazole QD was administered for 6 days and a single dose of 750 mg TVR was given on Day 6. The 2 treatment sessions were separated by a washout period of at least 7 days. The trial design is shown in the schematic below:

**Figure 1 Study Design Schematic**



*Reviewer's Comments:*
*-Because esomeprazole increases intragastric pH, it was important to evaluate the potential for it to alter TVR bioavailability. Esomeprazole has been known to affect the bioavailability of other PIs such as atazanavir, nelfinavir, and saquinavir.*

Study Doses Used and Dose Rationale

A dose of 750 mg TVR was the dose used in this study. It was the dose being used in clinical studies at the time and eventually used in phase 3 studies as the intended commercial dose. Esomeprazole (Nexium®) was formulated as a delayed release tablet, containing 40 mg of esomeprazole present as esomeprazole magnesium trihydrate. Esomeprazole was administered at a dose regimen of 40 mg QD. This is the labeled dose regimen for esomeprazole. Esomeprazole was to be taken 1 hour before the start of breakfast. TVR was to be taken within 30 minutes after the start of breakfast. In the clinic, a standardized breakfast was served that consisted of 4 slices of bread, 2 slices of ham or cheese, butter, jelly, and 2 cups of decaffeinated coffee or tea with milk and/or sugar. This meal was to be consumed in 30 minutes or less. TVR was taken within 10 minutes after the completion of the breakfast, but no later than 30 minutes after the start of the breakfast.

Formulation(s) Used

TVR was administered as the 375-mg core tablet. According to the Applicant's Summary of Biopharmaceutics Studies and Associated Analytical Methods document, it is the same formulation as was used in the phase 3 studies. Esomeprazole was administered as the commercially available delayed release tablet, Nexium®.

*Key Inclusion Criteria:*
-Male or female, aged between 18 and 55 years of age, extremes included
-Females were to be postmenopausal for at least 2 years, or were to have had a hysterectomy or tubal ligation (without reversal operation)
-Being nonsmoking or smoking no more than 10 cigarettes, 2 cigars, or 2 pipes per day in (at least) the 3 months preceding trial screening
-Having a normal weight at screening as defined by a body mass index (BMI) between 18 and 30 $kg/m^2$
-Being healthy on the basis of a medical evaluation that revealed the absence of any clinically relevant abnormality and included a physical examination, medical history, ECG, vital signs, blood biochemistry and hematology tests, and urinalysis carried out at screening

*Key Exclusion Criteria:*
-Subjects with a history of any illness that, in the opinion of the investigator or the subject's general practitioner, confounded the results of the study or posed an additional risk in administering study drug(s) to the subject
-Regular treatment with prescription medications. Subjects were to have ended any short courses of prescription medications at least 14 days prior to the screening visit. Prescription medications were not to be administered during the study. (Potential subjects were not to stop any chronic, prescribed medication being taken at the direction of a physician, without obtaining agreement from that physician)
-Regular treatment with over-the-counter medications. Subjects were to end over-the-counter medication on the date of the screening visit but no less than 2 days prior to administration of

study drug. Occasional use of acetaminophen or ibuprofen was allowed during the study for the treatment of pain (under supervision of the investigator)
-Subjects who consumed herbal medications or dietary medications, dietary supplements (e.g., St. John's Wort, ginkgo biloba, garlic supplements), vitamins, and grapefruit or grapefruit juice within 14 days before administration of study drug (Day 1).
-Subjects who consumed more than 2 units of alcoholic beverages per day or more than 14 units per week.
-Subjects who consumed an average of more than 5 cups of coffee or other caffeinated beverage
-Subjects who had a history of drug or alcohol abuse or addiction within 2 years prior to dosing, or who tested positive for alcohol or drugs of abuse such as cannabis, cocaine, amphetamines or opiates during the screening period
-Subjects who had participated in a clinical study involving administration of either an investigational or a marketed drug within 2 months or 5 half lives (whichever is longer) prior to the screening visit
-Subjects with a hemoglobin of <7.4 mmol/L
-Subjects who tested positive for any of the following infectious disease tests: hepatitis B antigen (HBsAg), hepatitis C virus antibody (HCVAb), human immunodeficiency virus 1 antibody (HIV1Ab), or human immunodeficiency virus 2 antibody (HIV2Ab)
-Subjects who had a female partner who was pregnant, nursing, or planning to become pregnant during the study or within 90 days of the TVR dose
-Having previously participated in a trial with TVR
-Breastfeeding women

Blood Sampling for PK

Treatment A: blood samples for determination of telaprevir and VRT-127394 (R-diastereomer of TVR) plasma concentrations were collected on day 1 at pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, and 24 hours post-dose.

Treatment B: blood samples for determination of telaprevir and VRT-127394 (R-diastereomer of TVR) plasma concentrations were collected on day 1 at pre-dose and on day 6 at pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, and 24 hours post-dose.

Bioanalytical Results

Plasma samples were analyzed for TVR and VRT-127394 by HPLC with tandem mass spectrometric detection (LC-MS/MS) by (b) (4) . Samples were received in frozen condition between April 25, 2008 and April 29, 2008. Samples were analyzed between April 29, 2008 and May 16, 2008. The samples were stored at -70°C. The maximum sample storage until analysis was 21 days, which is within the validated long-term frozen stability duration of 6 months.

The calibration standard concentrations for both TVR and VRT-127394 were 2.0, 4.0, 10.0, 50.0, 200.0, 500, 800, and 1000 ng/mL. The mean accuracy and precision estimates at each TVR and VRT-127394 standard concentration are presented in Tables 1 and 2, respectively, below. All accuracy and precision (%CV) values were within the acceptable range (≤20% from nominal at the LLOQ concentration and ≤15% from nominal at all other concentrations). Quality control concentrations for both analytes were 6.0, 250, and 800 ng/mL. The mean accuracy ranged from 96.3 to 103.3% for TVR and 96.3 to 101.8% for VRT-127394. The mean precision ranged from 3.0 to 4.2% for TVR and 4.0 to 6.2% for VRT-127394.

**Table 1 Mean Calibration Standard Concentrations and Statistics for TVR**

| | VX-950, ng/ml | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Analytical batch | 2.00 | 4.00 | 10.0 | 50.0 | 200 | 500 | 800 | 1000 |
| n | 20 | 19 | 20 | 20 | 19 | 20 | 20 | 20 |
| mean | 2.01 | 4.01 | 9.69 | 49.7 | 200 | 511 | 819 | 983 |
| std. dev. | 0.1 | 0.2 | 0.3 | 1.4 | 6.2 | 19.6 | 19.2 | 31.1 |
| %CV | 5.0 | 4.2 | 3.2 | 2.8 | 3.1 | 3.8 | 2.3 | 3.2 |
| % accuracy | 100.6 | 100.2 | 96.9 | 99.3 | 100.1 | 102.1 | 102.4 | 98.3 |

**Table 2 Mean Calibration Standard Concentrations and Statistics for VRT-127394**

| | VRT-127394, ng/ml | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Analytical batch | 2.00 | 4.00 | 10.0 | 50.0 | 200 | 500 | 800 | 1000 |
| n | 20 | 19 | 20 | 20 | 20 | 20 | 20 | 20 |
| mean | 2.01 | 4.01 | 9.70 | 50.0 | 202 | 508 | 810 | 985 |
| std. dev. | 0.2 | 0.2 | 0.4 | 2.5 | 10.3 | 22.9 | 28.1 | 32.1 |
| %CV | 7.5 | 5.0 | 3.8 | 5.1 | 5.1 | 4.5 | 3.5 | 3.3 |
| % accuracy | 100.5 | 100.2 | 97.0 | 99.9 | 101.1 | 101.5 | 101.3 | 98.5 |

*Reviewer's Comments:*
*-The bioanalytical results for this study are acceptable.*

Results

A total of 24 subjects were randomized and treated but only 23 subjects completed the trial (1 subject withdrew consent following the first session).

*Demographics*

| Parameter | Telaprevir – Esomeprazole + Telaprevir N = 12 | Esomeprazole + Telaprevir – Telaprevir N = 12 | All Subjects N = 24 |
|---|---|---|---|
| Age, years<br>Median (range) | 25.5 (19-54) | 38.0 (19-55) | 32.5 (19-55) |
| Height, cm<br>Median (range) | 182.5 (169-196) | 183.5 (168-193) | 183.0 (168-196) |
| Weight, kg<br>Median (range) | 82.0 (62-95) | 84.5 (68-96) | 82.0 (62-96) |
| BMI, $kg/m^2$<br>Median (range) | 24.65 (20.8-30.0) | 25.60 (18.3-29.0) | 24.85 (18.3-30.0) |
| Sex, n (%)<br>Female<br>Male | 1 (8.3)<br>11 (91.7) | 0<br>12 (100.0) | 1 (4.2)<br>23 (95.8) |
| Ethnic Origin, n (%)<br>Black<br>Caucasian/White | 2 (16.7)<br>10 (83.3) | 1 (8.3)<br>11 (91.7) | 3 (12.5)<br>21 (87.5) |
| Type of Smoker, n (%)<br>Light<br>Nonsmoker | 1 (8.3)<br>11 (91.7) | 5 (41.7)<br>7 (58.3) | 6 (25.0)<br>18 (75.0) |

*Safety*

The most commonly reported AEs (i.e., those reported for more than 3 subjects during the entire trial) were headache (9 [37.5%] subjects), nasopharyngitis (6 [25.0%] subjects), and fatigue (5 [20.8%] subjects). Except for headache and fatigue, AEs occurred in at most 2 subjects in any treatment phase. Their incidences were similar in the different treatment phases, except

for a higher incidence of fatigue after intake of telaprevir alone. (Please refer to the medical officer's review for further details.)

*Pharmacokinetics*

The co-administration of esomeprazole for 6 days did not significantly affect single-dose TVR exposure or exposure to VRT-127394. On average, when a single dose of TVR was added to steady-state esomeprazole, there was no effect on TVR or VRT-127394 concentrations compared to single-dose TVR administered alone (Table 3). Statistical analysis shows that the 90% CIs of the LSmeans ratio for all three parameters were within the no-effect limits (80-125%) for both TVR and VRT-127394, thus indicating that the differences are not clinically meaningful (Tables 4 and 5).

**Figure 2 Mean Plasma Concentration-Time Curves of TVR Following Administration of TVR at 750 mg Alone and in Combination with 40 mg QD Esomeprazole**

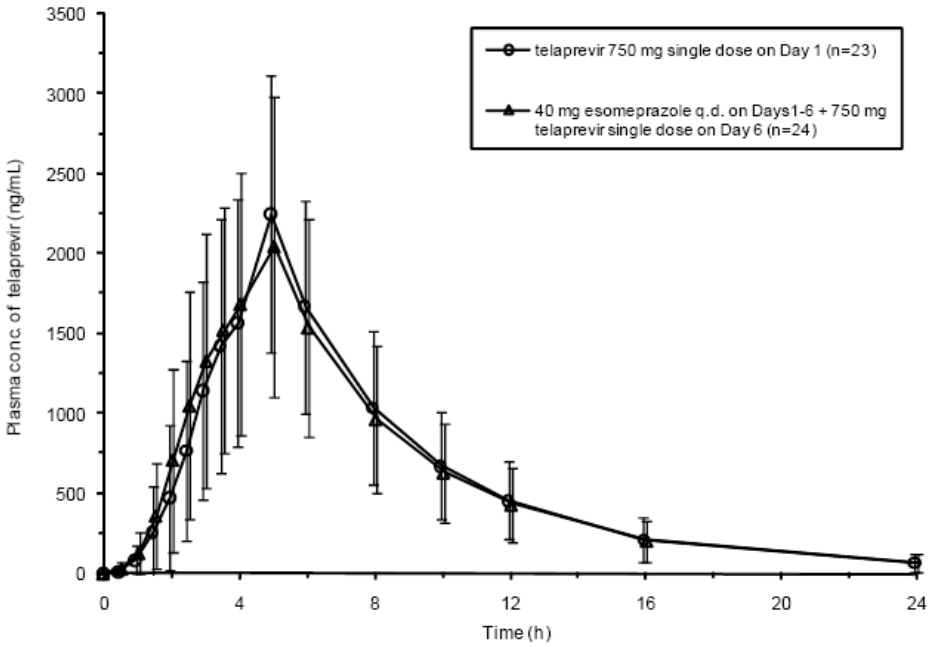



**Table 3 Summary of TVR PK Results Following Administration of TVR 750 mg Alone and in Combination with 40 mg QD Esomeprazole**

| *Pharmacokinetics of telaprevir* (mean ± SD, $t_{max}$: median [range]) | 750 mg telaprevir single dose on Day 1 (reference) | 40 mg esomeprazole q.d. on Days 1-6 + 750 mg telaprevir single dose on Day 6 (test) |
|---|---|---|
| n | 23 | 24 |
| $t_{max}$, h | 5.0 (3.5 - 6.0) | 5.0 (3.0 - 6.0) |
| $C_{max}$, ng/mL | 2288 ± 843.8 | 2237 ± 838.0 |
| $AUC_{last}$, ng.h/mL | 14060 ± 5973 | 13890 ± 5697 |
| $AUC_{\infty}$, ng.h/mL | 14510 ± 6355 | 14330 ± 6022 |
| $t_{1/2term}$, h | 3.872 ± 0.9388 | 3.983 ± 0.9104 |

**Table 4 Statistical Analysis of TVR PK Parameters of Following Administration of 750 mg TVR Alone and in Combination with 40 mg QD Esomeprazole**

| *Parameter* | LS means [a] | | LSmeans ratio, % | 90% CI,% [b] | p-value | |
|---|---|---|---|---|---|---|
| | 750 mg telaprevir single dose on Day 1 (reference) | 40 mg esomeprazole q.d. on Days 1-6 + 750 mg telaprevir single dose on Day 6 (test) | | | Period | Sequence |
| $C_{max}$, ng/mL | 2158 | 2058 | 95.33 | 85.85 - 105.9 | 0.2446 | 0.8568 |
| $AUC_{last}$, ng.h/mL | 12780 | 12480 | 97.67 | 90.81 - 105.1 | 0.6317 | 0.9596 |
| $AUC_{\infty}$, ng.h/mL | 13100 | 12820 | 97.85 | 90.97 - 105.3 | 0.7257 | 0.9479 |

**Table 5 Summary of VRT-127394 PK Results Following Administration of TVR 750 mg Alone and in Combination with 40 mg QD Esomeprazole**

| *Pharmacokinetics of VRT-127394* (mean ± SD, $t_{max}$: median [range]) | 750 mg telaprevir single dose on Day 1 (reference) | 40 mg esomeprazole q.d. on Days 1-6 + 750 mg telaprevir single dose on Day 6 (test) |
|---|---|---|
| n | 23 | 24 |
| $t_{max}$, h | 5.0 (5.0 - 8.0) | 5.0 (3.0 - 8.0) |
| $C_{max}$, ng/mL | 849.5 ± 334.1 | 922.6 ± 324.2 |
| $AUC_{last}$, ng.h/mL | 7028 ± 3244 | 7331 ± 3071 |
| $AUC_{\infty}$, ng.h/mL | 7446 ± 3621 | 7741 ± 3373 |
| $t_{1/2term}$, h | 4.224 ± 1.172 | 4.296 ± 1.147 |

Conclusions

Exposure to TVR and VRT-127394 as expressed by Cmax, $AUC_{last}$, and $AUC_{inf}$ following a single 750-mg dose of TVR was not influenced during co-administration with esomeprazole. The 90% CIs of the LSmeans ratios were all within the no-effect interval. The Applicant's proposed wording for the label is acceptable and is presented below.

**Section 7, below Table 5:**

*"In addition to the drugs included in Table 5, the interaction between* (b) (4) *and the following drug was evaluated in clinical studies and no dose adjustment is needed for either drug [see Clinical Pharmacology (12.3)]: esomeprozole."*

**Section 12, Table 6:**

| | Dose and Schedule | | | Effect on Telaprevir PK[a] | LS Mean Ratio (90% CI) of Telaprevir PK With/Without Coadministered Drug | | |
|---|---|---|---|---|---|---|---|
| **Drug** | **Drug** | **Telaprevir** | **N** | | **$C_{max}$** | **AUC or $C_{avg,ss}$[b]** | **$C_{min}$** |
| Esomeprazole | 40 mg qd for 6 days | 750 mg single dose | 24 | ↔ | 0.95 (0.86; 1.06) | 0.98 (0.91; 1.05) | NA |

**Individual Study Review—VX-950-TiDP24-C133**

Title (Study VX-950-TiDP24-C133)

"A Phase I, open-label, randomized, crossover trial in 16 healthy subjects to investigate the potential pharmacokinetic interaction between telaprevir and escitalopram at steady-state."

Objectives

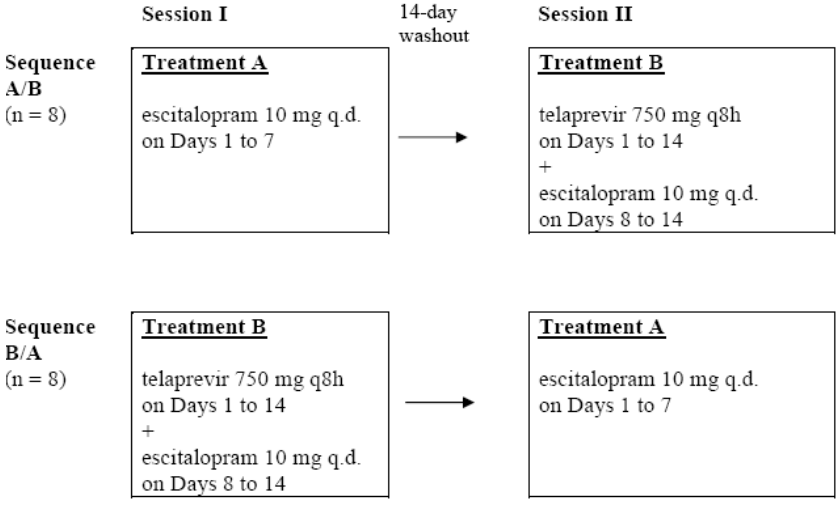
- To determine the effect of TVR 750 mg q8h at steady-state on the steady-state PK of escitalopram 10 mg QD in healthy subjects
- To determine the effect of escitalopram 10 mg QD at steady-state on the steady-state PK of TVR 750 mg q8h in healthy subjects
- To determine the short-term safety and tolerability of coadministration of TVR and escitalopram in healthy subjects

Study Dates and Location(s):
Study initiation: September 1, 2009
Study completion: November 17, 2009
Clinical Site: Centrum Badań Farmakologii Klinicznej Monipol; Kraków, Poland

Study Design

This study was a phase 1, open-label, randomized, 2-sequence, crossover trial in healthy subjects to investigate the effect of steady-state TVR 750 mg q8h on the steady-state PK of escitalopram 10 mg QD and vice versa. A total of 16 subjects were planned for this study. Subjects received two treatments in randomized order. In treatment A, subjects received escitalopram 10 mg QD for 7 days. In treatment B, subjects received TVR 750 mg q8h for 14 days, with co-administration of escitalopram 10 mg QD from day 8 to day 14. There was a washout period of at least 14 days between treatment periods (see Figure 1 below for the study design scheme). All study medication was to be taken with food. Escitalopram was taken once daily in the morning. During co-administration of TVR and escitalopram, the first dose of TVR was to be taken together with escitalopram in the morning.

**Figure 1 Study Design Schematic**



Study Doses Used and Dose Rationale

TVR 750 mg q8h was used in this study. It was the dose regimen being used in the phase 3 studies as the intended commercial dose. Escitalopram was administered as 10 mg QD. This dose is the recommended adult dose in the label for Lexapro® (escitalopram).

Formulation(s) Used

TVR was administered as the 375-mg core tablet. According to the Applicant's Summary of Biopharmaceutics Studies and Associated Analytical Methods document, it is the same formulation as was used in the phase 3 studies. Escitalopram was administered as commercially available 10-mg Lexapro tablets.

*Key Inclusion Criteria:*

-Male or female, aged between 18 and 55 years

-Females were to be postmenopausal for at least 2 years (amenorrheal for at least 3 years) or were to have undergone tubal ligation (or other permanent birth control methods), (total) hysterectomy, or (bilateral) oophorectomy. Subjects were not to be breastfeeding

-Nonsmoking or smoking no more than 10 cigarettes, 2 cigars, or 2 pipes per day from at least 3 months before study screening

-Body Mass Index (BMI) at screening between 18 and 30 $kg/m^2$

-Normal 12-lead electrocardiogram (ECG) at screening including:

- normal sinus rhythm (heart rate [HR] between 50 and 120 beats per minute [bpm])
- QTc interval ≤ 450 ms;
- 50 ms < QRS interval < 120 ms;
- PR interval < 210 ms;

-Healthy on the basis of physical examination, medical history, vital signs assessments, blood chemistry, hematology, coagulation, and urinalysis tests carried out at screening

*Key Exclusion Criteria:*

-Subjects with a history of any illness that, in the opinion of the investigator or the subject's general practitioner, confounded the results of the study or posed an additional risk in administering study drug(s) to the subject

-Regular treatment with prescription medications. Subjects were to have ended any short courses of prescription medications at least 14 days prior to the screening visit. Prescription medications were not to be administered during the study. (Potential subjects were not to stop any chronic, prescribed medication being taken at the direction of a physician, without obtaining agreement from that physician)

-Regular treatment with over-the-counter medications. Subjects were to end over-the-counter medication on the date of the screening visit but no less than 2 days prior to administration of study drug. Occasional use of acetaminophen or ibuprofen was allowed during the study for the treatment of pain (under supervision of the investigator)

-Subjects who consumed herbal medications or dietary medications, dietary supplements (e.g., St. John's Wort, ginkgo biloba, garlic supplements), vitamins, and grapefruit or grapefruit juice within 14 days before administration of study drug (Day 1).

-Subjects who consumed more than 2 units of alcoholic beverages per day or more than 14 units per week.

-Subjects who consumed an average of more than 5 cups of coffee or other caffeinated beverage

-Subjects who had a history of drug or alcohol abuse or addiction within 2 years prior to dosing, or who tested positive for alcohol or drugs of abuse such as cannabis, cocaine, amphetamines or opiates during the screening period
-Subjects who had participated in a clinical study involving administration of either an investigational or a marketed drug within 2 months or 5 half lives (whichever is longer) prior to the screening visit
-Subjects with a hemoglobin of <12.0 g/dL
-Subjects who tested positive for any of the following infectious disease tests: hepatitis B antigen (HBsAg), hepatitis C virus antibody (HCVAb), human immunodeficiency virus 1 antibody (HIV1Ab), or human immunodeficiency virus 2 antibody (HIV2Ab)
-Subjects who had a female partner who was pregnant, nursing, or planning to become pregnant during the study or within 90 days of the TVR dose
-Having previously participated in a trial with TVR

Blood Sampling for PK

Treatment A: Blood samples for determination of (S)-citalopram plasma concentrations were collected at pre-dose on days 1, 5, and 6. In addition, intensive PK sampling took place on day 7 at pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose. A blood sample for determination of TVR plasma concentration was collected at pre-dose on day 1.

Treatment B: Blood samples for determination of TVR plasma concentrations were collected at pre-dose on days 1, 5, 6, 12, and 13. In addition, intensive PK sampling took place on days 7 and 14 at pre-dose and 0.5, 1, 2, 3, 4, 5, 6, and 8 hours post-dose. Blood samples for determination of escitalopram plasma concentrations were collected at pre-dose on days 1, 12, and 13. In addition, intensive PK sampling took place on day 14 at pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 8, 12 and 16 hours post-dose.

Bioanalytical Results

Plasma samples were analyzed for TVR by HPLC with tandem mass spectrometric detection (LC-MS/MS) by (b) (4). Samples were received in frozen condition on October 15, 2009. Samples were analyzed between November 2, 2009 and November 10, 2009. The samples were stored at -70°C. The maximum sample storage time until analysis was 26 days, which is within the validated long-term frozen stability duration of 638 days.

The calibration standard concentrations for TVR were 2.0, 4.0, 10.0, 50.0, 200.0, 500, 800, and 1000 ng/mL. The mean accuracy and precision estimates at each TVR standard concentration are presented in Table 1 below. All accuracy and precision (%CV) values were within the acceptable range (≤20% from nominal at the LLOQ concentration and ≤15% from nominal at all other concentrations). Quality control concentrations were 6.0, 250, and 800 ng/mL. The mean accuracy ranged from 97.6 to 103.2% and the mean precision ranged from 3.6 to 4.6%.

Plasma samples were analyzed for (S)-citalopram by HPLC with tandem mass spectrometric detection (LC-MS/MS) by (b) (4). Samples were received in frozen condition between October 15, 2009 and November 4, 2009. Samples were analyzed between October 20, 2009 and November 10, 2009. The samples were stored at -20°C. The maximum sample storage until analysis was 26 days, which is within the validated long-term frozen stability duration of 73 days.

The calibration standard concentrations for (S)-citalopram were 0.2, 0.4, 1.0, 5.0, 20, 50, 80, and 100 ng/mL. The mean accuracy and precision estimates at each (S)-citalopram standard concentration are presented in Table 2 below. All accuracy and precision (%CV) values were within the acceptable range (≤20% from nominal at the LLOQ concentration and ≤15% from nominal at all other concentrations). Quality control concentrations were 0.6, 15, and 80 ng/mL. The mean accuracy ranged from 98to 99.8% and the mean precision ranged from 3.5 to 4.7%.

**Table 1 Mean Calibration Standard Concentrations and Statistics for TVR**

| | VX-950, ng/ml | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Analytical batch** | **2.00** | **4.00** | **10.0** | **50.0** | **200** | **500** | **800** | **1000** |
| n | 12 | 10 | 12 | 12 | 12 | 12 | 12 | 12 |
| mean | 2.00 | 4.08 | 9.65 | 48.6 | 209 | 511 | 806 | 970 |
| std. dev. | 0.0953 | 0.191 | 0.517 | 1.94 | 8.71 | 22.1 | 26.9 | 32.2 |
| %CV | 4.8 | 4.7 | 5.4 | 4.0 | 4.2 | 4.3 | 3.3 | 3.3 |
| % accuracy | 100.0 | 102.0 | 96.5 | 97.2 | 104.5 | 102.2 | 100.8 | 97.0 |

**Table 2 Mean Calibration Standard Concentrations and Statistics for (S)-citalopram**

| | (S)-citalopram, ng/ml | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Analytical batch** | **0.200** | **0.400** | **1.00** | **5.00** | **20.0** | **50.0** | **80.0** | **100** |
| n | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| mean | 0.200 | 0.393 | 1.05 | 4.87 | 20.3 | 50.2 | 80.3 | 97.0 |
| std. dev. | 0.00606 | 0.0232 | 0.0429 | 0.126 | 0.256 | 1.51 | 2.80 | 3.78 |
| %CV | 3.0 | 5.9 | 4.1 | 2.6 | 1.3 | 3.0 | 3.5 | 3.9 |
| % accuracy | 100.0 | 98.2 | 105.0 | 97.4 | 101.5 | 100.4 | 100.4 | 97.0 |

*Reviewer's Comments:*
*-The bioanalytical results for this study are acceptable.*

Results

A total of 16 subjects were randomized to receive treatments A and B and received at least one dose of study medication. Two subjects discontinued the trial due to AEs and 1 subject discontinued due to withdrawal of consent.

*Demographics*

| Parameter | Sequence A/B N=8 | Sequence B/A N=8 | All Subjects N=16 |
|---|---|---|---|
| Age, years<br>Median (range) | 26.5 (20;50) | 27.0 (20;38) | 26.5 (20;50) |
| Height, cm<br>Median (range) | 175.5 (168;188) | 179.0 (162;192) | 177.5 (162;192) |
| Weight, kg<br>Median (range) | 76.5 (63;90) | 79.0 (64;91) | 77.5 (63;91) |
| BMI, $kg/m^2$<br>Median (range) | 25.45 (20.1;28.7) | 24.55 (22.0;29.1) | 25.00 (20.1;29.1) |
| Sex, n (%)<br>Male | 8 (100.0) | 8 (100.0) | 16 (100.0) |
| Race, n (%)<br>White | 8 (100.0) | 8 (100.0) | 16 (100.0) |
| Smoker, n (%)<br>No<br>Yes[a] | <br>4 (50.0)<br>4 (50.0) | <br>5 (62.5)<br>3 (37.5) | <br>9 (56.3)<br>7 (43.8) |
| Alcohol consumption, n (%)<br>No<br>Yes | <br>2 (25.0)<br>6 (75.0) | <br>1 (12.5)<br>7 (87.5) | <br>3 (18.8)<br>13 (81.3) |

N=number of subjects
[a] All smokers were light smokers, i.e., no more than 10 cigarettes or 2 cigars or 2 pipes per day.
Treatment A: escitalopram 10 mg q.d. from Day 1 to 7
Treatment B: telaprevir 750 mg q8h from Day 1 to 14 plus escitalopram 10 mg q.d. from Day 8 to 14

*Safety*

One (6.3%) subject reported an SAE; grade 3 major depression was reported during the washout period after escitalopram alone administration in session 1 (sequence A/B). The subject permanently discontinued the study due to the SAE. Additionally, 1 subject in treatment sequence B/A discontinued escitalopram and TVR co-administration on day 8 of session 1 due to grade 3 lipase increase with onset on day 7 of TVR alone treatment. The most frequently reported AEs (i.e., in more than 1 subject during the whole trial) were somnolence (5 [31.3%] subjects), nasopharyngitis (4 [25.0%] subjects), headache (3 [18.8%] subjects), and rhinorrhoea (2 [12.5%] subjects). (Please refer to the medical officer's review for further details.)

*TVR Pharmacokinetics*

Although the general shape of the TVR concentration-time curve is similar whether TVR was administered alone or in combination with escitalopram, TVR plasma concentrations were slightly lower during combination treatment throughout the entire dosing interval (Figure 2). Mean TVR Cmax, Cmin, and $AUC_{0\text{-}8h}$ at steady-state were approximately 1%, 10%, and 9% lower, respectively, when TVR was co-administered with escitalopram compared with TVR alone (Table 3). Inter-subject variability in plasma concentrations was similar between treatments. The %CV ranged between 19.5% and 24.7% on day 7 (TVR alone) and between 19.7% and 27.7% on day 14 (TVR+escitalopram). TVR summary statistics show that the 90% CIs for the LSmeans ratios for all three parameters were contained within the no-effect limits (80-125%), indicating that there is no significant interaction effect on TVR exposures by escitalopram (Table 4).

**Figure 2 Mean Plasma Concentration-Time Curves of TVR Following Administration of TVR 750 q8h Alone (Days 1 to 7) and Co-administered with Escitalopram 10 mg QD (Days 8 to 14)**

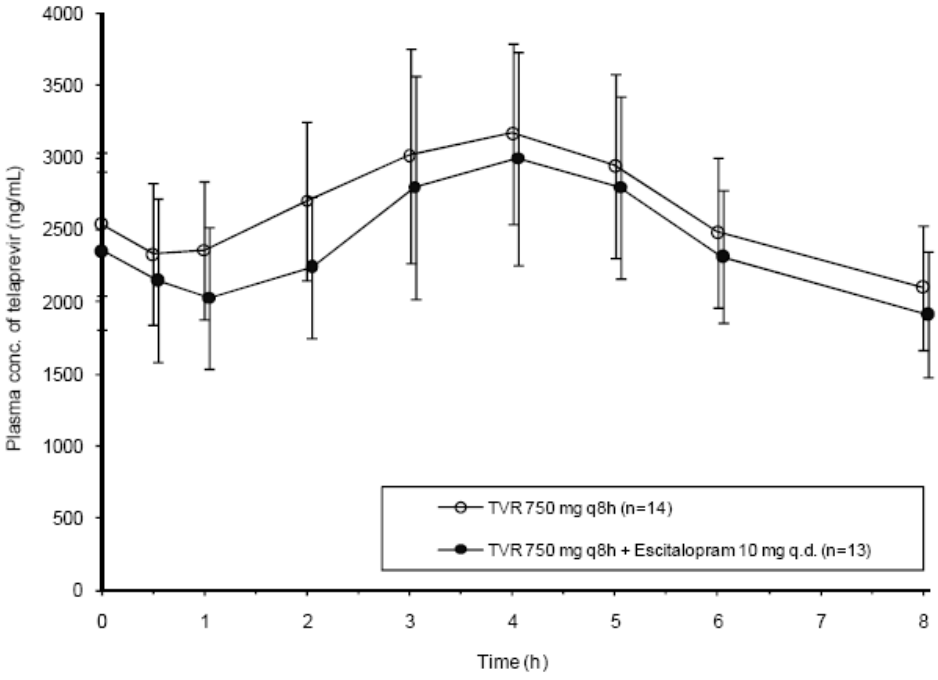


**Table 3 Summary of TVR PK Results Following Administration of TVR 750 q8h Alone and Co-administered with Escitalopram 10 mg QD**

| *Pharmacokinetics of telaprevir* (mean ± SD, $t_{max}$: median [range]) | telaprevir 750 mg q8h (reference) | telaprevir 750 mg q8h + escitalopram 10 mg q.d. (test) |
|---|---|---|
| n | 14 | 13 |
| **Day 5/Day 12** | | |
| $C_{0h}$, ng/mL | 2286 ± 509.3 | 1946 ± 600.1 |
| **Day 6/Day 13** | | |
| $C_{0h}$, ng/mL | 2541 ± 490.6 | 2432 ± 618.5 |
| **Day 7/Day 14** | | |
| $C_{0h}$, ng/mL | 2538 ± 495.0 | 2355 ± 545.8 |
| $C_{min}$, ng/mL | 2073 ± 400.8 | 1876 ± 458.4 |
| $C_{max}$, ng/mL | 3236 ± 637.1 | 3196 ± 662.8 |
| $t_{max}$, h | 4.0 (3.0-5.0) | 4.0 (3.0-5.0) |
| $AUC_{8h}$, ng.h/mL | 21190 ± 4266 | 19370 ± 4134 |
| $C_{ss,av}$, ng/mL | 2649 ± 533.2 | 2421 ± 516.7 |
| FI, % | 43.85 ± 8.242 | 55.13 ± 13.88 |

**Table 4 Summary Statistical Analysis of TVR PK Parameters**

| *Parameter* | LSmeans[a] | | LSmeans ratio | 90% CI[b] |
|---|---|---|---|---|
| | telaprevir 750 mg q8h (reference) | telaprevir 750 mg q8h + escitalopram 10 mg q.d. (test) | | |
| $C_{min}$, ng/mL | 2037 | 1859 | 0.91 | 0.86 - 0.97 |
| $C_{max}$, ng/mL | 3176 | 3178 | 1.00 | 0.95 - 1.05 |
| $AUC_{8h}$, ng.h/mL | 20800 | 19320 | 0.93 | 0.89 - 0.97 |

[a] n=14 for reference and n=13 for test
[b] 90% confidence intervals
[c] n=13 for reference and n= for test

*(S)-citalopram Pharmacokinetics*

(S)-citalopram plasma concentrations were lower during combination treatment throughout the entire dosing interval (Figure 3). Mean (S)-citalopram Cmax, Cmin, and $AUC_{24h}$ at steady-state were approximately 30%, 41%, and 35% lower, respectively, when escitalopram was co-administered with TVR compared with escitalopram alone (Table 5). Inter-subject variability in plasma concentrations was similar between treatments. The %CV ranged between 21.8% and 50.2% (escitalopram alone) and between 22.2% and 46.4% (escitalopram+TVR). (S)-citalopram summary statistics show that the 90% CIs for the LSmeans ratios for all three parameters were lower than the no-effect limits (80-125%), indicating that there is a significant lowering effect on (S)-citalopram exposures by TVR (Table 6).

*Reviewer's Comments:*
*-Similar to the findings from the methadone interaction study (C135), an increase in (S)-citalopram exposure would be anticipated due to TVR's inhibitory effects on CYP3A4. However, the opposite effect was observed. This could indicate that TVR has mixed (inhibitory and inductive) effects on CYP3A4. Escitalopram is also metabolized by CYP2C19; however, TVR has not shown to be an inhibitor or inducer of CYP2C19 in* in vitro *tests.*

**Figure 3 Mean Plasma Concentration-Time Curves of Escitalopram Following Administration of Escitalopram 10 mg QD Alone for 7 days and Co-administered with TVR 750 mg q8h**

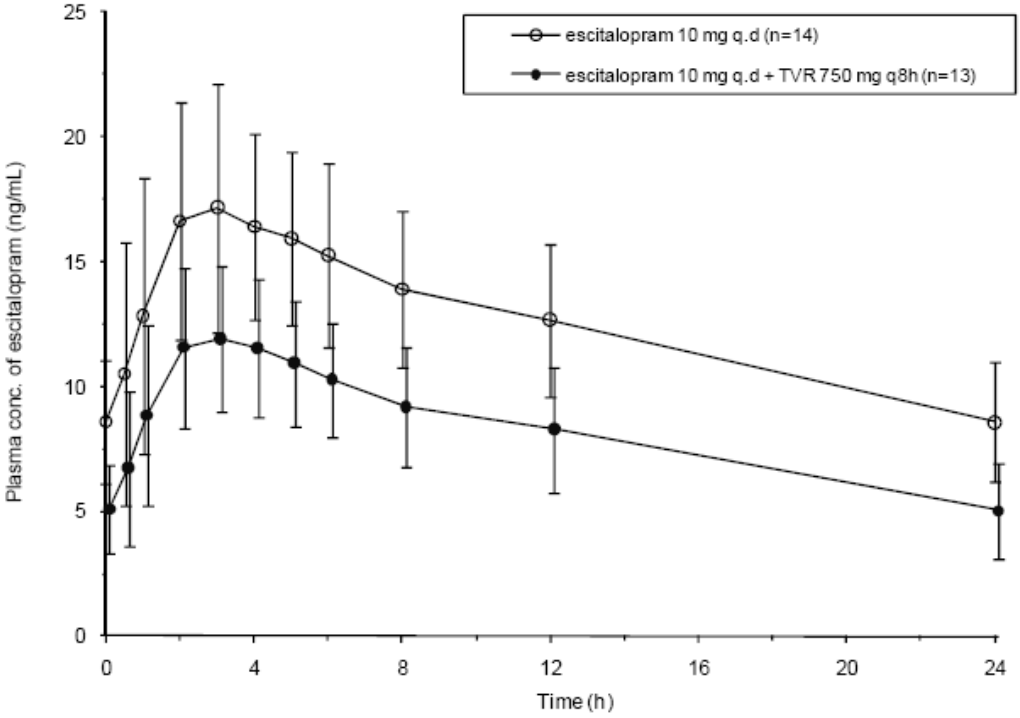



**Table 5 Summary of Escitalopram PK Results Following Administration of Escitalopram 10 mg QD alone and Co-administered with TVR 750 q8h**

| *Pharmacokinetics of escitalopram* (mean ± SD, $t_{max}$: median [range]) | escitalopram 10 mg q.d. (reference) | telaprevir 750 mg q8h + escitalopram 10 mg q.d. (test) |
|---|---|---|
| n | 14[a] | 13 |
| **Day 5/Day 12** | | |
| $C_{0h}$, ng/mL | 8.147 ± 2.261 | 5.236 ± 1.852 |
| **Day 6/Day 13** | | |
| $C_{0h}$, ng/mL | 9.122 ± 2.734 | 5.635 ± 2.056 |
| **Day 7/Day 14** | | |
| $C_{0h}$, ng/mL | 8.581 ± 2.475 | 5.097 ± 1.769 |
| $C_{min}$, ng/mL | 8.356 ± 2.386 | 4.904 ± 1.844 |
| $C_{max}$, ng/mL | 18.07 ± 4.587 | 12.66 ± 2.921 |
| $t_{max}$, h | 3.0 (1.0-5.0) | 3.0 (1.0-5.0) |
| $AUC_{24h}$, ng.h/mL | 298.9 ± 75.38 | 194.8 ± 55.71 |
| $C_{ss,av}$, ng/mL | 12.45 ± 3.141 | 8.117 ± 2.321 |
| FI, % | 78.44 ± 8.639 | 98.83 ± 22.40 |

[a] n=15 for Days 5 and 6

**Table 6 Summary Statistical Analysis of Escitalopram PK Parameters**

| *Parameter* | LSmeans[a] | | LSmeans ratio | 90% CI[b] | p-value | |
|---|---|---|---|---|---|---|
| | escitalopram 10 mg q.d. (reference) | telaprevir 750 mg q8h + escitalopram 10 mg q.d. (test) | | | Period | Sequence |
| $C_{min}$, ng/mL | 8.050 | 4.651 | 0.58 | 0.52 - 0.64 | 0.4734 | 0.6079 |
| $C_{max}$, ng/mL | 17.54 | 12.31 | 0.70 | 0.65 - 0.76 | 0.1264 | 0.5547 |
| $AUC_{24h}$, ng.h/mL | 290.3 | 188.1 | 0.65 | 0.60 - 0.70 | 0.1017 | 0.5309 |

[a] n=14 for reference and n=13 for test
[b] 90% confidence intervals
[c] n=13 for reference and n=13 for test

Conclusions

The results of this study show that escitalopram did not meaningfully affect TVR exposures at steady-state. However, TVR did significantly lower steady-state (S)-citalopram exposures. The Applicant has proposed that doses of escitalopram may need to be adjusted when combined with TVR therapy. This is reasonable since although escitalopram has a relatively wide therapeutic index, an overall 30-35% decrease in exposure to (S)-citalopram may have an effect on escitalopram's pharmacodynamic properties. There are no dose adjustment recommendations in the label for escitalopram (Lexapro®) concerning drug interactions that lower plasma concentrations of (S)-citalopram. The Applicant's proposed wording for the label (shown below) is acceptable.

**Section 7.3, Table 5**

| **Concomitant Drug Class: Drug Name** | **Effect on concentration of INCIVO or Concomitant Drug** | **Clinical Comment** |
|---|---|---|
| escitalopram* | ↔ telaprevir<br>↓ escitalopram | Concentrations of escitalopram were decreased when co-administered with telaprevir. Selective serotonin reuptake inhibitors such as escitalopram have a wide therapeutic index, but doses may need to be adjusted when combined with telaprevir. |

*These interactions have been studied. See Clinical Pharmacology (12.3), Tables 6 and 7.

**Section 12.3, Table 6**

| | **Dose and Schedule** | | | **Effect on Telaprevir PK[a]** | **LS Mean Ratio (90% CI) of Telaprevir PK With/Without Coadministered Drug** | | |
|---|---|---|---|---|---|---|---|
| **Drug** | **Drug** | **Telaprevir** | **N** | | **$C_{max}$** | **AUC or $C_{avg,ss}$[b]** | **$C_{min}$** |
| Escitalopram | 10 mg qd for 7 days | 750 mg q8h for 14 days | 13 | ↔ | 1.00 (0.95; 1.05) | 0.93 (0.89; 0.97) | 0.91 (0.86; 0.97) |

**Section 12.3, Table 7**

| Drug | Dose and Schedule | | N | Effect on Drug PK[a] | LS Mean Ratio (90% CI) of Drug PK With/Without Telaprevir | | |
|---|---|---|---|---|---|---|---|
| | Drug | Telaprevir | | | $C_{max}$ | AUC or $C_{avg,ss}$[b] | $C_{min}$ |
| Escitalopram | 10 mg qd, for 7 days | 750 mg q8h for 14 days | 13 | ↓ | 0.70 (0.65; 0.76) | 0.65 (0.60; 0.70) | 0.58 (0.52; 0.64) |

**Individual Study Review—VX-950-TiDP24-C134**

Title (Study VX950-TiDP24-C134)

"A phase I, open-label, randomized, crossover trial in 20 healthy subjects to investigate the pharmacokinetic interactions between the combination of efavirenz and tenofovir disoproxil fumarate and different dosages of telaprevir."

Objectives

- To determine the effect of EFV and TDF at steady-state on the steady-state pharmacokinetics of TVR and VRT-127394 after administration of TVR 1125 mg q8h and 1500 mg every 12 hours (q12h) in comparison with TVR 750 mg q8h alone
- To determine the effect of TVR 1125 mg q8h and 1500 mg q12h at steady-state on the steady-state pharmacokinetics of EFV and tenofovir
- To determine the short-term safety and tolerability of the co-administration of TVR, EFV, and TDF

Study Dates and Location(s):
Study initiation: February 4, 2009
Study completion: April 22, 2009
Clinical Site: Parexel International GmbH, Institut für Klinische Pharmakologie, Berlin, Germany

Study Design

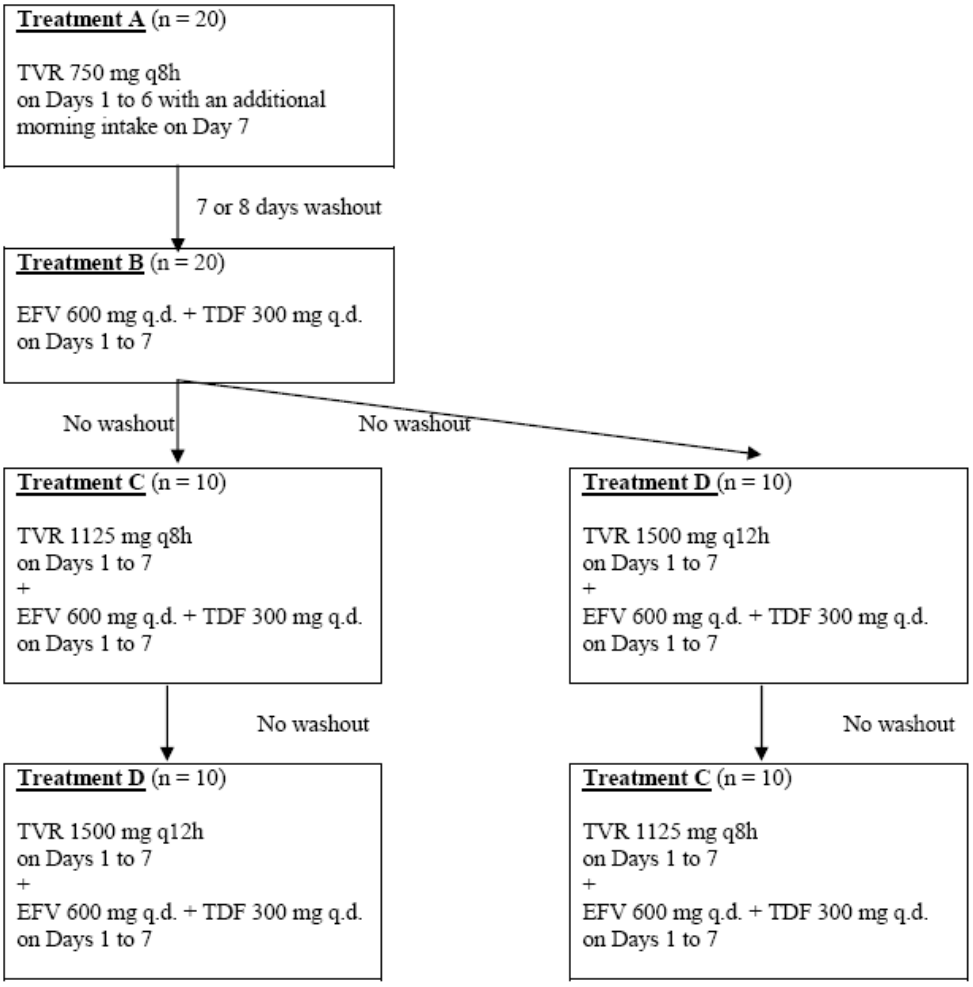
This is was phase 1, randomized, crossover study in 20 healthy subjects. A total of 4 treatment groups were used in the trial:

> Treatment A: TVR 750 mg q8h alone was administered for 6 days with an additional morning dose on Day 7
> Treatment B: EFV 600 mg QD and TDF 300 mg QD were administered for 7 days
> Treatment C: TVR 1125 mg q8h, EFV 600 mg QD and TDF 300 mg QD were administered for 7 days
> Treatment D: TVR 1500 mg q12h, EFV 600 mg QD and TDF 300 mg QD were administered for 7 days.

All subjects started with Treatment A followed by Treatment B. Treatment A and B were separated by a 7 or 8-day washout period. At the end of Treatment B, subjects were randomized (1:1) to sequence 1 (Treatment C followed by Treatment D) or sequence 2 (Treatment D followed by Treatment C). There was no washout period between Treatment B and C or D and no washout period between Treatment C and D or vice versa. Therefore, subjects received daily EFV 600 mg QD and TDF 300 mg QD for a total of 21 consecutive days with the addition of 2 different dosages of TVR (1125 mg q8h and 1500 mg q12h) during the last 14 days.

TVR was taken within 30 min after the start of a meal. EFV and TDF were taken on an empty stomach (2.5 hours after the start of breakfast). EFV (Sustiva®) is recommended to be taken on an empty stomach, whereas TDF (Viread®) is recommended to be taken orally without regard to food. In addition, when EFV and TDF are given in combination as Atripla® (EFV 600 mg/emtricitabine 200 mg/TDF 300 mg), it is to be administered on an empty stomach.

**Figure 1 Study Design Schematic**




Study Doses Used and Dose Rationale

The dosage of 750 mg q8h was being used in ongoing phase 3 trials at the time of this trial. The dose regimens of 1500 mg q12h and 1125 q8h were included in the trial to explore the possibility of a reduced dosing frequency of TVR and to mitigate the anticipated effects of EFV and TDF on TVR clearance (EFV has been shown to reduce exposure to TVR) to guide dose adjustment recommendations.

Formulation(s) Used

TVR was administered as the 375-mg core tablet. According to the Applicant's Summary of Biopharmaceutics Studies and Associated Analytical Methods document, it is the same formulation as was used in the phase 3 studies. EFV was administered as the commercially available Sustiva® 600 mg tablet and TDF was administered as the commercially available Viread® 300 mg tablet.

*Key Inclusion Criteria:*

-Male or female, between 18 and 55 years of age

-Females were to be post-menopausal (amenorrheal for at least 3 years), or were to have undergone tubal ligation (or other permanent birth control methods), or hysterectomy (total), or oophorectomy (bilateral)
-Nonsmoking or smoking no more than 10 cigarettes, or 2 cigars, or 2 pipes per day for at least 3 months before study screening
-Normal weight as defined by a body mass index (BMI) of 18 to 30 $kg/m^2$
-Normal 12-lead electrocardiogram (ECG) at screening including:

- Normal sinus rhythm (heart rate [HR] between 50 and 120 beats per minute [bpm]);
- QTc interval ≤ 450 ms;
- 50 ms < QRS interval < 120 ms;
- PR interval < 210 ms

-Healthy on the basis of a medical evaluation that revealed the absence of any clinically relevant abnormality and included a physical examination, medical history, ECG, vital signs, and the results of blood biochemistry, blood coagulation and hematology tests, and a urinalysis carried out at screening

*Key Exclusion Criteria:*
-Subjects with a history of any illness that, in the opinion of the investigator or the subject's general practitioner, confounded the results of the study or posed an additional risk in administering study drug(s) to the subject
-Regular treatment with prescription medications. Subjects were to have ended any short courses of prescription medications at least 14 days prior to the screening visit. Prescription medications were not to be administered during the study. (Potential subjects were not to stop any chronic, prescribed medication being taken at the direction of a physician, without obtaining agreement from that physician)
-Regular treatment with over-the-counter medications. Subjects were to end over-the-counter medication on the date of the screening visit but no less than 2 days prior to administration of study drug. Occasional use of acetaminophen or ibuprofen was allowed during the study for the treatment of pain (under supervision of the investigator)
-Subjects who consumed herbal medications or dietary medications, dietary supplements (e.g., St. John's Wort, ginkgo biloba, garlic supplements), vitamins, and grapefruit or grapefruit juice within 14 days before administration of study drug (Day 1).
-Subjects who consumed more than 2 units of alcoholic beverages per day or more than 14 units per week.
-Subjects who consumed an average of more than 5 cups of coffee or other caffeinated beverage
-Subjects who had a history of drug or alcohol abuse or addiction within 2 years prior to dosing, or who tested positive for alcohol or drugs of abuse such as cannabis, cocaine, amphetamines or opiates during the screening period
-Subjects who had participated in a clinical study involving administration of either an investigational or a marketed drug within 2 months or 5 half lives (whichever is longer) prior to the screening visit
-Donation of blood or having had a significant loss of blood within 2 months, or donation of more than 1 unit of plasma within 7 days before the first intake of study drug
-Subjects with a hemoglobin of <12.0 g/dL
-Subjects who tested positive for any of the following infectious disease tests: hepatitis B antigen (HBsAg), hepatitis C virus antibody (HCVAb), human immunodeficiency virus 1 antibody (HIV1Ab), or human immunodeficiency virus 2 antibody (HIV2Ab)

-Subjects who had a female partner who was pregnant, nursing, or planning to become pregnant during the study or within 90 days of the TVR dose
-Having previously participated in a trial with TVR
-Having any history of renal disease
-Having a serum creatinine abnormality grade 1 or higher (≥1.1 x upper limit of laboratory normal range)

Blood Sampling for PK

Treatment A: Blood samples for determination of TVR plasma concentrations were collected at pre-dose on days 4, 5, and 6 and on day 7 at the following timepoints: pre-dose, 0.5, 1, 2, 3, 4, 5, 6, and 8 hours post-dose.

Treatment B: Blood samples for determination of EFV and tenofovir plasma concentrations were collected at pre-dose on days 4, 5, and 6 and on day 7 at the following timepoints: pre-dose, 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose.

Treatment C: Blood samples for determination of TVR plasma concentrations were collected at pre-dose on days 4, 5, and 6 and on day 7 at the following timepoints: pre-dose, 0.5, 1, 2, 3, 4, 5, 6, and 8 hours post-dose. Blood samples for determination of EFV and tenofovir plasma concentrations were collected at pre-dose on days 4, 5, and 6 and on day 7 at the following timepoints: pre-dose, 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose.

Treatment D: Blood samples for determination of TVR plasma concentrations were collected at pre-dose on days 4, 5, and 6 and on day 7 at the following timepoints: pre-dose, 0.5, 1, 2, 3, 4, 5, 6, and 8 hours post-dose. Blood samples for determination of EFV and tenofovir plasma concentrations were collected at pre-dose on days 4, 5, and 6 and on day 7 at the following timepoints: pre-dose, 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose.

Bioanalytical Results

Plasma samples were analyzed for TVR by HPLC with tandem mass spectrometric detection (LC-MS/MS) by (b) (4). Samples were received in frozen condition on March 24, 2009. Samples were analyzed between April 16, 2009 and April 23, 2009. The samples were stored at -70°C. The maximum sample storage time until analysis was 30 days, which is within the validated long-term frozen stability duration of 6 months.

The calibration standard concentrations for TVR were 2.0, 4.0, 10.0, 50.0, 200.0, 500, 800, and 1000 ng/mL. The mean accuracy and precision estimates at each TVR standard concentration are presented in Table 1 below. All accuracy and precision (%CV) values were within the acceptable range (≤20% from nominal at the LLOQ concentration and ≤15% from nominal at all other concentrations). Quality control concentrations for TVR were 6.0, 250, and 800 ng/mL. The mean accuracy ranged from 103.5 to 113.2%. The mean precision ranged from 1.8 to 5.8%.

Plasma samples were analyzed for EFV by HPLC with tandem mass spectrometric detection (LC-MS/MS) by (b) (4). Samples were received in frozen condition on March 24, 2009. Samples were analyzed between March 30, 2009 and April 6, 2009. The samples were stored at -20°C. The maximum sample storage time until analysis was 13 days, which is within the validated long-term frozen stability duration of 60 days.

The calibration standard concentrations for EFV were 0.1, 0.2, 0.5, 1.0, 2.5, 5.0, 8.0, and 10.0 µg/mL. The mean accuracy and precision estimates at each EFV standard concentration are

presented in Table 2 below. All accuracy and precision (%CV) values were within the acceptable range (≤20% from nominal at the LLOQ concentration and ≤15% from nominal at all other concentrations). Quality control concentrations EFV were 0.30, 1.75, and 8.00 µg/mL. The mean accuracy ranged from 97.3 to 101.1%. The mean precision ranged from 6.1 to 7%.

Plasma samples were analyzed for tenofovir by HPLC with tandem mass spectrometric detection (LC-MS/MS) by (b) (4). Samples were received in frozen condition on March 24, 2009. Samples were analyzed between April 1, 2009 and April 07, 2009. The samples were stored at -20°C. The maximum sample storage time until analysis was 14 days, which is within the validated long-term frozen stability duration of 30 days.

The calibration standard concentrations for tenofovir were 2.0, 4.0, 10.0, 50.0, 100, 250, 400, and 500 ng/mL. The mean accuracy and precision estimates at each tenofovir standard concentration are presented in Table 3 below. All accuracy and precision (%CV) values were within the acceptable range (≤20% from nominal at the LLOQ concentration and ≤15% from nominal at all other concentrations). Quality control concentrations were 6.0, 75, and 400 ng/mL. The mean accuracy ranged from 95.6 to 96.3%. The mean precision ranged from 4.4 to 12.6%.

**Table 1 Mean Calibration Standard Concentrations and Statistics for TVR**

| | VX-950, ng/ml | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Analytical batch** | **2.00** | **4.00** | **10.0** | **50.0** | **200** | **500** | **800** | **1000** |
| n | 16 | 16 | 16 | 16 | 16 | 16 | 16 | 16 |
| mean | 2.01 | 4.00 | 9.81 | 50.1 | 199 | 498 | 808 | 1010 |
| std. dev. | 0.0463 | 0.171 | 0.247 | 0.841 | 3.38 | 10.7 | 20.7 | 24.1 |
| %CV | 2.3 | 4.3 | 2.5 | 1.7 | 1.7 | 2.1 | 2.6 | 2.4 |
| % accuracy | 100.5 | 100.0 | 98.1 | 100.2 | 99.5 | 99.6 | 101.0 | 101.0 |

**Table 2 Mean Calibration Standard Concentrations and Statistics for EFV**

| | Efavirenz, µg/ml | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Analytical batch** | **0.100** | **0.200** | **0.500** | **1.00** | **2.50** | **5.00** | **8.00** | **10.0** |
| n | 8 | 8 | 8 | 8 | 8 | 8 | 7 | 8 |
| mean | 0.0990 | 0.207 | 0.494 | 0.957 | 2.45 | 4.91 | 8.37 | 10.3 |
| std. dev. | 0.00239 | 0.0103 | 0.0192 | 0.0537 | 0.117 | 0.130 | 0.383 | 0.354 |
| %CV | 2.4 | 5.0 | 3.9 | 5.6 | 4.8 | 2.6 | 4.6 | 3.4 |
| % accuracy | 99.0 | 103.5 | 98.8 | 95.7 | 98.0 | 98.2 | 104.6 | 103.0 |

**Table 3 Mean Calibration Standard Concentrations and Statistics for Tenofovir**

| | Tenofovir, ng/ml | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Analytical batch** | **2.00** | **4.00** | **10.0** | **50.0** | **100** | **250** | **400** | **500** |
| n | 9 | 9 | 8 | 9 | 9 | 9 | 9 | 9 |
| mean | 2.01 | 3.94 | 10.1 | 49.8 | 102 | 246 | 404 | 492 |
| std. dev. | 0.07 | 0.23 | 0.5 | 2.9 | 3 | 13 | 19 | 24 |
| %CV | 3.3 | 5.8 | 5.0 | 5.7 | 2.5 | 5.1 | 4.8 | 5.0 |
| % accuracy | 100.6 | 98.4 | 101.0 | 99.6 | 102.5 | 98.6 | 100.9 | 98.5 |

*Reviewer's Comments:*
*-The bioanalytical results are acceptable.*

Results

A total of 20 subjects were enrolled and received at least one dose of study medication. Two (10.0%) subjects discontinued study medication during administration of EFV+TDF alone (due to AEs) and were not randomized to receive treatments C and D. Eighteen (90.0%) subjects were randomized after treatment B. Eight subjects were randomized to sequence C-D and 10 subjects to sequence D-C. Fourteen (70.0%) subjects completed the study. Six (30.0%) subjects prematurely discontinued the study (all due to AEs).

*Demographics*

| Parameter | Treatment A/B only N = 2 | Treatment A/B/C/D N = 8 | Treatment A/B/D/C N = 10 | All Subjects N = 20 |
|---|---|---|---|---|
| Age, years Median (range) | 37.5 (22-53) | 43.5 (21-54) | 48.0 (26-50) | 45.0 (21-54) |
| Height, cm Median (range) | 179.0 (176-182) | 170.0 (156-190) | 171.5 (155-186) | 171.5 (155-190) |
| Weight, kg Median (range) | 82.5 (74-91) | 69.5 (51-96) | 67.0 (51-93) | 69.5 (51-96) |
| BMI, $kg/m^2$ Median (range) | 25.7 (24-28) | 23.5 (19-29) | 23.5 (20-29) | 24.1 (19-29) |
| Sex, n (%) | | | | |
| Male | 2 (100.0) | 5 (62.5) | 5 (50.0) | 12 (60.0) |
| Female | 0 | 3 (37.5) | 5 (50.0) | 8 (40.0) |
| Race, n (%) | | | | |
| White | 2 (100.0) | 8 (100.0) | 10 (100.0) | 20 (100) |
| Smoker, n (%) | | | | |
| No | 0 | 4 (50.0) | 5 (50.0) | 9 (45.0) |
| Yes[a] | 2 (100.0) | 4 (50.0) | 5 (50.0) | 11 (55.0) |

N = total number of subjects with data; n = number of subjects with that observation
[a] All smokers were light smokers, i.e., no more than 10 cigarettes or 2 cigars or 2 pipes per day.
Treatment A: TVR 750 mg q8h alone for 6 days with an additional morning dose on Day 7;
Treatment B: EFV 600 mg q.d and TDF 300 mg q.d. for 7 days;
Treatment C: TVR 1125 mg q8h, EFV 600 mg q.d., and TDF 300 mg q.d. for 7 days;
Treatment D: TVR 1500 mg q12h, EFV 600 mg q.d., and TDF 300 mg q.d. for 7 days.

*Safety*

Overall, 6 (30.0%) subjects permanently discontinued study medication due to an AE. Two (10.0%) subjects discontinued study medication during treatment B for an AE that started during administration of EFV+TDF alone (treatment B). Three (16.7%) subjects had AEs leading to permanent study medication discontinuation that started during co-administration of TVR 1125 mg q8h and EFV+TDF (treatment C). One subject discontinued study medication during treatment C for an AE that started during administration of EFV+TDF alone and for other AEs that started during co-administration of TVR 1125 mg q8h and EFV+TDF. The most frequently reported AEs (i.e., in at least 6 subjects during the whole trial) were somnolence (13 [65.0%] subjects), dizziness and headache (10 [50.0%] subjects each), diarrhea (7 [35.0%] subjects), and fatigue (6 [30.0%] subjects). (Please refer to the medical officer's review for further details.)

*TVR Pharmacokinetics*

The co-administration of EFV+TDF with TVR resulted in decreased exposure to TVR at both the 1125 mg q8h and 1500 mg q12h TVR doses relative to the 750 mg q8h dose alone. The pattern of decreased plasma concentrations was consistent throughout the concentration-time profile (Figure 2). Day 7 TVR Cmax, Cmin, and $AUC_\tau$ were approximately 15%, 25%, and 20% lower, respectively, for the TVR 1125 mg q8h+EFV+TDF regimen than for TVR 750 mg q8h alone (Table 4). The day 7 Cmax and Cmin were approximately 5% and 44% lower, respectively, for the TVR 1500 mg q12h+EFV+TDF regimen than for TVR 750 mg q8h alone.

However, due to a longer dosing interval and sampling time for the 1500 mg q12h regimen, the $AUC_{\tau}$ was approximately 18% higher than the TVR 750 mg q8h alone regimen.

Inter-subject variability based on the %CV of Cmin, Cmax, and $AUC_{8h}$ (treatments A and C) or $C_{ss,av}$ (treatments A and D) ranged from 26% to 35% for TVR at 750 mg q8h administered alone and from 27% to 54% for TVR at 1125 mg q8h or at 1500 mg q12h in combination with EFV and TDF. The statistical analyses showed that neither TVR regimen (1125 mg q8h or the 1500 q12h) had 90% CIs that were within 80-125% for all three PK parameters tested when compared against TVR 750 mg q8h alone. In general, Cmin was the parameter with the lowest LSmeans ratio in all three comparisons (Tables 5-7).

*Reviewer's Comments:*
*-The exposures resulting from the 1125 mg dose of TVR cannot be accurately normalized to account for the therapeutic dose (750 mg) since TVR is not dose proportional in this dose range.*

**Figure 2 Mean Plasma Concentration-Time Curves of TVR Following Administration of TVR (750 mg q8h)Alone, TVR (1125 mg q8h)+EFV +TDF, and TVR (1500 mg q12h)+EFV+TDF**

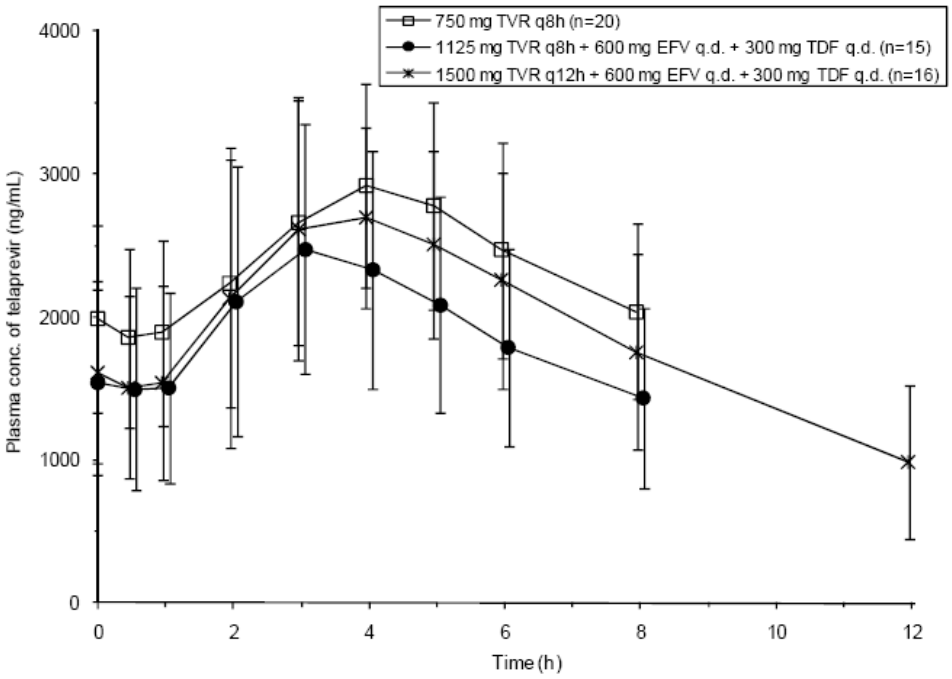


**Table 4 TVR PK Results of TVR Following Administration of TVR (750 mg q8h) Alone, TVR (1125 mg q8h)+EFV +TDF, and TVR (1500 mg q12h)+EFV+TDF**

| *Pharmacokinetics of TVR* (mean ± SD, $t_{max}$: median [range]) | TVR 750 mg q8h (reference) | TVR 1125 mg q8h and EFV + TDF (test 1) | TVR 1500 mg q12h and EFV + TDF (test 2) |
|---|---|---|---|
| n | 20 | 15[b] | 16 |
| **Day 4** | | | |
| $C_{0h}$, ,ng/mL | 2472 ± 676.4 | 2359 ± 1121 | 1199 ± 547.1 |
| **Day 5** | | | |
| $C_{0h}$, ng/mL | 2277 ± 770.6 | 2017 ± 1284 | 1336 ± 632.6 |
| **Day 6** | | | |
| $C_{0h}$, ng/mL | 2019 ± 729.2 | 2169 ± 963.9 | 1715 ± 746.6 |
| **Day 7** | | | |
| $C_{0h}$, ng/mL | 1986 ± 653.6 | 1542 ± 647.9 | 1613 ± 639.1 |
| $C_{min}$, ng/mL | 1752 ± 621.0 | 1309 ± 614.5 | 989.1 ± 536.4 |
| $C_{max}$, ng/mL | 3080 ± 788.6 | 2631 ± 919.2 | 2931 ± 780.5 |
| $t_{max}$, h | 4.0 (3.0-6.0) | 3.0 (2.0-5.0) | 4.0 (2.0-6.0) |
| $AUC_{\tau}$, ng.h/mL[a] | 19150 ± 5449 | 15350 ± 5628 | 22680 ± 7883 |
| $C_{ss,av}$, ng/mL | 2394 ± 681.2 | 1917 ± 703.6 | 1891 ± 656.5 |
| FI, % | 58.55 ± 20.21 | 72.69 ± 22.13 | 112.1 ± 42.28 |

[a] τ=8h for reference and test 1, τ=12h for test 2
[b] n=17 for Day 4, 5 and 6

**Table 5 Summary Statistical Analysis of TVR PK Parameters (TVR 750 q8h alone vs. TVR 1125 q8h+EFV+TDF)**

| *Parameter* | LSmeans[a] | | LSmeans ratio, % | 90% CI,%[c] |
|---|---|---|---|---|
| | TVR 750 mg q8h (reference) | TVR 1125 mg q8h and EFV + TDF (test 1) | | |
| $C_{min}$, ng/mL | 1640 | 1235 | 75.31 | 65.59 - 86.47 |
| $C_{max}$, ng/mL | 2985 | 2569 | 86.07 | 76.10 - 97.34 |
| $AUC_{8h}$, ng.h/mL | 18390 | 15090 | 82.07 | 73.25 - 91.95 |

[a] n=20 for reference and n=15 for test 1
[b] n=15 for reference and test 1
[c] 90% confidence intervals

**Table 6 Summary Statistical Analysis of TVR PK Parameters (TVR 750 q8h alone vs. TVR 1500 q12h+EFV+TDF)**

| *Parameter* | LSmeans[a] | | LSmeans ratio, % | 90% CI,%[c] |
|---|---|---|---|---|
| | TVR 750 mg q8h (reference) | TVR 1500 mg q12h and EFV + TDF (test 2) | | |
| $C_{min}$, ng/mL | 1640 | 848.2 | 51.74 | 41.83 - 63.99 |
| $C_{max}$, ng/mL | 2985 | 2885 | 96.64 | 87.76 - 106.4 |
| $C_{ss,av}$, ng/mL | 2298 | 1849 | 80.45 | 73.25 - 88.35 |

[a] n=20 for reference and n=16 for test 2
[b] n=16 for reference and test 2
[c] 90% confidence intervals

**Table 7 Summary Statistical Analysis of TVR PK Parameters (TVR 1125 q8h+EFV+TDF vs. TVR 1500 mg q12h+EFV+TDF)**

| *Parameter* | LSmeans[a] | | LSmeans ratio, % | 90% CI,%[c] | p-value | |
|---|---|---|---|---|---|---|
| | TVR 1125 mg q8h and EFV + TDF (test 1) | TVR 1500 mg q12h and EFV + TDF (test 2) | | | Period | Sequence |
| $C_{min}$, ng/mL | 1213 | 794.5 | 65.50 | 52.07 - 82.41 | 0.3107 | 0.1562 |
| $C_{max}$, ng/mL | 2539 | 2813 | 110.8 | 100.9 - 121.7 | 0.1414 | 0.3714 |
| $C_{ss,av}$, ng/mL | 1847 | 1773 | 95.96 | 86.00 - 107.1 | 0.5009 | 0.3358 |

[a] n=15 for test 1 n=16 for test 2
[b] n=14 for test 1 and test 2
[c] 90% confidence intervals

*EFV Pharmacokinetics*

Similar to EFV/TDF's effect on TVR, TVR also lowered exposure to EFV when given in combination with TDF as compared to EFV+TDF administration alone. However, mean plasma concentrations of EFV when co-administered with TVR at 1125 mg q8h or at 1500 mg q12h, both in combination with TDF, were not significantly different (Figure 3). The day 7 Cmax, Cmin, and $AUC_{24h}$ were approximately 24%, 9%, and 18% lower, respectively, for the TVR 1125 mg q8h+EFV+TDF regimen than for EFV+TDF alone (Table 8). The day 7 Cmax, Cmin, and $AUC_{24h}$ were approximately 22%, 6%, and 13% lower, respectively, for the TVR 1500 mg q12h+EFV+TDF regimen than for TVR 750 mg q8h alone.

Inter-subject variability based on the %CV of Cmin, Cmax, $AUC_{24h}$, and $C_{ss,av}$ was slightly lower (values ranging from 31% to 54%) when EFV and TDF were administered alone compared to co-administration with TVR q8h or q12h (values ranging from 40% to 75%). The statistical analyses showed that only the comparison between TVR 1125 q8h+ EFV+TDF and TVR 1500 q12h+EFV+TDF had 90% CIs that were within 80-125% for all three PK parameters tested (Tables 9-11).

**Figure 3 Mean Plasma Concentration-Time Curves of EFV Following Administration of EFV+TDF, TVR (1125 mg q8h)+EFV +TDF, and TVR (1500 mg q12h)+EFV+TDF**

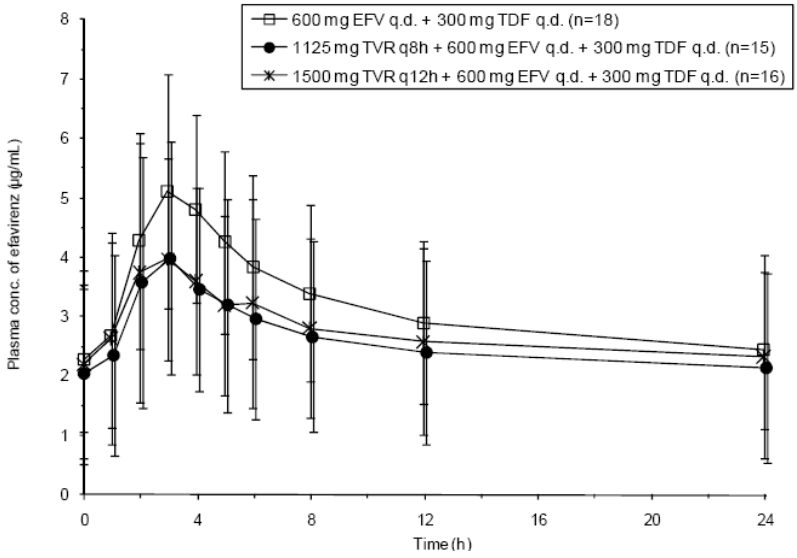


**Table 8 EFV PK Results of TVR Following Administration of EFV+TDF, TVR (1125 mg q8h)+EFV +TDF, and TVR (1500 mg q12h)+EFV+TDF**

| *Pharmacokinetics of EFV* (mean ± SD, $t_{max}$: median [range]) | EFV and TDF (reference) | TVR 1125 mg q8h and EFV +TDF (test 1) | TVR 1500 mg q12h and EFV + TDF (test 2) |
|---|---|---|---|
| n | 18[a] | 15[b] | 16 |
| **Day 4** | | | |
| $C_{0h}$, µg/mL | 1.650 ± 0.7511 | 2.096 ± 1.173 | 2.244 ± 1.482 |
| **Day 5** | | | |
| $C_{0h}$, µg/mL | 1.893 ± 0.8082 | 2.140 ± 1.429 | 2.151 ± 1.509 |
| **Day 6** | | | |
| $C_{0h}$, µg/mL | 2.094 ± 0.9588 | 2.037 ± 1.388 | 2.217 ± 1.578 |
| **Day 7** | | | |
| $C_{0h}$, µg/mL | 2.267 ± 1.202 | 2.034 ± 1.517 | 2.200 ± 1.576 |
| $C_{min}$, µg/mL | 2.222 ± 1.206 | 2.016 ± 1.517 | 2.086 ± 1.505 |
| $C_{max}$, µg/mL | 5.516 ± 1.718 | 4.217 ± 2.105 | 4.371 ± 1.742 |
| $t_{max}$, h | 3.0 (2.0-5.0) | 3.0 (2.0-4.0) | 3.0 (2.0-6.0) |
| $AUC_{24h}$, µg.h/mL | 75.59 ± 33.62 | 61.80 ± 38.87 | 65.97 ± 38.80 |
| $C_{ss,av}$, µg/mL | 3.161 ± 1.390 | 2.575 ± 1.620 | 2.749 ± 1.617 |
| FI, % | 117.5 ± 44.86 | 101.3 ± 38.09 | 103.3 ± 46.85 |

[a] n=19 for Day 4, 5 and 6
[b] n=17 for Day 4 and 5, n=16 for Day 6

*Reviewer's Comments:*
*-Based on the difference in $C_{0h}$ values between day 4 and day 7 for EFV during EFV+TDF alone treatment and the overall pattern of increasing concentrations, it is unclear whether EFV had reached steady-state by day 7. Because EFV has auto-induction properties (CYP3A4), it may take longer for EFV to reach steady-state. According to the label, it takes 6-10 days for EFV to reach steady-state. Thus, the reference arm values may be an underestimate of exposure, and the differences relative to the test arms may be larger than those reported.*

**Table 9 Summary Statistical Analysis of EFV PK Parameters (EFV+TDF vs. TVR 1125 q8h+EFV+TDF)**

| *Parameter* | LSmeans[a] | | LSmeans ratio, % | 90% CI,%[c] |
|---|---|---|---|---|
| | EFV and TDF (reference) | TVR 1125 mg q8h and EFV + TDF (test 1) | | |
| $C_{min}$, µg/mL | 1.955 | 1.762 | 90.13 | 80.78 - 100.6 |
| $C_{max}$, µg/mL | 5.287 | 4.009 | 75.82 | 67.89 - 84.68 |
| $AUC_{24h}$, µg.h/mL | 69.53 | 56.93 | 81.88 | 74.22 - 90.33 |

[a] n=18 for reference and n=15 for test 1
[b] n=15 for reference and test 1
[c] 90% confidence intervals

**Table 10 Summary Statistical Analysis of EFV PK Parameters (EFV+TDF vs. TVR 1500 q12h+EFV+TDF)**

| *Parameter* | LSmeans[a] | | LSmeans ratio, % | 90% CI,%[c] |
|---|---|---|---|---|
| | EFV and TDF (reference) | TVR 1500 mg q12h and EFV + TDF (test 2) | | |
| $C_{min}$, µg/mL | 1.955 | 1.739 | 88.99 | 82.25 - 96.28 |
| $C_{max}$, µg/mL | 5.287 | 4.209 | 79.61 | 74.05 - 85.58 |
| $AUC_{24h}$, µg.h/mL | 69.53 | 58.87 | 84.67 | 78.64 - 91.17 |

[a] n=18 for reference and n=16 for test 2
[b] n=16 for reference and test 2
[c] 90% confidence intervals

**Table 11 Summary Statistical Analysis of EFV PK Parameters (TVR 1125 q8h+ EFV+TDF vs. TVR 1500 q12h+EFV+TDF)**

| *Parameter* | LSmeans[a] | | LSmeans ratio, % | 90% CI,%[c] | p-value | |
|---|---|---|---|---|---|---|
| | TVR 1125 mg q8h and EFV + TDF (test 1) | TVR 1500 mg q12h and EFV + TDF (test 2) | | | Period | Sequence |
| $C_{min}$, µg/mL | 1.718 | 1.705 | 99.21 | 91.40 - 107.7 | 0.4685 | 0.7118 |
| $C_{max}$, µg/mL | 3.998 | 4.138 | 103.5 | 95.89 - 111.7 | 0.5155 | 0.3358 |
| $AUC_{24h}$, µg.h/mL | 56.31 | 57.20 | 101.6 | 95.23 - 108.4 | 0.5048 | 0.6359 |

[a] n=15 for test 1 n=16 for test 2
[b] n=14 for test 1 and test 2
[c] 90% confidence intervals

*Tenofovir Pharmacokinetics*

In contrast to TVR's effect on EFV, TVR slightly increased exposure to tenofovir when given in combination with EFV as compared to EFV+TDF administration alone. Mean plasma concentrations of tenofovir when co-administered with TVR at 1125 mg q8h compared with EFV+TDF administration alone were not significantly different (Figure 4). The day 7 Cmax, Cmin, and $AUC_{24h}$ were approximately 20%, 15%, and 9% higher, respectively, for the TVR 1125 mg q8h+EFV+TDF regimen than for EFV+TDF alone (Table 12). The day 7 Cmax, Cmin, and $AUC_{24h}$ were approximately 22%, 6%, and 7% higher, respectively, for the TVR 1500 mg q12h+EFV+TDF regimen than for TVR 750 mg q8h alone.

Inter-subject variability based on the %CV of Cmin Cmax, $AUC_{24h}$, and $C_{ss,av}$ was slightly lower (values ranging from 28% to 34%) when EFV and TDF were administered alone compared to co-administration with TVR q8h or q12h (values ranging from 31% to 46%). The statistical analyses showed that based on the 90% CIs for all three PK parameters tested, the TVR 1500 q12h+ EFV+TDF was the regimen closest to achieving the no-effect level when compared with EFV+TDF alone (Tables 13-15).

**Figure 4 Mean Plasma Concentration-Time Curves of Tenofovir Following Administration of EFV+TDF, TVR (1125 mg q8h)+EFV +TDF, and TVR (1500 mg q12h)+EFV+TDF**

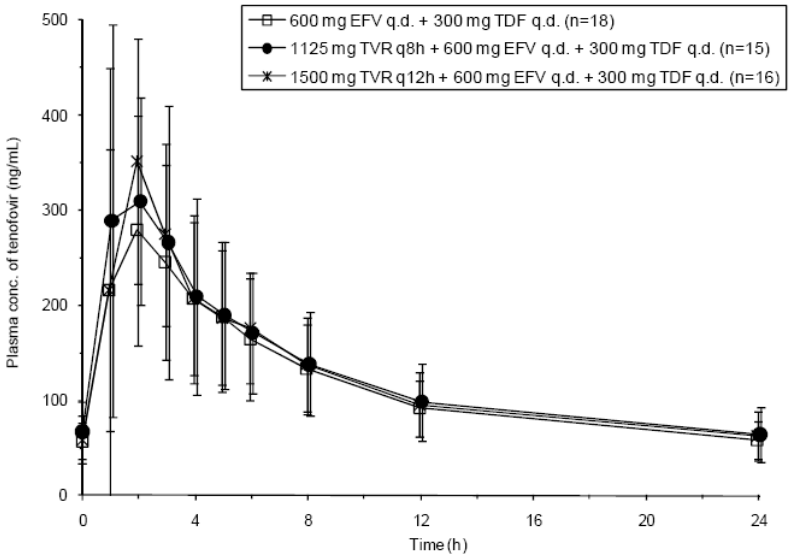



**Table 12 Tenofovir PK Results of TVR Following Administration of EFV+TDF, TVR (1125 mg q8h)+EFV +TDF, and TVR (1500 mg q12h)+EFV+TDF**

| *Pharmacokinetics of Tenofovir* (mean ± SD, $t_{max}$: median [range]) | EFV and TDF (reference) | TVR 1125 mg q8h and EFV + TDF (test 1) | TVR 1500 mg q12h and EFV + TDF (test 2) |
|---|---|---|---|
| n | 18[a] | 15[b] | 16 |
| **Day 4** | | | |
| $C_{0h}$, ng/mL | 56.10 ± 24.07 | 80.20 ± 38.67 | 66.95 ± 31.44 |
| **Day 5** | | | |
| $C_{0h}$, ng/mL | 66.41 ± 25.29 | 79.74 ± 36.62 | 69.67 ± 33.33 |
| **Day 6** | | | |
| $C_{0h}$, ng/mL | 58.99 ± 21.47 | 71.24 ± 33.39 | 61.31 ± 29.04 |
| **Day 7** | | | |
| $C_{0h}$, ng/mL | 56.93 ± 19.25 | 67.07 ± 32.46 | 58.74 ± 25.21 |
| $C_{min}$, ng/mL | 53.86 ± 18.35 | 62.77 ± 28.61 | 56.84 ± 25.30 |
| $C_{max}$, ng/mL | 356.7 ± 99.52 | 428.3 ± 134.1 | 436.0 ± 143.3 |
| $t_{max}$, h | 2.0 (0.98-3.0) | 1.0 (1.0-3.0) | 2.0 (1.0-3.0) |
| $AUC_{24h}$, ng.h/mL | 2857 ± 924.9 | 3114 ± 1170 | 3055 ± 1046 |
| $C_{ss,av}$, ng/mL | 119.6 ± 38.22 | 129.8 ± 48.74 | 127.3 ± 43.59 |
| FI, % | 258.0 ± 44.41 | 291.0 ± 48.85 | 304.4 ± 51.99 |

[a] n=19 for Day 4, 5 and 6
[b] n=17 for Day 4 and 5, n=16 for Day 6

**Table 13 Summary Statistical Analysis of Tenofovir PK Parameters (EFV+TDF vs. TVR 1125 q8h+EFV+TDF)**

| *Parameter* | LSmeans[a] | | LSmeans ratio, % | 90% CI,%[c] |
|---|---|---|---|---|
| | EFV and TDF (reference) | TVR 1125 mg q8h and EFV + TDF (test 1) | | |
| $C_{min}$, ng/mL | 51.31 | 59.85 | 116.6 | 106.3 - 127.9 |
| $C_{max}$, ng/mL | 343.5 | 418.6 | 121.9 | 111.6 - 133.1 |
| $AUC_{24h}$, ng.h/mL | 2730 | 3008 | 110.2 | 102.9 - 118.0 |

[a] n=18 for reference and n=15 for test 1
[b] n=15 for reference and test 1
[c] 90% confidence intervals

**Table 14 Summary Statistical Analysis of Tenofovir PK Parameters (EFV+TDF vs. TVR 1500 q12h+EFV+TDF)**

| *Parameter* | LSmeans[a] | | LSmeans ratio, % | 90% CI,%[c] |
|---|---|---|---|---|
| | EFV and TDF (reference) | TVR 1500 mg q12h and EFV + TDF (test 2) | | |
| $C_{min}$, ng/mL | 51.31 | 54.55 | 106.3 | 97.96 - 115.4 |
| $C_{max}$, ng/mL | 343.5 | 425.8 | 124.0 | 112.6 - 136.5 |
| $AUC_{24h}$, ng.h/mL | 2730 | 3000 | 109.9 | 102.9 - 117.3 |

[a] n=18 for reference and n=16 for test 2
[b] n=16 for reference and test 2
[c] 90% confidence intervals

**Table 15 Summary Statistical Analysis of Tenofovir PK Parameters (TVR 1125 q8h+ EFV+TDF vs. TVR 1500 q12h+EFV+TDF)**

| *Parameter* | LSmeans[a] | | LSmeans ratio, % | 90% CI,%[c] | p-value | |
|---|---|---|---|---|---|---|
| | TVR 1125 mg q8h and EFV + TDF (test 1) | TVR 1500 mg q12h and EFV + TDF (test 2) | | | Period | Sequence |
| $C_{min}$, ng/mL | 58.85 | 53.67 | 91.19 | 82.93 - 100.3 | 0.8814 | 0.2784 |
| $C_{max}$, ng/mL | 413.0 | 409.9 | 99.26 | 89.92 - 109.6 | 0.0770 | 0.1599 |
| $AUC_{24h}$, ng.h/mL | 2973 | 2957 | 99.48 | 92.51 - 107.0 | 0.6955 | 0.3205 |

[a] n=15 for test 1 and n=16 for test 2
[b] n=14 for test 1 and test 2
[c] 90% confidence intervals

*Reviewer's Comments:*
*-While tenofovir Cmax was increased by ~20% when TVR 1125 mg q8h was co-administered with EFV+TDF, no other parameters were significantly affected. In a previous ddi study (C123), TDF alone was given in combination with TVR 750 mg q8h for 7 days. That study demonstrated that tenofovir exposures were increased by TVR co-administration more significantly than in this study. The presence of EFV (in this study) is likely diminishing TVR's effect on tenofovir.*

Conclusions

The co-administration of EFV and TDF with TVR resulted in decreased exposures to TVR and EFV as compared with either TVR administration alone or EFV+TDF administration alone, respectively. There was no significant effect on tenofovir exposures following co-administration of either TVR regimen. Although the increase in TVR dose to 1500 q12h

somewhat ameliorated the decrease in TVR exposure caused by EFV+TDF treatment, neither TVR regimen was able to compensate for the decreased exposure to EFV caused by TVR co-administration. The Applicant's recommended wording for the label are presented below. The recommended changes to the Applicant's wording are presented in red and blue. For changes in Table 5, please also refer to the individual study review for study VX-950-TiDP24-C123.

**Section 7.4, Table 5**

| Concomitant Drug Class: Drug Name | Effect on concentration of INCIVO or Concomitant Drug | Clinical Comment |
|---|---|---|
| efavirenz* | ↓ telaprevir<br>↓ efavirenz | (b) (4) |
| tenofovir disoproxil fumarate* | ↔ telaprevir<br>↑ tenofovir<br>(b) (4) | |

**Section 12.3, Table 6**

| | Dose and Schedule | | | Effect on Telaprevir PK[a] | LS Mean Ratio (90% CI) of Telaprevir PK With/Without Coadministered Drug | | |
|---|---|---|---|---|---|---|---|
| **Drug** | **Drug** | **Telaprevir** | **N** | | **$C_{max}$** | **AUC or $C_{avg,ss}$[b]** | **$C_{min}$** |
| Tenofovir disoproxil fumarate (TDF) and efavirenz (EFV) | 600 mg EFV /300 mg TDF qd for 7 days | 1125 mg q8h for 7 days | 15 | ↓ | 0.86[c] (0.76; 0.97) | 0.82[c] (0.73; 0.92) | 0.75[c] (0.66; 0.86) |

[c] Value with co-administered drug and telaprevir / value with telaprevir 750 mg q8h alone

**Section 12.3, Table 7**

| Drug | Dose and Schedule | | N | Effect on Drug PK[a] | LS Mean Ratio (90% CI) of Drug PK With/Without Telaprevir | | |
|---|---|---|---|---|---|---|---|
| | Drug | Telaprevir | | | $C_{max}$ | AUC or $C_{avg,ss}$[b] | $C_{min}$ |
| Efavirenz (EFV), coadministered with tenofovir disoproxil fumarate (TDF) | 600 mg EFV /300 mg TDF qd for 7 days | 1125 mg q8h for 7 days | 15 | ↓ | 0.76[c] (0.68; 0.85) | 0.82[c] (0.74; 0.90) | 0.90[c] (0.81; 1.01) |
| | 600 mg EFV /300 mg TDF qd for 7days | 1500 mg q12h for 7days | 16 | ↓ | 0.80[c] (0.74; 0.86) | 0.85[c] (0.79; 0.91) | 0.89[c] (0.82; 0.96) |

[c] Value with co-administered drug and telaprevir / value with telaprevir 750 mg q8h alone

**Individual Study Review—VX-950-TiDP24-C135**

Title (Study VX-950-TiDP24-C135)

"A Phase I, open-label, single-sequence drug-drug interaction trial in subjects on stable methadone maintenance therapy, to investigate the potential interaction between telaprevir 750 mg q8h and methadone, at steady-state."

Objectives

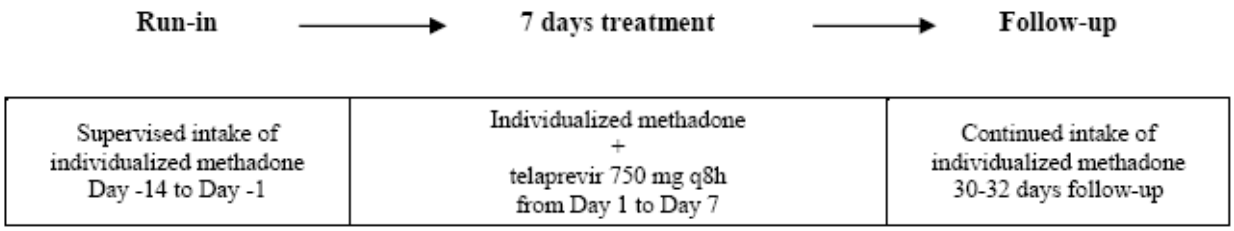
- To evaluate the potential effect of telaprevir on the pharmacodynamic effects of methadone therapy
- To evaluate the steady-state pharmacokinetics of telaprevir 750 mg q8h in subjects on stable methadone maintenance therapy in comparison with historical controls
- To evaluate the short-term safety and tolerability of coadministration of telaprevir and methadone in subjects on stable methadone maintenance therapy

Study Dates and Location(s):
Study initiation: July 31, 2009
Study completion: December 16, 2009
Clinical Sites: Kendle Early Stage, Ontario, Canada

Study Design

This was a Phase I, open-label, single-sequence drug-drug interaction trial in subjects on stable methadone maintenance therapy to investigate the potential interaction between telaprevir 750 mg every 8 hours (q8h) and methadone, at steady-state. A total of 16 subjects were planned for enrollment. TVR 750 mg q8h was added for 7 days to subjects' current methadone therapy. The methadone dosage was not to be changed from screening until day 7. All intake of methadone (from day –14 until day 8) and TVR (from day 1 until day 7) were supervised. From day –2 until day 8, methadone was taken after completion of breakfast, immediately after the morning dose of TVR. TVR was taken with food. Pharmacodynamic assessments of the symptoms of methadone withdrawal (Short Opiate Withdrawal Scale [SOWS], Desires for Drugs Questionnaire [DDQ], and pupillometry) were performed on day –7 and daily from day –2 until day 7, within 2 hours before the intake of methadone.

**Figure 1 Study Design Schematic**




Study Doses Used and Dose Rationale

TVR 750 mg q8h was used in this study. It was the dose regimen being used in the phase 3 studies as the intended commercial dose. Methadone was administered at the individualized dose used for maintenance therapy for each subject, between 30 and 130 mg daily, and the dose

was not to be changed throughout the trial (unless an immediate adjustment of the methadone dosage was warranted by the investigator's assessment of the subject's safety).

Formulation(s) Used

The 375-mg core tablet of TVR was used in this study. According to the Applicant's Summary of Biopharmaceutics Studies and Associated Analytical Methods document, it is the same formulation as was used in the phase 3 studies. Methadone was administered as a commercially available solution.

*Key Inclusion Criteria:*

-Male or female, aged between 18 and 55 years of age
-Females were to be postmenopausal for at least 2 years (amenorrheal for at least 3 years), or were to have undergone bilateral tubal ligation (or other permanent birth control methods), or hysterectomy (total), or oophorectomy (bilateral). A pregnancy test performed at screening had to be negative for females (not applicable for females with hysterectomy or oopherectomy)
-Subjects were to be receiving once-daily oral methadone maintenance therapy at a stable individualized dose of 30 to 130 mg q.d. for at least 2 weeks prior to screening, formulated as commercially available tablets or solution
-The subject was to agree:
    -not to change the current methadone dose from screening until Day 7 included;
    -to have a daily observed and documented methadone intake from Day –14 until Day 8 and a daily observed and documented telaprevir intake from Day 1 until Day 7
-Body mass index (BMI) at screening between 18.0 and 30.0 $kg/m^2$

*Key Exclusion Criteria:*

-History of any illness that, in the opinion of the investigator or the subject's general practitioner or addiction physician, could confound the results of the trial or pose an additional risk in administering study drug(s) to the subject
-Consumption of herbal medications or dietary supplements (e.g., St. John's Wort, ginkgo biloba, garlic supplements), vitamins, and grapefruit or grapefruit juice, apple juice or orange juice within 14 days before day –1
-Current alcohol use, which, in the assessment of the investigator, could compromise subject's safety or compliance with the study protocol procedures
-Test positive for drugs of abuse such as cocaine, amphetamines, barbiturates, benzodiazepines, or opiates on Day -2 unless explained by allowed concomitant medications
Note: Positive drug screening tests for the following did not result in exclusion of a subject:
    -cannabinoids, when used via inhalation (smoking);
    -temazepam, oxazepam, lorazepam, chlordiazepoxide, and codeine, when used in a prescribed dose
-Participation in a clinical study involving administration of an investigational drug within 60 days or 5 half-lives (whichever was longer) prior to the screening visit
-Donation of blood or having had a significant loss of blood within 2 months (500 mL or more), or donation of more than 1 unit of plasma within 7 days before the first dose of TVR
-Hemoglobin level of <12.0 g/dL at screening
-Positive result for any of the following infectious disease tests: hepatitis A infection (confirmed by hepatitis A antibody immunoglobulin M [IgM]), HBsAg, HCV infection (confirmed by hepatitis C virus antibody [HCVAb]), HIV1Ab, or HIV2ab

-Male subject with female partner planning to become pregnant during the trial or within 90 days after the last dose of TVR
-Having participated previously in a trial with TVR

Blood Sampling for PK

Full 24-hour PK profiles of both isomers of methadone (R-methadone and S-methadone) were determined on day -1 (methadone alone) and on day 7 (methadone + TVR). Profiles of both isomers were determined since R-methadone is mainly responsible for the opioid effect and S-methadone has been linked to the QTc prolongation effect of methadone. Since the trial was conducted in subjects who were already maintained on methadone treatment, the PK of TVR alone could not be studied in the same subjects. Thus, the PK of TVR in the subjects in this trial (on methadone) was compared to that of historical controls.

Blood samples for determination of TVR plasma concentrations were collected at pre-dose on study days 2, 3, 4, 5, and 6. Intensive PK sampling took place on day 7 at the following timepoints: pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, and 8 hours post-dose. Blood samples for determination of R- and S-methadone plasma concentrations were collected at pre-dose on study days -4, -3, -2, 2, 3, 4, 5, and 6. Intensive PK sampling took place on days -1 and 7 at the following timepoints: pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, and 24 hours post-dose.

Bioanalytical Results

Plasma samples were analyzed for TVR by HPLC with tandem mass spectrometric detection (LC-MS/MS) by (b) (4). Samples were received in frozen condition on September 23, 2009 and October 28, 2009. Samples were analyzed between November 11, 2009 and November 16, 2009. The samples were stored at -70° C. The maximum possible sample storage time until analysis was 54 days, which is within the validated long-term frozen stability duration of 638 days.

The calibration standard concentrations for TVR were 2.0, 4.0, 10.0, 50.0, 200.0, 500, 800, and 1000 ng/mL. The mean accuracy and precision estimates at each TVR standard concentration are presented in Table 1 below. All accuracy and precision (%CV) values were within the acceptable range (≤20% from nominal at the LLOQ concentration and ≤15% from nominal at all other concentrations). Quality control concentrations were 6.0, 250, and 800 ng/mL. The mean accuracy ranged from 96.1 to 99% and the mean precision ranged from 4.1 to 4.9%.

Plasma samples were analyzed for R-/S-methadone by HPLC with tandem mass spectrometric detection (LC-MS/MS) by (b) (4). Samples were received in frozen condition between September 23, 2009 and October 28, 2009. Samples were analyzed between October 13, 2009 and November 8, 2009. The samples were stored at -20° C. The maximum sample storage time until analysis was 76 days, which is within the validated long-term frozen stability duration of 219 days.

The calibration standard concentrations for both R- and S-methadone were 5.0, 8.0, 15.0, 40.0, 120.0, 350, 800, and 1000 ng/mL. The mean accuracy and precision estimates at each methadone standard concentration are presented in Tables 2 and 3 below. All accuracy and precision (%CV) values were within the acceptable range (≤20% from nominal at the LLOQ concentration and ≤15% from nominal at all other concentrations). Quality control concentrations for both R- and S-methadone were 10, 25, 70, 200, and 750 ng/mL. The mean

accuracy ranged from 98.9 to 103% for R-methadone and 99.7 to 103% for S-methadone. The mean precision ranged from 2.62 to 3.93% for R-methadone and 2.56 to 5.44% for S-methadone.

**Table 1 Mean Calibration Standard Concentrations and Statistics for TVR**

| | VX-950, ng/ml | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Analytical batch** | **2.00** | **4.00** | **10.0** | **50.0** | **200** | **500** | **800** | **1000** |
| n | 10 | 10 | 10 | 10 | 10 | 10 | 9 | 10 |
| mean | 1.99 | 4.12 | 9.40 | 48.7 | 207 | 519 | 808 | 979 |
| std. dev. | 0.0773 | 0.116 | 0.251 | 0.990 | 5.39 | 8.45 | 23.7 | 26.6 |
| %CV | 3.9 | 2.8 | 2.7 | 2.0 | 2.6 | 1.6 | 2.9 | 2.7 |
| % accuracy | 99.5 | 103.0 | 94.0 | 97.4 | 103.5 | 103.8 | 101.0 | 97.9 |

**Table 2 Mean Calibration Standard Concentrations and Statistics for R-Methadone**

| **Analytical** | **(R)-Methadone, ng/mL** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Batch** | **5.00** | **8.00** | **15.0** | **40.0** | **120** | **350** | **800** | **1000** |
| n | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 |
| Mean | 5.05 | 7.98 | 14.8 | 39.1 | 119 | 354 | 817 | 1000 |
| S.D. | 0.217 | 0.354 | 0.611 | 0.940 | 2.81 | 10.0 | 20.4 | 20.7 |
| %C.V. | 4.30 | 4.43 | 4.14 | 2.40 | 2.35 | 2.83 | 2.50 | 2.06 |
| % Accuracy | 101 | 99.8 | 98.3 | 97.7 | 99.6 | 101 | 102 | 100 |

**Table 3 Mean Calibration Standard Concentrations and Statistics for S-Methadone**

| **Analytical** | **(S)-Methadone, ng/mL** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Batch** | **5.00** | **8.00** | **15.0** | **40.0** | **120** | **350** | **800** | **1000** |
| n | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 |
| Mean | 4.94 | 8.12 | 15.2 | 39.5 | 118 | 352 | 808 | 997 |
| S.D. | 0.200 | 0.283 | 0.507 | 1.11 | 2.69 | 9.69 | 28.1 | 21.7 |
| %C.V. | 4.05 | 3.49 | 3.34 | 2.81 | 2.28 | 2.76 | 3.48 | 2.17 |
| % Accuracy | 98.9 | 102 | 101 | 98.8 | 98.4 | 100 | 101 | 99.7 |

*Reviewer's Comments:*
*-The bioanalytical results are acceptable.*

Results

A total of 18 subjects were enrolled in the trial. Out of those 18 subjects, 15 subjects completed the entire study.

*Demographics*

| Parameter | FA Set N = 16 |
|---|---|
| Sex, n (%) | |
| Female | 2 (12.5) |
| Male | 14 (87.5) |
| Race, n (%) | |
| Asian | 1 (6.3) |
| White | 15 (93.8) |
| Ethnicity, n (%) | |
| Hispanic or Latino | 1 (6.3) |
| Not Hispanic or Latino | 15 (93.8) |
| Age (years) | |
| Median (Range) | 33.0 (23; 45) |
| Weight (kg) | |
| Median (Range) | 78.5 (65; 96) |
| BMI (kg/m$^2$) | |
| Median (Range) | 25.25 (20.7; 30.0) |
| Type of smoker, n (%) | |
| Light smoker[a] | 4 (25.0) |
| Moderate smoker[b] | 12 (75.0) |

*Safety*

Overall, 15 (93.8%) subjects experienced at least 1 AE during this trial. Twelve (75.0%) subjects experienced at least 1 AE during the run-in phase and 13 (81.3%) subjects during the methadone+TVR phase. The most frequently reported AEs during the methadone+TVR phase were headache (in 6 [37.5%] subjects), nausea (in 6 [37.5%] subjects), euphoric mood (in 5 [31.3%] subjects), and pruritus (in 3 [18.8%] subjects). All AEs occurring in this trial were grade 1 or 2 in severity, except for AST increased reported as grade 3 AE during follow-up in 1 (6.3%) subject. This grade 3 AE was considered possibly related to TVR and not related to methadone. (Please refer to the medical officer's review for further details.)

*TVR Pharmacokinetics*

Steady-state TVR PK parameters were similar to those observed after administration of TVR alone (750 mg q8h) in healthy subjects in trials VX-950-C123 and VX-950-C133. In those trials, mean Cmin values were 1903 ng/mL and 2073 ng/mL, respectively. Mean Cmax values were 3338 ng/mL and 3236 ng/mL, respectively, and mean $AUC_{8h}$ values were 20,810 ng*h/mL and 21,190 ng*h/mL, respectively (Table 4). Inter-subject variability (%CV) of the calculated PK parameters on day 7 ranged between 32.2% and 47.8%.

**Table 4 PK Results of TVR Following Administration of TVR at 750 mg q8h for 7 Days Added to Stable Methadone Maintenance Therapy**

| Time Point<br>Pharmacokinetic Parameter:<br>mean ± SD, $t_{max}$: median (range) | Individualized Methadone Therapy + 750 mg Telaprevir q8h |
|---|---|
| **Day 7** | |
| N | 15 |
| $C_{0h}$, ng/mL | 2476 ± 1021 |
| $C_{min}$, ng/mL | 1894 ± 904.7 |
| $C_{max}$, ng/mL | 3376 ± 1260 |
| $t_{max}$, h | 4.0 (2.5 - 8.0) |
| $AUC_{8h}$, ng.h/mL | 20480 ± 7628 |
| $C_{ss,av}$, ng/mL | 2561 ± 953.4 |
| Fluctuation index, % | 61.10 ± 19.68 |

*R- and S-Methadone Pharmacokinetics*

The range of methadone doses used between day -1 and day 7 was between 40 and 120 mg. Mean plasma concentrations for both R- and S-methadone were lower in the presence of TVR across the dosing interval, compared to methadone maintenance therapy alone (Figures 2 and 3). R-methadone Cmin, Cmax, and $AUC_{24h}$ were lower by 33%, 26%, and 31%, respectively. Likewise, S-methadone Cmin, Cmax, and $AUC_{24h}$ were lower by 38%, 30%, and 36%, respectively (Tables 5 and 6).

On day -1 (methadone alone), inter-subject variability ranged between 27.6% and 58.3% and on day 7 (methadone+TVR), inter-subject variability ranged between 29.6% and 61.0%. For S-methadone inter-subject variability was also similar on day -1 and day 7; %CV ranged between 32.0% and 73.4% and between 38.2% and 71.5%, respectively.

*Reviewer's Comments:*
*-Since TVR is a known CYP3A4 inhibitor, an increase in R- and S-methadone exposure would be anticipated. However, the opposite effect was observed. This could indicate that TVR has mixed (inhibitory and inductive) effects on CYP3A4 and/or CYP2B6. CYP2B6 has recently been shown in vitro to play a more prominent role in methadone metabolism than CYP3A4. It metabolizes with greater selectivity for S-methadone over R-methadone; thus co-administration of methadone with CYP2B6 inducers usually results in increases in the R/S ratio. HIV protease inhibitors that are associated with either CYP3A4 inhibition or mixed effects also have also been shown to decrease exposure to R- and S-methadone (e.g., nelfinavir, lopinavir/ritonavir).*
*-During coadministration of TVR and methadone, fewer subjects experienced withdrawal symptoms than during treatment with methadone alone (as measured by means of the SOWS). The desire for heroin was comparable (as measured by means of the DDQ). As reported by the Applicant, the median resting pupil diameter was smaller during coadministration of TVR and methadone than when subjects only received methadone, indicating that there were no signs of opiate withdrawal. These results suggest that the decreased concentrations of methadone observed during co-administration with TVR did not result in clinically significant changes in withdrawal symptoms.*

**Figure 2 Mean Plasma Concentration-Time Curves of R-Methadone**

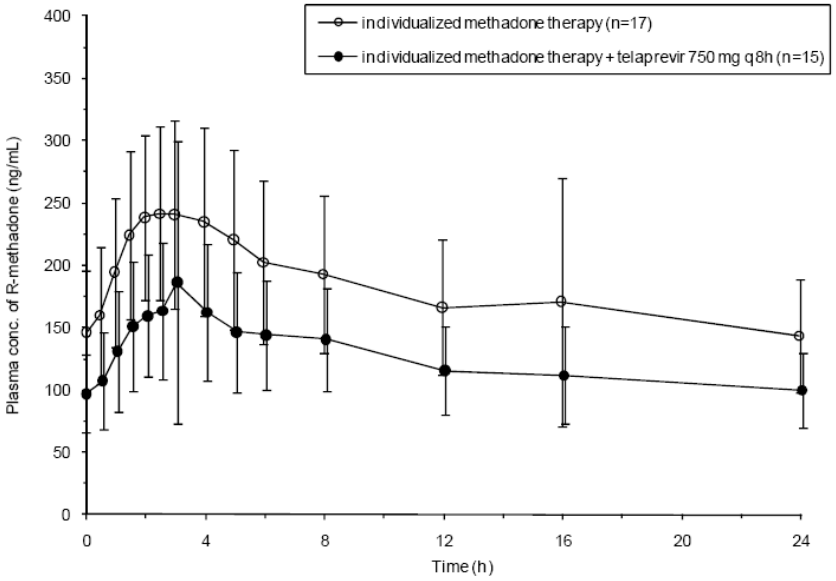


**Table 5 PK Results of R-Methadone Following Stable Methadone Therapy Alone and Following Administration of TVR at 750 mg q8h for 7 Days Added to Stable Methadone Maintenance Therapy**

| Time Point Reference/Test<br>Pharmacokinetic Parameter:<br>mean ± SD, $t_{max}$: median (range) | Individualized Methadone Therapy (Reference) | Individualized Methadone Therapy<br>+ 750 mg telaprevir q8h (Test) |
|---|---|---|
| **Day -4/Day 4** | | |
| N | 18 | 16 |
| $C_{0h}$, ng/mL | 143.0 ± 53.28 | 108.1 ± 34.76 |
| **Day -3/Day 5** | | |
| N | 18 | 15 |
| $C_{0h}$, ng/mL | 145.2 ± 58.11 | 108.8 ± 32.95 |
| **Day -2/Day 6** | | |
| N | 17 | 15 |
| $C_{0h}$, ng/mL | 142.7 ± 46.43 | 108.4 ± 35.46 |
| **Day -1/Day 7** | | |
| N | 17 | 15 |
| $C_{0h}$, ng/mL | 146.3 ± 49.78 | 96.98 ± 31.38 |
| $C_{min}$, ng/mL | 139.2 ± 45.31 | 93.47 ± 28.63 |
| $C_{max}$, ng/mL | 257.7 ± 92.69 | 189.8 ± 113.8 |
| $t_{max}$, h | 2.5 (1.5 - 16.0) | 3.0 (1.5 - 4.0) |
| $AUC_{24h}$, ng.h/mL | 4334 ± 1542 | 2991 ± 959.6 |
| $C_{ss,av}$, ng/mL | 180.6 ± 64.24 | 124.6 ± 39.98 |
| Fluctuation index, % | 65.55 ± 15.58 | 70.91 ± 38.90 |

**Figure 3 Mean Plasma Concentration-Time Curves of S-Methadone During Stable Methadone Maintenance Therapy alone and in the Presence of Steady-State TVR at 750 mg q8h**

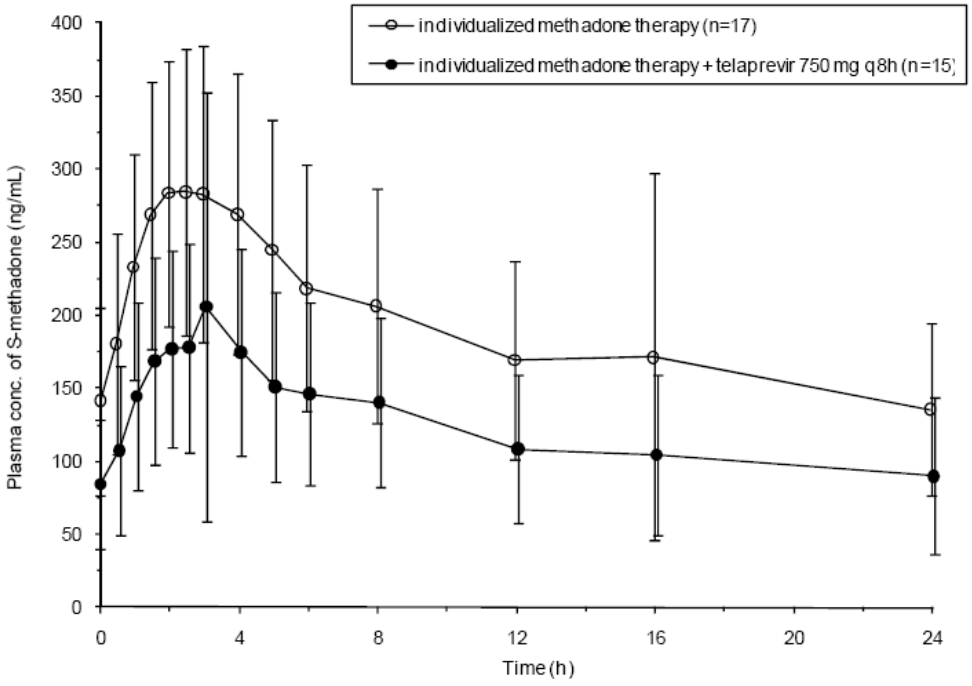


**Table 6 PK Results of R-Methadone Following Stable Methadone Therapy Alone and Following Administration of TVR at 750 mg q8h for 7 Days Added to Stable Methadone Maintenance Therapy**

| Time Point Reference/Test<br>Pharmacokinetic Parameter:<br>mean ± SD, $t_{max}$: median (range) | Individualized Methadone Therapy (Reference) | Individualized Methadone Therapy + 750 mg telaprevir q8h (Test) |
|---|---|---|
| **Day -4/Day 4** | | |
| N | 18 | 16 |
| $C_{0h}$, ng/mL | 137.6 ± 62.70 | 98.73 ± 42.40 |
| **Day -3/Day 5** | | |
| N | 18 | 15 |
| $C_{0h}$, ng/mL | 142.0 ± 69.74 | 100.7 ± 47.28 |
| **Day -2/Day 6** | | |
| N | 17 | 15 |
| $C_{0h}$, ng/mL | 139.2 ± 58.14 | 96.49 ± 45.37 |
| **Day -1/Day 7** | | |
| N | 17 | 15 |
| $C_{0h}$, ng/mL | 141.2 ± 64.10 | 84.55 ± 44.40 |
| $C_{min}$, ng/mL | 132.8 ± 57.12 | 81.97 ± 42.79 |
| $C_{max}$, ng/mL | 301.8 ± 114.4 | 211.9 ± 145.3 |
| $t_{max}$, h | 2.5 (1.5 - 16.0) | 2.5 (1.0 - 4.0) |
| $AUC_{24h}$, ng.h/mL | 4562 ± 1982 | 2941 ± 1378 |
| $C_{ss,av}$, ng/mL | 190.1 ± 82.59 | 122.5 ± 57.41 |
| Fluctuation index, % | 92.82 ± 27.95 | 103.1 ± 46.60 |

Conclusions

Based on a cross-study comparison of TVR PK parameters in healthy subjects (studies C123 and C133) and TVR PK in subjects maintained on methadone treatment (current study), methadone does not appear to affect the plasma concentrations of TVR at steady-state. On the contrary, TVR lowers plasma exposure to R- and S-methadone by approximately 30-40%. Since R-methadone is primarily responsible for the opioid effect, lower exposure to this component could have clinical consequences on patients maintained on methadone treatment. However, because methadone dosing is extremely individualized and co-administration of TVR with methadone in this study did not result in increased signs of withdrawal, the starting dose may not need adjustment. Dose adjustment based on clinical monitoring for signs of withdrawal would be warranted. The Applicant's proposed wording for the label (below) is acceptable.

**Section 7.3, Table 5**

| Concomitant Drug Class:<br>Drug Name | Effect on concentration of INCIVO or Concomitant Drug | Clinical Comment |
|---|---|---|
| methadone* | ↓ R-methadone | Concentrations of methadone were reduced when co-administered with telaprevir. No adjustment of methadone dose is required when initiating co-administration of telaprevir. However, clinical monitoring is recommended as the dose of methadone during maintenance therapy may need to be adjusted in some patients. (b) (4) |

*These interactions have been studied. See Clinical Pharmacology (12.3), Tables 6 and 7.

**Section 12.3, Table 7**

| Drug | Dose and Schedule | | N | Effect on Drug PK[a] | LS Mean Ratio (90% CI) of Drug PK With/Without Telaprevir | | |
|---|---|---|---|---|---|---|---|
| | Drug | Telaprevir | | | $C_{max}$ | AUC or $C_{avg,ss}$[b] | $C_{min}$ |
| *R*-Methadone | Methadone maintenance therapy (40 to 120 mg/daily) | 750 mg q8h for 7 days | 15 | ↓ | 0.71 (0.66; 0.76) | 0.71 (0.66; 0.76) | 0.69 (0.64; 0.75) |
| *S*-Methadone | Methadone maintenance therapy (40 to 120 mg/daily) | 750 mg q8h for 7 days | 15 | ↓ | 0.65 (0.60; 0.71) | 0.64 (0.58; 0.70) | 0.60 (0.54; 0.67) |

**Individual Study Review—VX09-950-021**

Title (Study VX09-950-021)

"An Open-Label Phase 1 Study in Healthy Adult Subjects to Examine the Effects of Telaprevir on the Pharmacokinetics of Cyclosporine and Tacrolimus"

Objectives

- To evaluate the effect of single and multiple doses of TVR (750 mg every 8 hours) on the PK of cyclosporine administered as a single dose in healthy subjects
- To determine the safety and tolerability of a single dose of cyclosporine with and without co-administration of TVR
- To evaluate the effect of multiple doses of TVR on the PK of tacrolimus administered as a single dose in healthy subjects
- To determine the safety and tolerability of a single dose of tacrolimus with and without co-administration of TVR

Study Dates and Location(s):
Study initiation: January 7, 2010
Study completion: April 6, 2010
Clinical Site: Covance Clinical Research Unit, Inc., Dallas, Texas

Study Design

This study was a 2-part, open-label, single-sequence, crossover drug interaction study. Part A included 2 periods and a total of 10 subjects. In period 1, 100 mg of cyclosporine (CsA) was administered alone. In period 2, CsA and TVR were administered together on days 1 and 8 only (see Figure 1 below), while TVR was administered every day from day 1 to day 11. Based on CsA's half-life of 8 hours, there was a washout period of 8 days between period 1 and 2.

In part B, a single dose of 2 mg tacrolimus was administered on day 1 of period 1. This period was followed by a 14-day washout due to tacrolimus' 35-hour half-life. In period 2, tacrolimus and TVR were administered together on day 8 only, while TVR was administered every day from day 1 to day 13. Both CsA and tacrolimus were administered 2 hours following TVR administration w/ food since food has been shown to decrease exposure to both CsA and tacrolimus.

**Figure 1 Study Design Schematic**

**Part A**[a]

| | Period 1 Cyclosporine | Period 2 Cyclosporine and Telaprevir | | | |
|---|---|---|---|---|---|
| | Day 1 | Day 1 | Days 2 to 7 | Day 8 | Days 9 to 11 |
| Cyclosporine without food | 100 mg | 10 mg | -- | 10 mg | -- |
| Telaprevir with food | -- | 750 mg q8h | 750 mg q8h | 750 mg q8h | 750 mg q8h |

**Part B**[b]

| | Period 1 Tacrolimus | Period 2 Tacrolimus and Telaprevir | | |
|---|---|---|---|---|
| | Day 1 | Days 1 to 7 | Day 8 | Days 9 to 13 |
| Tacrolimus without food | 2 mg | -- | 0.5 mg | -- |
| Telaprevir with food | -- | 750 mg q8h | 750 mg q8h | 750 mg q8h |

[a] In Part A, there was a minimum washout period of 8 days between Day 1 of Period 1 and Day 1 of Period 2.
[b] In Part B there was a minimum washout period of 14 days between Day 1 of Period 1 and Day 1 of Period 2.

*Reviewer's Comments:*
*-According to the Applicant, part A was repeated using a new set of enrolled subjects due to an inadvertent use of* (b) (4) *to stabilize plasma samples rather than* (b) (4).

Study Doses Used and Dose Rationale

TVR 750 mg q8h was used in this study. It was the dose regimen being used in the phase 3 studies as the intended commercial dose. The doses of both CsA and tacrolimus were reduced when co-administered with TVR in period 2 in anticipation of the significant increase in CsA and tacrolimus exposures caused by TVR.

*Reviewer's Comments:*
*-The 100-mg dose of CsA is equivalent to approximately 1.5 mg/kg for the average subject in part A of the study. The recommended initial starting dose for CsA in kidney transplant patients (from the Neoral® label) is 9 mg/kg/day.*
*-The 2-mg dose of tacrolimus is equivalent to approximately 0.025 mg/kg for the average subject in part B of the study. The recommended starting dose for tacrolimus in kidney transplant patients (from the Prograf® label) is 0.2 mg/kg/day when used in combination with azathioprine or 0.1 mg/kg/day when used in combination with MMF and IL-2 receptor antagonist.*

Formulation(s) Used

TVR was administered as the 375-mg tablet. However, it is unclear whether it is the same formulation as was used in the phase 3 studies. Commercially available Neoral® (100 mg/mL solution) was used for the CsA formulation and Prograf® (0.5 mg capsules) was used as the tacrolimus formulation.

*Key Inclusion Criteria:*
-Healthy female (non-childbearing potential) and male subjects between 18 and 60 years of age
-Female subjects of non-childbearing potential. Female subjects were considered of non-childbearing potential if they had a tubal ligation or were post-menopausal or both
-All female subjects with documented tubal ligation and male subjects met the contraception requirements outlined in the clinical study protocol
-The body mass index (BMI) ranged from 18 to 30 kg/$m^2$ (inclusive) at the Screening Visit and Day -1, and the subjects weighed more than 50 kg at the Screening Visit
-There were no clinically significant abnormal results for physical examination during the Screening Visit and Day -1 as judged by the investigator.
-There were no clinically significant out of range results in hematology tests, clinical chemistry, coagulation tests, and urinalysis at the Screening Visit and Day -1 as judged by the investigator
-There were no abnormal electrocardiogram (ECG) readings at the Screening Visit and Day -1 as judged by the investigator
-Systolic blood pressure was between 90 and 130 mmHg, diastolic blood pressure was between 55 and 90 mmHg and supine heart rate was between 45 and 100 beats per minute (all limits inclusive) at the Screening Visit and Day -1

*Key Exclusion Criteria:*
-Subjects with a history of any illness that, in the opinion of the investigator or the subject's general practitioner, confounded the results of the study or posed an additional risk in administering study drug(s) to the subject
-Regular treatment with prescription medications. Subjects were to have ended any short courses of prescription medications at least 14 days prior to the screening visit. Prescription medications were not to be administered during the study. (Potential subjects were not to stop any chronic, prescribed medication being taken at the direction of a physician, without obtaining agreement from that physician)
-Regular treatment with over-the-counter medications. Subjects were to end over-the-counter medication on the date of the screening visit but no less than 2 days prior to administration of study drug. Occasional use of acetaminophen or ibuprofen was allowed during the study for the treatment of pain (under supervision of the investigator)
-Subjects who consumed herbal medications or dietary medications, dietary supplements (e.g., St. John's Wort, ginkgo biloba, garlic supplements), vitamins, and grapefruit or grapefruit juice within 14 days before administration of study drug (Day 1).
-Subjects who consumed more than 2 units of alcoholic beverages per day or more than 14 units per week.
-Subjects who consumed an average of more than 5 cups of coffee or other caffeinated beverage
-Subjects who had a history of drug or alcohol abuse or addiction within 2 years prior to dosing, or who tested positive for alcohol or drugs of abuse such as cannabis, cocaine, amphetamines or opiates during the screening period
-Subjects who had participated in a clinical study involving administration of either an investigational or a marketed drug within 2 months or 5 half lives (whichever is longer) prior to the screening visit
-Subjects who tested positive for any of the following infectious disease tests: hepatitis B antigen (HBsAg), hepatitis C virus antibody (HCVAb), human immunodeficiency virus 1 antibody (HIV1Ab), or human immunodeficiency virus 2 antibody (HIV2Ab)
-Illness within 5 days before the start of study drug dosing ("illness" is defined as a recent non-serious, non-acute condition, e.g., the flu or the common cold). Such subjects could be enrolled at the discretion of the investigator
-Male subject with a female partner who was pregnant, nursing, or planning to become pregnant during the study or within 90 days after the last dose of study drug
-Female subjects with documented tubal ligation, who were not lactating and had a negative serum pregnancy test, but who were not willing to follow contraception requirements outlined in CSP Section 12.3.5.1
-Subjects who were vaccinated within 1 month before study enrollment or were planning to get vaccinated within 1month after study enrollment.

Blood Sampling for PK

Part A: Blood samples for determination of CsA plasma concentrations were collected on day 1 in period 1, day 1 in period 2, and day 8 in period 2 at pre-dose and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, and 48 hours post-dose.

Blood samples for determination of TVR plasma concentrations were collected on day 1 in period 2 and day 8 in period 2 at pre-dose and 0.5, 1, 2, 2.5, 3, 4, 6, and 8 hours post-dose.

Part B: Blood samples for determination of tacrolimus plasma concentrations were collected on day 1 in period 1 and day 8 in period 2 at pre-dose and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 48, 72, 120, and 144 hours post-dose.

Blood samples for determination of TVR plasma concentrations were collected day 7 in period 2 at pre-dose and 0.5, 1, 2, 2.5, 3, 4, 6, and 8 hours post-dose. Additionally, pre-dose samples were collected on days 3 and 5 in period 2.

Bioanalytical Results

Plasma samples were analyzed for CsA and tacrolimus by HPLC with tandem mass spectrometric detection (LC-MS/MS) by (b) (4). Samples were received between February 4, 2010 and April 1, 2010 and analyzed between February 22, 2010 and May 6, 2010. The samples were stored at -60°-80° C. The maximum sample storage time until analysis was 59 days for tacrolimus 119 days for CsA, which is the duration during which the long-term frozen stability was validated for each moiety.

The calibration standard concentrations for tacrolimus were 50.0, 100, 250, 500, 2000, 5000, 9000, and 10000 pg/mL. The calibration standard concentrations for CsA were 0.5, 1.0, 4.0, 10.0, 40, 100, 160, and 200 ng/mL. The mean accuracy and precision estimates at each tacrolimus and CsA standard concentration are presented in Tables 1 and 2 below. All accuracy and precision (%CV) values were within the acceptable range (≤20% from nominal at the LLOQ concentration and ≤15% from nominal at all other concentrations). Quality control concentrations for tacrolimus were 150, 1000, and 8000 pg/mL. The mean accuracy ranged from 101 to 103.9% and the mean precision ranged from 3.0 to 4.9%. Quality control concentrations for CsA were 1.5, 25, and 150 ng/mL. The mean accuracy ranged from 95.3 to 97.6% and the mean precision ranged from 7.6 to 10.3%.

Plasma samples were analyzed for TVR and VRT-127394 by HPLC with tandem mass spectrometric detection (LC-MS/MS) by by (b) (4). Samples were received between February 11, 2010 and March 25, 2010 and analyzed between February 22, 2010 and May 6, 2010. The samples were stored at -60°-80° C. The maximum sample storage time until analysis was 84 days, which is within the validated long-term frozen stability duration of 638 days.

Two analytical methods were used in the analysis of study samples: V9LHPP and V9HHPP. The nominal calibration and QC concentrations as well as accuracy and precision results will be presented separately for each method. The V9LHPP calibration standard concentrations for both TVR and VRT-127394 were 2.0, 4.0, 10.0, 50.0, 200.0, 500, 800, and 1000 ng/mL. The V9HHPP calibration standard concentrations for both TVR and VRT-127394 were 20, 40, 100, 250, 650, 1600, 4000, and 5000 ng/mL. The mean accuracy and precision estimates at each TVR and VRT-127394 standard concentration are presented in Tables 3 through 6, below. All mean accuracy and precision (%CV) values were within the acceptable range (≤20% from nominal at the LLOQ concentration and ≤15% from nominal at all other concentrations). Quality control concentrations using the V9LHPP method for both analytes were 6.0, 60, 250, and 750 ng/mL. Quality control concentrations using the V9HHPP method for both analytes were 60, 500, and 3750 ng/mL. For the V9LHPP method, the mean accuracy ranged from 105.1 to 108.8% for TVR and 95.1to 102% for VRT-127394. For the V9HHPP method, the mean accuracy ranged from 92.8 to 101.2% for TVR and 96.2 to 100% for VRT-127394. The mean precision ranged from 2.8 to 32.1% for TVR and 2.2 to 30.2% for VRT-127394 (there was a possible mis-injection in one run and the low QC resulted in a near-zero value).

**Table 1 Mean Calibration Standard Concentrations and Statistics for Tacrolimus**

| | 50.0 (pg/mL) | 100 (pg/mL) | 250 (pg/mL) | 500 (pg/mL) | 2000 (pg/mL) | 5000 (pg/mL) | 9000 (pg/mL) | 10000 (pg/mL) |
|---|---|---|---|---|---|---|---|---|
| Mean | 48.0 | 101 | 252 | 506 | 2010 | 5060 | 8950 | 9980 |
| S.D. | 4.60 | 6.73 | 9.00 | 14.6 | 44.2 | 92.3 | 166 | 186 |
| RSD (%) | 9.6 | 6.7 | 3.6 | 2.9 | 2.2 | 1.8 | 1.9 | 1.9 |
| %Bias | -4.0 | 1.0 | 0.8 | 1.2 | 0.5 | 1.2 | -0.6 | -0.2 |
| n | 16 | 16 | 16 | 16 | 16 | 16 | 16 | 16 |

**Table 2 Mean Calibration Standard Concentrations and Statistics for CsA**

| | 0.500 (ng/mL) | 1.00 (ng/mL) | 4.00 (ng/mL) | 10.0 (ng/mL) | 40.0 (ng/mL) | 100 (ng/mL) | 160 (ng/mL) | 200 (ng/mL) |
|---|---|---|---|---|---|---|---|---|
| Mean | 0.506 | 0.988 | 3.92 | 9.80 | 39.1 | 101 | 162 | 208 |
| S.D. | 0.0237 | 0.0812 | 0.245 | 0.660 | 2.16 | 6.81 | 7.45 | 12.0 |
| RSD (%) | 4.7 | 8.2 | 6.3 | 6.7 | 5.5 | 6.7 | 4.6 | 5.8 |
| %Bias | 1.2 | -1.2 | -2.0 | -2.0 | -2.3 | 1.0 | 1.3 | 4.0 |
| n | 17 | 21 | 22 | 23 | 24 | 24 | 22 | 23 |

**Table 3 Mean Calibration Standard Concentrations and Statistics for TVR (V9LHPP)**

| Assay Date | Analytical Run Number | 2.00 (ng/mL) | 4.00 (ng/mL) | 10.0 (ng/mL) | 50.0 (ng/mL) | 200 (ng/mL) | 500 (ng/mL) | 800 (ng/mL) | 1000 (ng/mL) |
|---|---|---|---|---|---|---|---|---|---|
| 13-Apr-2010 | 26 | 2.04 | 3.70 | 9.19 | 48.0 | 199 | 497 | 819 | 1030 |
| | | 2.12 | 3.84 | 9.72 | 49.8 | 197 | 518 | 852 | 1060 |
| Mean | | 2.08 | 3.77 | 9.46 | 48.9 | 198 | 508 | 836 | 1050 |
| %Bias | | 4.0 | -5.8 | -5.4 | -2.2 | -1.0 | 1.6 | 4.5 | 5.0 |
| n | | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |

**Table 4 Mean Calibration Standard Concentrations and Statistics for TVR (V9HHPP)**

| | 20.0 (ng/mL) | 40.0 (ng/mL) | 100 (ng/mL) | 250 (ng/mL) | 650 (ng/mL) | 1600 (ng/mL) | 4000 (ng/mL) | 5000 (ng/mL) |
|---|---|---|---|---|---|---|---|---|
| Mean | 19.8 | 40.7 | 100 | 256 | 643 | 1650 | 3890 | 4840 |
| S.D. | 0.558 | 1.29 | 3.99 | 10.4 | 14.7 | 41.8 | 136 | 185 |
| RSD (%) | 2.8 | 3.2 | 4.0 | 4.1 | 2.3 | 2.5 | 3.5 | 3.8 |
| %Bias | -1.0 | 1.8 | 0.0 | 2.4 | -1.1 | 3.1 | -2.8 | -3.2 |
| n | 12 | 12 | 11 | 12 | 12 | 11 | 11 | 11 |

**Table 5 Mean Calibration Standard Concentrations and Statistics for VRT-127394 (V9LHPP)**

| Assay Date | Analytical Run Number | 2.00 (ng/mL) | 4.00 (ng/mL) | 10.0 (ng/mL) | 50.0 (ng/mL) | 200 (ng/mL) | 500 (ng/mL) | 800 (ng/mL) | 1000 (ng/mL) |
|---|---|---|---|---|---|---|---|---|---|
| 13-Apr-2010 | 26 | *2.91 | 3.74 | 11.1 | 51.6 | 203 | 501 | 787 | 1010 |
| | | 2.14 | 3.62 | 9.48 | 51.9 | 198 | 510 | 778 | 983 |
| Mean | | 2.14 | 3.68 | 10.3 | 51.8 | 201 | 506 | 783 | 997 |
| %Bias | | 7.0 | -8.0 | 3.0 | 3.6 | 0.5 | 1.2 | -2.1 | -0.3 |
| n | | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |

**Table 6 Mean Calibration Standard Concentrations and Statistics for VRT-127394 (V9HHPP)**

| | 20.0 (ng/mL) | 40.0 (ng/mL) | 100 (ng/mL) | 250 (ng/mL) | 650 (ng/mL) | 1600 (ng/mL) | 4000 (ng/mL) | 5000 (ng/mL) |
|---|---|---|---|---|---|---|---|---|
| Mean | 20.2 | 39.5 | 98.0 | 254 | 639 | 1650 | 3950 | 5010 |
| S.D. | 0.820 | 1.94 | 5.79 | 8.06 | 22.0 | 42.0 | 169 | 167 |
| RSD (%) | 4.1 | 4.9 | 5.9 | 3.2 | 3.4 | 2.5 | 4.3 | 3.3 |
| %Bias | 1.0 | -1.3 | -2.0 | 1.6 | -1.7 | 3.1 | -1.3 | 0.2 |
| n | 12 | 12 | 11 | 12 | 12 | 11 | 11 | 11 |

*Reviewer's Comments:*
*-The bioanalytical results are acceptable.*

Results

A total of 30 subjects were enrolled in this study (10 in part A, 10 in part A-repeat, and 10 in part B). However, only 27 subjects completed both study periods of their respective part (either A or B).

*Demographics*

| Variable | Part A (N=10) | Part A-Repeat (N=10) | Part B (N=10) | Total (N=30) |
|---|---|---|---|---|
| **Age (years)** | | | | |
| Mean (SD) | 38.3 (10.20) | 45.8 (9.19) | 38.0 (10.97) | 40.7 (10.46) |
| Min, Max | 25, 59 | 30, 59 | 24, 60 | 24, 60 |
| **Weight (kg)** | | | | |
| Mean (SD) | 72.97 (7.008) | 68.49 (11.644) | 77.42 (11.655) | 72.96 (10.641) |
| Min, Max | 64.2, 86.7 | 55.8, 89.9 | 55.1, 97.4 | 55.1, 97.4 |
| **BMI ($kg/m^2$)** | | | | |
| Mean (SD) | 24.30 (1.581) | 24.41 (2.557) | 25.36 (3.528) | 24.69 (2.627) |
| Min, Max | 22.4, 27.5 | 20.2, 28.5 | 19.1, 30.1 | 19.1, 30.1 |
| **Sex (n[%])** | | | | |
| Male | 9 (90.0) | 3 (30.0) | 10 (100.0) | 22 (73.3) |
| Female | 1 (10.0) | 7 (70.0) | -- | 8 (26.7) |
| **Race (n[%])** | | | | |
| Black or African American | 2 (20.0) | 1 (10.0) | 3 (30.0) | 6 (20.0) |
| White | 8 (80.0) | 8 (80.0) | 7 (70.0) | 23 (76.7) |
| Other | -- | 1 (10.0) | -- | 1 (3.3) |

*Safety*

There were no SAEs in any of the treatment groups. The most common AE's were classified as "skin and subcutaneous tissue disorders" and "infections and infestations." Two subjects discontinued prematurely because of AEs: hypertriglyceridemia in subject 1005 in part A/period 2 and neutropenia in subject 1102 in part A-repeat/period 1. (Please refer to the medical officer's review for further details.)

*TVR and VRT-127394 Pharmacokinetics Part A-Repeat*

Plasma concentrations of both TVR and VRT-127394 were increased significantly between day 1 and day 8 with concomitant treatment with CsA (Figures 2 and 3). Since there was no control group in this study, a cross-study comparison of day 1 (single-dose TVR+CsA) results with historical single-dose TVR (alone) PK results show that mean $AUC_{0\text{-}8h}$ and Cmax values for both TVR and VRT-127394 are not significantly different (Table 7). Similarly, when comparing the day 8 PK results and historical multiple-dose data, $AUC_{0\text{-}8h}$ and Cmax values are not significantly different, indicating that CsA is not altering the TVR accumulation factor from single-dose to steady-state. Since cyclosporine inhibits P-gp, OATP1B1/3 and BCRP, lack of a significant effect on TVR exposure may rule-out the involvement of these transporters in its disposition.

**Figure 2 Mean TVR Plasma Concentration vs. Time When Co-administered with CsA (Day 1 vs. Day 8)**

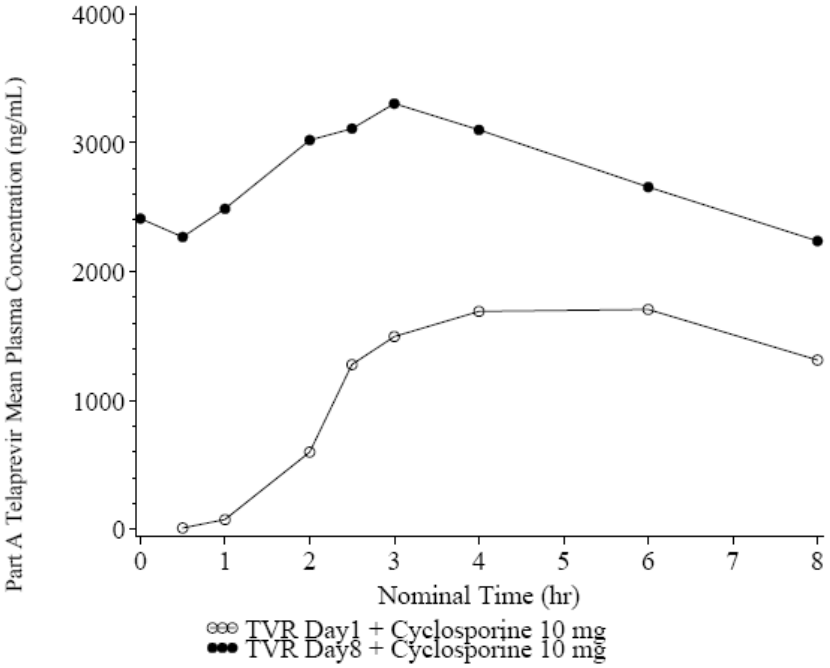


**Figure 3 Mean VRT-127394 Plasma Concentration vs. Time Profiles Following TVR Administration Alone and Co-administation with CsA**

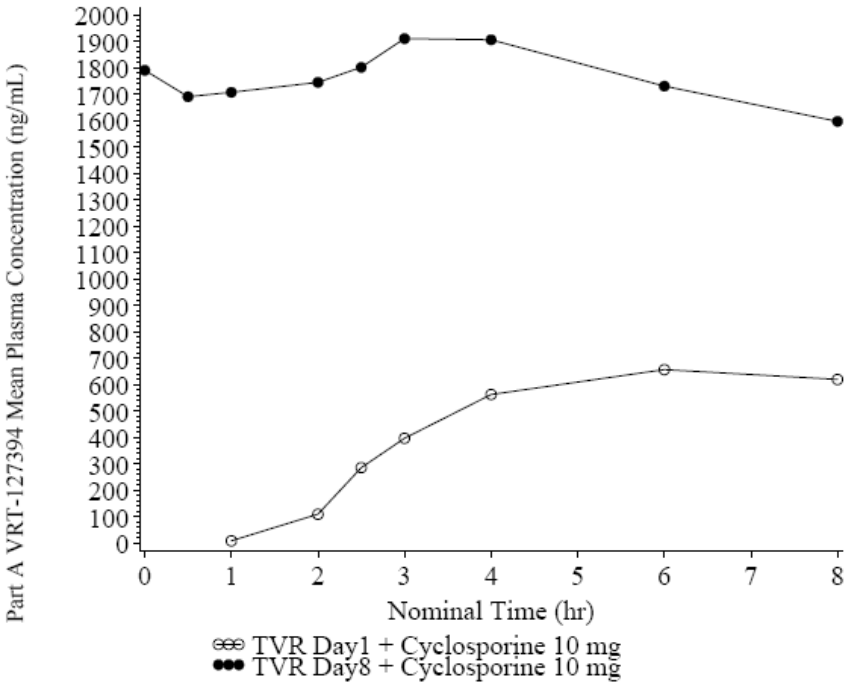



**Table 7 Mean (SD) TVR and VRT-127394 PK Parameters Following Co-Administration of TVR and CsA**

| PK Parameter | Telaprevir Day 1+ Cyclosporine (N = 10) | Telaprevir Day 8 + Cyclosporine (N = 9) |
|---|---|---|
| **Telaprevir** | | |
| $AUC_{0-8}$ (ng·hr/mL) | 9359.86 (3559.19) | 21930.11 (2810.76) |
| $C_{max}$ (ng/mL) | 2174.56 (830.07) | 3432.22 (543.39) |
| $C_{min}$ (ng/mL) | NA | 2174.44 (282.58) |
| $t_{max}$[a] (hr) | 4.00 ( 2.50, 7.92) | 3.00 ( 1.92, 6.00) |
| **VRT-127394** | | |
| $AUC_{0-8}$ (ng·hr/mL) | 3249.74 (1313.05) | 14028.89 (1582.50) |
| $C_{max}$ (ng/mL) | 737.67 (242.14) | 1983.33 (244.80) |
| $C_{min}$ (ng/mL) | NA | 1584.44 (166.37) |
| $t_{max}$[a] (hr) | 6.00 ( 4.00, 7.92) | 3.03 ( 0.00, 4.00) |

[a] Median (min, max).

*CsA Pharmacokinetics Part A-Repeat*

When the dose of CsA is normalized (to account for the 10-fold lower dose when co-administered with TVR), co-administration with TVR resulted in a significant increase in mean CsA plasma concentrations (Figure 4). A comparison of the dose-normalized PK parameters following administration of CsA alone versus co-administration of CsA with TVR shows that mean Cmax increased from 4.89 ng/mL/mg to 6.57 ng/mL/mg on day 1 and 6.22 ng/mL/mg on

day 8 (Table 8). Mean $AUC_{inf}$ increased from 18.83 ng*hr/mL/mg to 80.47 ng*hr/mL/mg on day 1 and 85.25 ng*hr/mL/mg on day 8 (~4-5-fold difference), and mean $AUC_{0\text{-last}}$ increased from 18.37 ng*hr/mL/mg to 67.41 ng*hr/mL/mg on day 1 and 79.27 ng*hr/mL/mg on day 8 (~3-4 fold difference). A significant decrease in CsA clearance coupled with an increase in half-life was observed when TVR was co-administered, indicating that TVR is inhibiting CsA metabolism. Without dose normalization, the 10-fold lower dose of CsA resulted in ~87% lower Cmax and a 53% lower $AUC_{inf}$ during co-administration with TVR.

**Figure 4 Mean Dose-Normalized CsA Plasma Concentration vs. Time Profiles Following CsA Administration Alone and Co-administration with TVR**

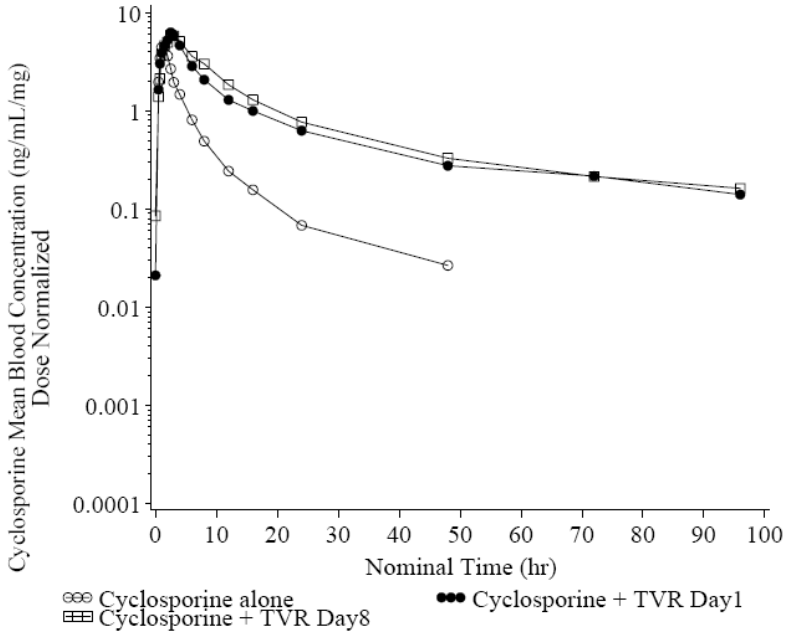



**Table 8 Mean (SD) CsA PK Parameters Following CsA Administration Alone and Co-Administration with TVR**

| PK Parameter | Cyclosporine 100 mg (N = 10) | Cyclosporine 10 mg + telaprevir Day 1 (N = 9) | Cyclosporine 10 mg + telaprevir Day 8 (N = 9) |
|---|---|---|---|
| $AUC_{0\text{-}\infty}$ (ng·hr/mL)[a] | 1882.60 (488.66) | 804.72 (306.47) | 852.53 (217.65) |
| DN_$AUC_{0\text{-}\infty}$ (ng·hr/mL/mg)[a] | 18.83 (4.89) | 80.47 (30.65) | 85.25 (21.77) |
| $AUC_{0\text{-last}}$ (ng·hr/mL) | 1837.39 (445.81) | 674.06 (246.38) | 792.66 (198.58) |
| DN_$AUC_{0\text{-last}}$ (ng·hr/mL/mg) | 18.37 (4.46) | 67.41 (24.64) | 79.27 (19.86) |
| $C_{max}$ (ng/mL) | 488.60 (141.79) | 65.73 (24.90) | 62.20 (18.90) |
| DN_$C_{max}$ (ng/mL/mg) | 4.89 (1.42) | 6.57 (2.49) | 6.22 (1.89) |
| $t_{½}$ (hr)[a] | 11.95 (1.67) | 52.50 (20.51) | 42.12 (11.26) |
| $t_{max}$ (hr)[b] | 1.50 ( 0.75, 2.00) | 2.50 ( 2.50, 4.28) | 2.50 ( 1.50, 3.05) |
| $V_z/F$ (L)[a] | 954.80 (195.26) | 1006.30 (444.41) | 735.32 (197.71) |
| CL/F (L/hr)[a] | 56.29 (14.03) | 14.29 (5.86) | 12.46 (3.33) |

DN: dose normalized; N: Number of subjects;

[a] N=9 for cyclosporine (100-mg dose) arm and cyclosporine (10-mg dose) and telaprevir coadministration on Day 1 arm; N=8 for cyclosporine (10-mg dose) and telaprevir coadministration on Day 8 arm, as values were excluded due to Rsq <0.9 for estimation of $\lambda_z$. See Section 9.8.2.1.

[b] Median (min, max)

*TVR and VRT-127394 Pharmacokinetics Part B*

Since there was no control group that included TVR administration alone in this study, a cross-study comparison of day 8 (TVR+tacrolimus) PK results with day 8 (TVR+CsA) PK results (from Part A-Repeat) show that mean $AUC_{0\text{-}8h}$ and Cmax values for both TVR and VRT-127394 are slightly lower when TVR is co-administered with tacrolimus than when TVR is co-administered with CsA (Table 9). However, TVR exposures following TVR+CsA treatment were comparable to historical steady-state values from previous studies.

**Table 9 Mean (SD) TVR and VRT-127394 PK Parameters Following Co-Administration of TVR and Tacrolimus**

| PK Parameter | Telaprevir Day 8 + Tacrolimus (N = 9) |
|---|---|
| **Telaprevir** | |
| $AUC_{0\text{-}\tau}$ (ng·hr/mL) | 16577.38 (3340.31) |
| $C_{max}$ (ng/mL) | 2496.67 (625.52) |
| $C_{min}$ (ng/mL) | 1720.00 (439.06) |
| $t_{max}$[a] (hr) | 4.00 (0.00, 4.10) |
| **VRT-127394** | |
| $AUC_{0\text{-}\tau}$ (ng·hr/mL) | 10426.33 (2277.34) |
| $C_{max}$ (ng/mL) | 1452.22 (257.48) |
| $C_{min}$ (ng/mL) | 1176.78 (288.19) |
| $t_{max}$[a] (hr) | 0.00 (0.00, 6.00) |

[a] Median (min, max).

*Tacrolimus Pharmacokinetics Part B*

Co-administration with TVR resulted in higher plasma concentrations of tacrolimus throughout the plasma concentration vs. time profile (Figure 5). A comparison of dose-normalized PK parameters following administration of tacrolimus alone versus co-administration with telaprevir shows that mean Cmax increased from 1,986.55 pg/mL/mg to 17,408.89 pg/mL/mg (Table 10). Mean $AUC_{inf}$ increased from 33,649.51 pg*hr/mL/mg to 2,616,368.64 pg*hr/mL/mg (~77-fold increase), and mean $AUC_{0\text{-}last}$ increased from 30,215.46 pg*hr/mL/mg to 1,025,779.27 pg*hr/mL/mg (~34-fold increase). When comparing non-dose normalized PK data, concomitant administration with TVR resulted in a ~2-fold increase in tacrolimus $AUC_{inf}$ and Cmax.

**Figure 5 Mean Dose-Normalized TVR Plasma Concentration vs. Time Profiles Following TVR Administration Alone and Co-administration with Tacrolimus**

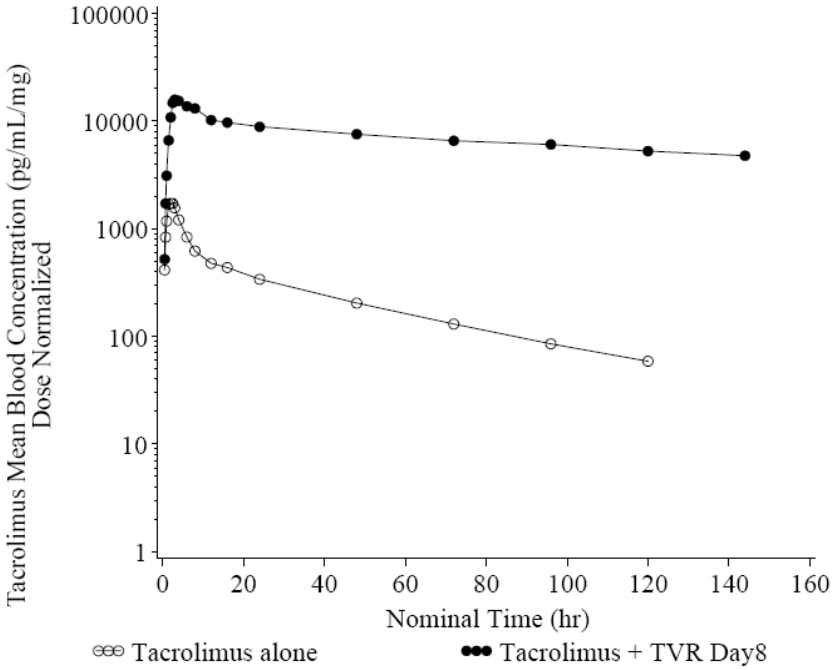



**Table 10 Mean (SD) Tacrolimus PK Parameters Following Tacrolimus Administration Alone and Co-Administration with TVR**

| PK Parameter | Tacrolimus 2 mg (N = 10) | Tacrolimus 0.5 mg + telaprevir Day 8 (N = 9) |
|---|---|---|
| $AUC_{0-\infty}$ (pg·hr/mL)[a] | 67299.02 (17282.18) | 1308184.32 (865605.74) |
| $DN\_AUC_{0-\infty}$ (pg·hr/mL/mg)[a] | 33649.51 (8641.09) | 2616368.64 (1731211.47) |
| $AUC_{0-last}$ (pg·hr/mL) | 60430.92 (16100.71) | 512889.64 (130478.45) |
| $DN\_AUC_{0-last}$ (pg·hr/mL/mg) | 30215.46 (8050.35) | 1025779.27 (260956.90) |
| $C_{max}$ (pg/mL) | 3973.10 (1820.58) | 8704.44 (3233.17) |
| $DN\_C_{max}$ (pg/mL/mg) | 1986.55 (910.29) | 17408.89 (6466.34) |
| $t_{½}$ (hr)[a] | 40.74 (5.85) | 196.04 (158.66) |
| $t_{max}$ (hr)[b] | 2.25 (1.50, 12.00) | 3.03 (2.50, 24.00) |
| $V_z/F$ (L)[a] | 1913.75 (859.05) | 106.13 (34.22) |
| CL/F (L/hr)[a] | 31.98 (10.17) | 0.48 (0.19) |

[a] λz related parameters should be interpreted with caution, since the extrapolated AUC was greater than 25%. N=8 for tacrolimus (0.5-mg dose) and telaprevir arm, as 1 value was excluded due to Rsq <0.9 for estimation of λz.
[b] Median (min, max).

*Reviewer's Comments:*
*-CsA and tacrolimus are both dose proportional in the dose ranges studied; thus, performing dose normalization for PK comparison is valid for this study.*
*-CsA is a known OATP1B1 inhibitor, thus a comparison of TVR concentrations in this study with historical values may provide insight into whether TVR is an OATP1B1 substrate. Although TVR*

*exposures in this study were not significantly different from historical studies, it does not preclude the possibility of TVR being an OATP1B1 substrate since the CsA Cmax achieved in this study is approximately 8-9 fold below the Ki concentration of CsA known to cause inhibition of OATP1B1 function in vitro. In addition, any potential effect on TVR exposure would have been confounded by the inhibitory effects of CsA on CYP3A4 and P-gp.*

Conclusions

CsA and tacrolimus are both substrates for CYP3A and P-gp and TVR is an inhibitor of both CYP3A and P-gp; thus, the increase in CsA and tacrolimus exposures was anticipated. Based on the PK results of this study and dose proportionality for tacrolimus, an 88% lower dose of tacrolimus would likely be needed when given in combination with TVR (an extrapolated 0.25 mg dose of tacrolimus when given with TVR would provide approximately equivalent exposures to 2-mg tacrolimus alone dose). Likewise, a 20-mg dose of CsA in combination with TVR would likely result in exposures approximating a 100-mg dose of CsA alone. However, CsA Cmin concentrations (commonly accepted measure for CsA therapeutic drug monitoring) were not assessed in this study. Therefore, it is unclear how the addition of TVR would affect CsA Cmin values. Because the therapeutic indices for both CsA and tacrolimus are relatively narrow, and TVR has not been studied in organ transplant patients, the use of TVR in organ transplant patients should not be recommended. In addition, because the magnitude of increase in tacrolimus exposure was dramatic (~70-fold) and tacrolimus has been shown to prolong the QT interval, the use of tacrolimus should be contraindicated. The Applicant's proposed wording for the label is presented below (reviewer-proposed changes in red).

(b) (4)

(b) (4)

**Section 12.3, Table 7 Summary of PK Parameters for Co-administered Drug in the Presence of Telaprevir**

| | Dose and Schedule | | | | LS Mean Ratio (90% CI) of Drug PK With/Without Telaprevir | | |
|---|---|---|---|---|---|---|---|
| Drug | Drug | Telaprevir | N | Effect on Drug PK[a] | $C_{max}$ | AUC or $C_{avg,ss}$[b] | $C_{min}$ |
| Cyclosporine A (CsA) | 100 mg single dose when administered alone; 10 mg single dose when coadministered with telaprevir (D8) | 750 mg q8h for 11 days | 9 | ↑ | 0.13 (0.11;0.16) **Dose norm.:** 1.32 (1.08;1.60) | 0.46 (0.39; 0.55) **Dose norm.:** (b) (4) (3.90;5.51) | NA |

**Section 12.3, Table 7**

| | Dose and Schedule | | | | LS Mean Ratio (90% CI) of Drug PK With/Without Telaprevir | | |
|---|---|---|---|---|---|---|---|
| Drug | Drug | Telaprevir | N | Effect on Drug PK[a] | $C_{max}$ | AUC or $C_{avg,ss}$[b] | $C_{min}$ |
| Tacrolimus | 2 mg single dose when administered alone; 0.5 mg single dose when coadministered with telaprevir (D8) | 750 mg q8h for 13 days | 9 | ↑ | 2.34 (1.68;3.25) **Dose norm.:** 9.35 (6.73;13.0) | 17.6 (13.2; 23.3) **Dose norm.:** 70.3 (52.9;93.4) | NA |

**An Open-label, Multiple-Dose Phase 1 Study of Telaprevir (VX-950) in Combination with Low Dose Ritonavir in Healthy Male Subjects**

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**Individual Study Review—VX06-950-009 and VX06-950-009a**

**Objectives:**

Primary

To evaluate the single-dose and steady-state pharmacokinetics (PK) of telaprevir 250 mg every 12 hours (q12h) or 750 mg q12h in combination with ritonavir 100 mg q12h

Secondary

- To assess the safety and tolerability of multiple doses of telaprevir in combination with ritonavir
- To assess the effect of food on the single-dose and steady-state PK of telaprevir 750 mg q12h in combination with ritonavir 100 mg q12h
- To evaluate the single-dose and steady-state PK of ritonavir 100 mg q12h dosed in combination with telaprevir 250 mg q12h or 750 mg q12h

**Study Rationale:** In vitro studies with human liver microsomes showed that cytochrome P450 (CYP) 3A4 is the primary CYP isozyme responsible for telaprevir metabolism. A previous clinical study indicated that a single 100-mg dose of ritonavir, an inhibitor of CYP3A4, increased telaprevir exposures and increased the median half-life of telaprevir. These results suggest that dosing twice daily with telaprevir in conjunction with low-dose ritonavir (100 mg) may produce trough levels of telaprevir that are similar to or greater than those produced by dosing every 8 hours (q8h) with telaprevir alone. A dosing regimen that is twice daily rather than three times daily may be easier for patients, resulting in better compliance.

Food increases exposure to telaprevir. A treatment regimen that does not require dosing with food may improve compliance. Therefore, this Phase 1 clinical study was designed to assess telaprevir in combination with ritonavir by evaluating the pharmacokinetics (PK) and safety of the coadministration of multiple doses of telaprevir and low-dose ritonavir in the fasted and fed states.

**Study Population:** Twenty-four of the 48 healthy male subjects (age 18-55) were enrolled in The Netherlands under protocol VX06-950-009. Due to recruitment difficulties, a second clinical site was opened, and the remaining 24 subjects were enrolled in the United States under protocol VX06-950-009a, which was the same protocol as protocol VX06-950-009. PK results only include 24 subjects in the Netherland site.

**Study Design:** This was an open-label, multiple-dose, randomized, parallel-group study. Subjects were randomly assigned to receive 1 of the following 4 doses:

| Group | telaprevir | ritonavir | Food |
|---|---|---|---|
| A | 250 mg / q12h | 100 mg | Yes |
| B | 750 mg / q12h | 100 mg | Yes |
| C | 750 mg / q12h | 100 mg | No - Fast |
| D | 750 mg / q8h | -- | Yes |

Dosing for all groups begins with a morning dose followed by dosing 8 or 12 hours later.

**Formulation:**
Telaprevir: Tablet (250 mg); 1 or 3 tablets per dose, given orally. Batch number: C0849004
Ritonavir: Soft gelatin capsule (100 mg) given orally per package insert. Batch numbers: 41392VA for VX06-950-009; 438372E21 for VX06-950-009a

**Pharmacokinetic Sampling:** Intensive blood sampling for telaprevir and ritonavir PK analysis was collected in the morning of Days 1 and 14 at predose, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, and 12 hours postdose. A single blood sample was taken before the morning dose on Days 2, 4, 6, 8, 10, and 12.

**Analytical Method:** Plasma concentrations of telaprevir, VRT-127394, and ritonavir were analyzed by validated LC/MS/MS methods. The maximum sample storage until analysis was 88 days, which is well within the validated long-term frozen stability of 6 months for VX-950 and VRT-127394 and 182 days for ritonavir.

The calibration curve and quality control data met the pre-specified acceptance criteria for all batches of samples analyzed. The calibration standards ranged from 2.00 to 1000 ng/mL for telaprevir and VRT-127394 and from 10.0 to10000 ng/mL for ritonavir. Interassay precision (%CV) ranged from 3.7 to 18.6 for quality control standards of telaprevir, 4.8 to 5.4 for VRT-127394, and 5.4 to 6.8 for ritonavir. The analytical methods for telaprevir, VRT-127394, and ritonavir are acceptable.

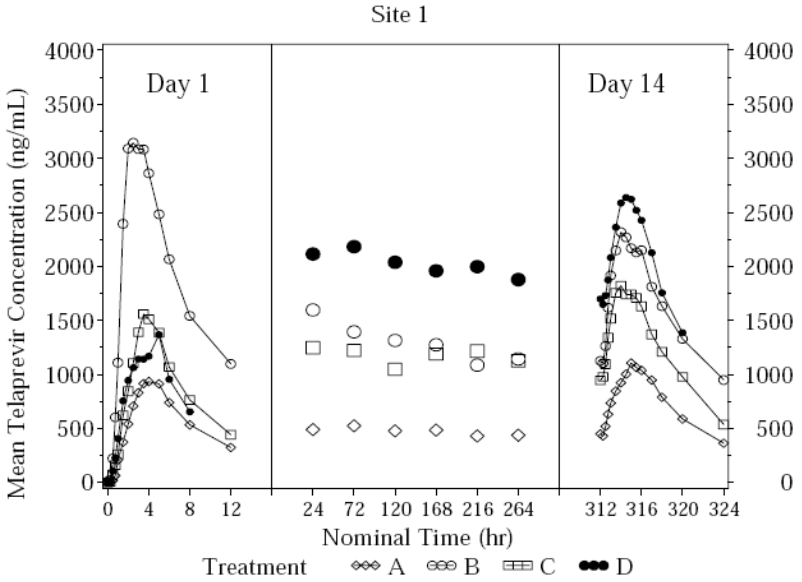
**Results**

Pharmacokinetics: The noncompartmental PK and statistical analysis set included only the 24 subjects enrolled in The Netherlands, due to a protocol deviation that occurred at the US site (subjects in 3 groups were erroneously dosed under fasting instead of fed conditions on the morning of the 2 intensive PK days). All 24 subjects in The Netherlands were included in the Day 1 PK analysis. One subject in The Netherlands withdrew from the study, for personal reasons, on Day 11, and therefore was not included in the Day 14 PK analysis.

*Telaprevir PK:*

Mean telaprevir plasma concentrations over time following a single dose (Day 1) and multiple doses (Day 14) of telaprevir with and without ritonavir in the fed and fasted states are presented in Figure 1.

**Figure 1** **Mean Telaprevir Plasma Concentration-Time Profiles During Administration of Telaprevir With and Without Ritonavir in the Fed and Fasted States From Day 1 to Day 14**




Source: Table 14.2.2.1
A: 250 mg telaprevir q12h + ritonavir in the fed state
B: 750 mg telaprevir q12h + ritonavir in the fed state
C: 750 mg telaprevir q12h + ritonavir in the fasted state
D: 750 mg telaprevir q8h in the fed state

Table 1 summarizes the single dose PK parameters of telaprevir by group and Table 2 shows the statistic results of these parameters by group.

**Table 1** **Mean (SD) Telaprevir PK Parameters after a Single Dose (Day 1) of Telaprevir With and Without Ritonavir in the Fed and Fasted States**

| Treatment | $AUC_{0\text{-last}}$ (hr*ng/mL) | $C_{avg}$ (ng/mL) | $C_{trough}$ (ng/mL) | * $C_{max}$ (ng/mL) | $t_{1/2}$[a] (hr) | $t_{max}$[b] (hr) |
|---|---|---|---|---|---|---|
| 250 mg telaprevir q12h + ritonavir, fed (Group A, N=6) | 6657.84 (1891.89) | 554.82 (157.66) | 324 (79.78) | 990.5 (299.9) | 4.31 (0.02)[c] | 4.5 (2.0, 5.0) |
| 750 mg telaprevir q12h + ritonavir, fed (Group B, N=6) | 22366.57 (5898.84) | 1863.88 (491.57) | 1097.17 (362.55) | 3608.33 (1171.83) | 4.7 (0.36)[c] | 2.75 (1.5, 3.5) |
| 750 mg telaprevir q12h + ritonavir, fasted (Group C, N=6) | 10086.35 (2145.75) | 840.53 (178.81) | 442 (117.77) | 1640.5 (414.95) | 4.06 (0.46)[d] | 3.5 (3.0, 4.0) |
| 750 mg telaprevir q8h, fed (Group D, N=6) | 6994.68 (2292.23) | 874.34 (286.53) | 654 (296.82) | 1612.5 (532.19) | 2.13 (0.32)[c] | 4.0 (1.5, 5.0) |

Source: Table 14.2.2.2
[a] Caution should be applied in interpreting the results due to insufficient sampling period, especially for Group D.
[b] $t_{max}$ is presented as median (min, max)
[c] N=2
[d] N=4

* Ctrough was the concentration at 12 hours postdose for Groups A to C and concentration at 8 hours postdose for Group D at Day 1 and Day 14

**Table 2 Comparison of Telaprevir PK Parameters Following a Single Dose of Telaprevir With and Without Ritonavir in the Fed and Fasted States**

| Parameter | Group (N=6 per group) | GLS Mean | Ratio [a] (%) | 90% CI |
|---|---|---|---|---|
| $C_{max}$ (ng/mL) | A | 951.1 | 61.8 | 45.2, 84.5 |
| | B | 3446 | 224 | 164, 306 |
| | C | 1596 | 104 | 75.8, 142 |
| | D | 1539 | NA | NA |
| $C_{trough}$(ng/mL) | A | 316.2 | 52.6 | 37.5, 73.8 |
| | B | 1044 | 174 | 124, 244 |
| | C | 428.8 | 71.3 | 50.8, 100 |
| | D | 601.3 | NA | NA |
| $C_{avg}$ (ng/mL) | A | 536.6 | 64 | 48.5, 84.4 |
| | B | 1804 | 215 | 163, 284 |
| | C | 824.7 | 98.4 | 74.6, 130 |
| | D | 838.1 | NA | NA |

Source: Table 14.2.2.5 and Appendix 16.2.5.1.1
N=6 per group
NA: not applicable
A: 250 mg telaprevir q12h + ritonavir in the fed state
B: 750 mg telaprevir q12h + ritonavir in the fed state
C: 750 mg telaprevir q12h + ritonavir in the fasted state
D: 750 mg telaprevir q8h in the fed state
[a] Group D is the reference in the denominator.
* Ctrough is the concentration at 12 hours postdose for Groups A to C and concentration at 8 hours postdose for Group D at Day 1 and Day 14

The data show that after single dose administration:

- Telaprevir tmax was similar among the 4 groups. However, the tmax tended to be shorter after coadministration of 750 mg telaprevir q12hr and ritonavir in the fed state
- The exposure to telaprevir was about 2 times higher following a single 750-mg dose of telaprevir given with ritonavir in the fed versus fasted state.
- Exposure to telaprevir (mean Cmax, Ctrough, and Cavg) was approximately 2 times higher following a single 750-mg dose of telaprevir given in the fed state with ritonavir (Group B) versus without ritonavir (Group D).
- The exposure to telaprevir was lower following a single 250-mg dose of telaprevir coadministered with ritonavir (Group A) as compared with 750 mg telaprevir administered alone (Group D).
- Exposure to telaprevir was about the same following a single 750 mg dose of telaprevir coadministered with ritonavir in fasted state (Group C) as compared with that following a single dose of 750 mg telaprevir alone in fed state (Group D).

Table 3 summarizes telaprevir PK parameters by group and Table 4 shows the comparison of these parameters by group on Day 14.

**Table 3** **Mean (SD) Telaprevir PK Parameters after Multiple Doses (Day 14) of Telaprevir With and Without Ritonavir in the Fed and Fasted States**

| Treatment | Stat | $AUC_{0\text{-last}}$ (hr*ng/mL) | $C_{avg}$ (ng/mL) | $C_{trough}$ (ng/mL) | $C_{max}$ (ng/mL) | $t_{1/2}$ (hr) | $t_{max}$[a] (hr) | $t_{1/2,eff}$ (hr) | CLss/F (L/hr) |
|---|---|---|---|---|---|---|---|---|---|
| 250 mg telaprevir q12h + ritonavir, fed (Group A) | N | 6 | 6 | 6 | 6 | 5 | 6 | ND[b] | 6 |
| | Mean (SD) | 8535.01 (2728.04) | 711.25 (227.34) | 362.83 (70.99) | 1202.83 (479.98) | 5.00 (0.65) | 3.26 (1.5,5) | | 31.60 (8.87) |
| 750 mg telaprevir q12h + ritonavir, fed (Group B) | N | 5 | 5 | 5 | 5 | ND | 5 | ND | 5 |
| | Mean (SD) | 19059.13 (2878.05) | 1588.26 (239.84) | 948.6 (156.15) | 2368.4 (340.29) | | 2.02 (2,4) | | 40.0 (26.6) |
| 750 mg telaprevir q12h + ritonavir, fasted (Group C) | N | 6 | 6 | 6 | 6 | 3 | 6 | ND | 6 |
| | Mean (SD) | 14218.31 (3768.22) | 1184.86 (314.02) | 536.83 (117.85) | 1925 (600.27) | 4.60 (1.09) | 2.25 (1.5,4) | | 56.1 (6.29) |
| 750 mg telaprevir q8h, fed (Group D) | N | 6 | 6 | 6 | 6 | ND | 6 | 6 | 6 |
| | Mean (SD) | 16602.38 (2069.76) | 2075.3 (258.72) | 1386.17 (202.27) | 2808.17 (436.08) | | 2.5 (1.5,4) | 10.97 (3.45) | 45.82 (15.62) |

Source: Table 14.2.2.2
[a] $t_{max}$ is presented as median (min, max)
[b] ND: not done

**Table 4** **Comparison of Telaprevir PK Parameters Following Multiple Doses of Telaprevir With and Without Ritonavir in the Fed and Fasted States**

| Parameter | Group | GLS Mean | Ratio[a] (%) | 90% CI |
|---|---|---|---|---|
| $C_{max}$ (ng/mL) | A | 1131 | 40.7 | 30.9, 53.6 |
| | B | 2349 | 84.6 | 63.3, 113 |
| | C | 1846 | 66.4 | 50.4, 87.5 |
| | D | 2778 | | |
| $C_{trough}$ (ng/mL) | A | 357.1 | 26.0 | 21.7, 31.0 |
| | B | 938.1 | 68.2 | 56.6, 82.2 |
| | C | 527.3 | 38.4 | 32.1, 45.8 |
| | D | 1375 | NA | NA |
| $C_{avg}$ (ng/mL) | A | 683.7 | 33.2 | 26.4, 41.7 |
| | B | 1575 | 76.4 | 60.1, 97.1 |
| | C | 1149 | 55.8 | 44.4, 70.1 |
| | D | 2061 | NA | NA |

Source: Table 14.2.2.6 and Appendix 16.2.5.1.1
NA: not applicable
A: 250 mg telaprevir q12h + ritonavir in the fed state (N=6)
B: 750 mg telaprevir q12h + ritonavir in the fed state (N=5)
C: 750 mg telaprevir q12h + ritonavir in the fasted state (N=5)
D: 750 mg telaprevir q8h in the fed state (N=6)
[a] Treatment D is the reference in the denominator.

The data show that after 14-day multiple dose administration:

- Exposure to telaprevir (mean Cmax, Ctrough, and Cavg) was lower after multiple-dose (Day 14) administration of 250 mg telaprevir q12h with ritonavir (Group A), or 750 mg telaprevir q12h with ritonavir (Group B) than with 750 mg telaprevir q8h alone (Group D) in the fed state.

- Exposure to telaprevir was much lower after multiple-dose administration of 750 mg telaprevir q12h with ritonavir in the fasted state (Group C) than with 750 mg telaprevir q8h alone in the fed state (Group D).
- The t1/2 values could not be evaluated for the other treatment groups (Group B, C), since the extrapolated AUC values from tlast to infinity were greater than 25% due to insufficient sampling period.
- Exposure to telaprevir was about 30% higher in the fed versus the fasted state following administration of 750 mg telaprevir q12h with ritonavir.

*VRT-127394 PK:* Mean VRT-127394 PK parameters and statistic analysis results after a single dose of telaprevir with and without ritonavir in the fed and fasted states are presented in Tables 5 and 6. Mean VRT-127394 plasma concentrations over time and statistic analysis results following 14 days of telaprevir or telaprevir and ritonavir coadministration in the fed and fasted states are summarized in Tables 7 and 8.

**Table 5 Mean (SD) VRT-127394 PK Parameters after a Single Dose (Day1) of Telaprevir With and Without Ritonavir in the Fed and Fasted States**

| Treatment | $AUC_{0\text{-last}}$ (hr*ng/mL) | $C_{avg}$ (ng/mL) | $C_{trough}$ (ng/mL) | $C_{max}$ (ng/mL) | $t_{max}$[a] (hr) |
|---|---|---|---|---|---|
| 250 mg telaprevir q12h + ritonavir, fed (Group A) | 3230.33 (1079.69) | 269.19 (89.97) | 244.33 (71.88) | 426.17 (151.19) | 5 (5, 6) |
| 750 mg telaprevir q12h + ritonavir, fed (Group B) | 12687.99 (3338.36) | 1057.33 (278.2) | 888.5 (250.76) | 1598.17 (388.71) | 4.5 (3.5,6.0) |
| 750 mg telaprevir q12h + ritonavir, fasted (Group C) | 5096.73 (554.09) | 424.73 (46.17) | 340.83 (70.86) | 684.17 (62.63) | 5 (3,5) |
| 750 mg telaprevir q8h, fed (Group D) | 3032.52 (1419.15) | 379.06 (177.39) | 441.33 (254.02) | 662.33 (336.49) | 5 (3.5,5) |

Source: Table 14.2.2.3
N=6 per group
[a] $t_{max}$ is presented as median (min, max)

**Table 6 Comparison of VRT-127394 PK Parameters after a Single Dose of Telaprevir With and Without Ritonavir in the Fed and Fasted States**

| Parameter | Group | GLS Mean | Ratio[a] (%) | 90% CI |
|---|---|---|---|---|
| $C_{max}$ (ng/mL) | A | 405.8 | 67.2 | 49.5, 91.4 |
| | B | 1564 | 259 | 191, 352 |
| | C | 681.8 | 113 | 83.2, 154 |
| | D | 603.5 | NA | NA |
| $C_{trough}$(ng/mL) | A | 236.3 | 61.3 | 42.3, 89 |
| | B | 856.4 | 222 | 153, 323 |
| | C | 334.4 | 86.8 | 59.8, 126 |
| | D | 385.3 | NA | NA |
| $C_{avg}$ (ng/mL) | A | 258 | 73.5 | 54.9, 98.5 |
| | B | 1029 | 293 | 219, 393 |
| | C | 422.7 | 120 | 89.9, 161 |
| | D | 351 | NA | NA |

Source: Table 14.2.2.5 and Appendix 16.2.5.1.1
N=6 per group
NA: not applicable
A: 250 mg telaprevir q12h + ritonavir in the fed state
B: 750 mg telaprevir q12h + ritonavir in the fed state
C: 750 mg telaprevir q12h + ritonavir in the fasted state
D: 750 mg telaprevir q8h in the fed state
[a] Group D is the reference in the denominator

**Table 7 Mean (SD) VRT-127394 PK Parameters after Multiple Doses (Day 14) of Telaprevir With and Without Ritonavir in the Fed and Fasted States**

| Treatment | | $AUC_{0\text{-last}}$ (hr*ng/mL) | $C_{avg}$ (ng/mL) | $C_{trough}$ (ng/mL) | $C_{max}$ (ng/mL) | $t_{max}$[a] (hr) | CLss/F (L/hr) | Ratio of AUC (Day 14 /Day 1) |
|---|---|---|---|---|---|---|---|---|
| 250 mg telaprevir q12h + ritonavir, fed (Group A) | N | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| | Mean | 5233.15 | 436.1 | 296.5 | 622.5 | 4.25 | 50.87 | 1.65 |
| | SD | (1520.57) | (126.71) | (55.72) | (204.56) | (3.02, 6) | (12.99) | (0.24) |
| 750 mg telaprevir q12h + ritonavir, fed (Group B) | N | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| | Mean | 14083.52 | 1173.63 | 876.6 | 1598.8 | 4 | 54.58 | 1.09 |
| | SD | (2705.74) | (225.48) | (171.73) | (234.35) | (4, 5) | (8.68) | (0.18) |
| 750 mg telaprevir q12h + ritonavir, fasted (Group C) | N | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| | Mean | 9730.75 | 810.9 | 460.83 | 1090.83 | 3.75 | 80.15 | 1.91 |
| | SD | (2265.23) | (188.77) | (131.83) | (247.59) | (2, 4) | (16.28) | (0.38) |
| 750 mg telaprevir q8h, fed (Group D) | N | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| | Mean | 11208.97 | 1401.12 | 1142.33 | 1708.67 | 3.0 | 68.05 | 4.13 |
| | SD | (1679.29) | (209.91) | (256.95) | (209.29) | (1.5, 6) | (9.25) | (1.31) |

Source: Table 14.2.2.3
[a] $t_{max}$ is presented as median (min, max)

**Table 8 Comparison of VRT-127394 PK Parameters Following Multiple Doses of Telaprevir With and Without Ritonavir in the Fed and Fasted States**

| Parameter | Group | GLS Mean | Ratio[a] (%) | 90% CI |
|---|---|---|---|---|
| $C_{max}$ (ng/mL) | A | 595.5 | 35.1 | 28.1, 43.8 |
| | B | 1586 | 93.4 | 74, 118 |
| | C | 1068 | 62.9 | 50.4, 78.5 |
| | D | 1698 | NA | NA |
| $C_{trough}$ (ng/mL) | A | 292.2 | 26.0 | 21.1, 32.1 |
| | B | 864.2 | 77.0 | 61.9, 95.9 |
| | C | 447.6 | 39.9 | 32.4, 49.1 |
| | D | 1122 | NA | NA |
| $C_{avg}$ (ng/mL) | A | 422 | 30.4 | 24.6, 37.5 |
| | B | 1158 | 83.4 | 66.9, 104 |
| | C | 794.5 | 57.2 | 46.4, 70.6 |
| | D | 1389 | NA | NA |

Source: Table 14.2.2.6 and Appendix 16.2.5.1.1
NA: not applicable
A: 250 mg telaprevir q12h + ritonavir in the fed state (N=6)
B: 750 mg telaprevir q12h + ritonavir in the fed state (N=5)
C: 750 mg telaprevir q12h + ritonavir in the fasted state (N=6)
D: 750 mg telaprevir q8h in the fed state (N=6)
[a] Treatment D is the reference in the denominator.

VRT-127394 PK data show that:

- VRT-127394 exposures in Group A, B, or C relative to Group D (the proposed to-be marketed dose 750 mg telaprevir q8 hr in the fed state) are similar to telaprevir exposures.
- The percent of total exposure (telaprevir AUC + VRT-127394 AUC) attributable to telaprevir was similar following telaprevir with or without ritonavir coadministration and was approximately 70% on Day 1 and 60% on Day 14 across treatment groups.

*Ritonavir PK:*

The mean Cmax, Ctrough and Cavg values were higher following single- or multiple-dose 100 mg ritonavir and 750 mg telaprevir coadministration in fed state (Group B) compared to that in Group A (100 mg ritonavir and 250 mg telaprevir, fed, no statistic analysis was conducted), indicating telaprevir is a concentration-dependent CYP3A inhibitor. Exposure to ritonavir following single dose or multiple doses of 100 mg ritonavir and 750 mg telaprevir was 4%-16% higher in the fed state than in the fasted state.

**Table 9 Ritonavir PK Parameters**

| | $C_{avg}$ | | | $C_{max}$ | | | $C_{trough}$ | | |
|---|---|---|---|---|---|---|---|---|---|
| Telaprevir Dose (mg), Regimen, Food (Group) | 250, q12h, fed (A) | 750, q12h, fed (B) | 750, q12h, fasted (C) | 250, q12h, fed (A) | 750, q12h, fed (B) | 750, q12h, fasted (C) | 250, q12h, fed (A) | 750, q12h, fed (B) | 750, q12h, fasted (C) |
| Day 1 | 259.49 (109.29) | 422.06 (209.43) | 348.62 (129.87) | 591.83 (284.59) | 979.67 (344.9) | 882.33 (331.97) | 139.05 (43.37) | 263.87 (285.28) | 138.27 (84.73) |
| Day 14 | 529.83 (176.01) | 786.23 (339.29) | 693.91 (152.79) | 1067 (496.54) | 1664 (586.55) | 1606.17 (653.39) | 297.33 (63.32) | 418 (433.55) | 207.5 (66.4) |

Safety: The Full Analysis set for safety included the 48 subjects who received at least 1 dose of study drug in Studies VX06-950-009 and VX06-950-009a. The coadministration of telaprevir with ritonavir was well-tolerated. Most (69%) subjects reported at least 1 adverse event. The overall incidence of adverse events was similar among the 4 treatment groups. Most of the adverse events were mild. The most frequent adverse events, regardless of the causality, were generalized pruritus and headache, which were also the most frequent study drug-related adverse events. There were no serious, life threatening, or severe adverse events. One subject discontinued due to a mild rash.

**Discussion:** Telaprevir is a CYP3A and P-gp substrate. Ritonavir is an inhibitor and an inducer of CYP3A and P-gp. Therefore ritonavir increased telapravir exposure in the current study in a time-dependent manner. In this study, mean trough concentrations of telaprevir in subjects given 750 mg telaprevir q8h without ritonavir (Group D) reached maximum levels on Day 2 of multiple-dose administration. In subjects given 750 mg telaprevir q12h with ritonavir, telaprevir mean trough concentrations increased then decreased over time (20% decrease on Ctrough from Day 2 to Day 14 for 750 mg telaprevir alone q8h regimen). The telaprevir mean trough concentrations after administration of 750 mg telaprevir alone q8h also demonstrated a time-dependent decline. In contrast, mean trough concentrations remained relatively stable over time in subjects given 250 mg telaprevir q12h with ritonavir. Inhibition and induction of CYP3A4 by telaprevir has also been demonstrated previously in vitro. These data indicate that both telaprevir and ritonavir may have time and concentration-dependent effects on telaprevir exposure.

**Conclusions:**

- Although the addition of ritonavir increased telaprevir exposure after a single dose, exposure was lower after multiple dosing, possibly due to inductive effects of ritonavir and/or telaprevir autoinduction on CYP3A4 or P-gp (or other transporters).
- A combination of 750 mg telaprevir q12h (1500 mg per day) and 100 mg ritonavir q12h seems inadequate to compensate for the effect of the lower daily doses of telaprevir (1500 mg versus 2250 mg telaprevir per day in the 750 mg q12h versus q8h regimens) and may result in suboptimal exposure to telaprevir.
- Telaprevir increased ritonavir exposure in a dose-dependent manner.
- Telaprevir in combination with ritonavir in the fed state resulted in a two-fold increase of telaprevir exposure after a single dose. Following multiple doses of telaprevir and ritonavir coadministration, the increase in telaprevir exposure due to food effect decreased to 20%-30%.

Food had no significant effect on ritonavir exposure following coadministration of telaprevir and ritonavir.

- The combination of telaprevir with ritonavir was well-tolerated. The most frequently reported adverse events were generalized pruritus and headache.

**An Open-Label Phase 1 Study in Healthy Adult Subjects to Examine the Effects of Telaprevir (VX-950) on the Pharmacokinetics of Midazolam and Digoxin**

**Individual Study Review—VX09-950-011**

**Objectives:**

Primary

- To evaluate the effect of telaprevir on the single-dose pharmacokinetics of midazolam (a cytochrome P450 3A4 [CYP3A4] model substrate drug) administered intravenously and orally to healthy adult subjects
- To evaluate the effect of telaprevir on the single-dose pharmacokinetics of digoxin (a P-glycoprotein [P-gp] model substrate drug) administered orally to healthy adult subjects

Secondary

- To assess the safety and tolerability of co-administration of telaprevir with a single dose of intravenous (IV) midazolam or single oral doses of midazolam and digoxin in healthy adult subjects
- To evaluate the effect of telaprevir on the AUC0-∞ ratio of 1-hydroxymidazolam to midazolam
- To evaluate the effect of telaprevir on the renal clearance of digoxin
- To assess the pharmacokinetics of telaprevir and VRT-127394 when telaprevir is co-administered with a single dose of IV midazolam or single oral doses of midazolam and digoxin

**Study Rationale:** In vitro studies indicated that telaprevir is a CYP3A4 inhibitor when midazolam is the substrate. This indicates the potential for telaprevir to cause drug-drug interactions when it is co-administered with drugs that are substrates of CYP3A4.

Telaprevir is also a substrate for P-glycoprotein (P-gp), a transmembrane efflux transporter that is involved with the absorption, distribution, and elimination of substrate drugs. It is not known whether telaprevir is an inducer or an inhibitor of P-gp, or just a substrate. Inhibition or induction of P-gp can affect the disposition of other drugs that are also substrates of P-gp, such as digoxin.

Therefore, the present clinical trial was designed to characterize the effects of telaprevir on the pharmacokinetics of midazolam (a CYP3A4 model substrate) and the pharmacokinetics of digoxin (a model substrate of P-gp).

**Study Population:** Twenty four male and female healthy subjects between 18 and 60 years of age (inclusive) were enrolled, and analyzed.

**Study Design:** This was an Open-label, single-center, non-randomized study. All subjects received the same treatment. The following table shows the drug dose, route of administration and schedule:

| | Study Days | | | | | | |
|---|---|---|---|---|---|---|---|
| Study Drug | 1 | 3 | 8 - 16 | 17 | 18 | 19 | 20 – 23 |
| IV midazolam 0.5 mg | X | --- | --- | X | --- | --- | --- |
| Oral midazolam 2 mg | --- | X | --- | --- | --- | X | --- |
| Oral digoxin 0.5 mg | --- | X | --- | --- | --- | X | --- |
| Oral telaprevir 750 mg | --- | --- | X | X | X | X | X |

Telaprevir was administered in the fed state (30 minutes after the start of a meal or snack). Oral midazolam was administered 1.5 hours after the start of a standard breakfast. IV midazolam was administered 3.5 hours after the start of a standard breakfast. The IV dose was infused over a period of 2 minutes. Digoxin was administered orally 2.5 hours after the start of a standard breakfast. Food was allowed 3 hours after the administration of the oral dose of digoxin.

**Formulation:**
Telaprevir: 250-mg tablets, Lot # C0849004
IV midazolam: 1-mg/mL solution, Lot # 45-461-DK and 46-485-DK
Oral midazolam: 2-mg/mL syrup, Lot# 657797A
Digoxin: 0.25-mg tablets, Lot# 62P0475B

**Pharmacokinetic Sampling:**

**Midazolam Plasma Sampling**

| | (Pre-morning dose) | Minutes Post Morning Dose | | | | | Hours Post Morning Dose | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Day | 0 | 10 | 15 | 20 | 30 | 45 | 1 | 1.5 | 2 | 4 | 6 | 8 | 10 | 12 | 24 |
| Days 1 and 17 | X | X | --- | X | X | X | X | --- | X | X | X | X | X | X | X |
| Days 3 and 19 | X | --- | X | --- | X | X | X | X | X | X | X | X | X | X | X |

**Digoxin Plasma Sampling**

| | (Pre-morning dose) | Minutes Post Morning Dose | | | Hours Post Morning Dose | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Day | 0 | 15 | 30 | 45 | 1 | 1.5 | 2 | 4 | 6 | 8 | 10 | 12 |
| Days 3 and 19 | X | X | X | X | X | X | X | X | X | X | X | X |
| Days 4, 5, 6, 7, 8, 20, 21, 22, 23, and 24[a] | X | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |

[a] These samples were taken 24, 48, 72, 96, 120 hours post-digoxin doses beginning on Days 3 and 19.

**Telaprevir Plasma Sampling**

| | (Pre-morning dose) | Hours Post Morning Dose | | | | | |
|---|---|---|---|---|---|---|---|
| Study Day | 0 | 1 | 2 | 3 | 4 | 6 | 8 |
| Days 12 and 16 | X | --- | --- | --- | --- | --- | --- |
| Days 17 and 19 | X | X | X | X | X | X | X |

Urine was collected in 24-hour intervals on Days 3, 4, 5, 6, 7 and 8 for the determination of digoxin levels.

**Analytical Method:** Midazolam, 1'-hydroxymidazolam, digoxin, VX-950 (telaprevir), and VRT-127394 in human plasma and digoxin in human urine samples were analyzed by validated LC/MS/MS methods. The standard curve and QC data indicated that the assay methods for midazolam, 1'-hydroxymidazolam, digoxin, VX-950 (telaprevir), and VRT-127394 were precise and accurate as shown in the following table. The Applicant indicated that the storage stability longer than that of the study samples from collection to analysis.

**Summary of Quality Control (QC) Results**

| Analyte | Linear range (ng/mL) | Between Run Precision (%CV) | Between Run Bias (% Deviation) | QC samples (ng/mL) | Validation sample for stability and conditions |
|---|---|---|---|---|---|
| telaprevir | 2 – 1000 (VX9HPP) $R^2 > 0.999$ | NA | 6.7 to 13.7 | 6.0, 250 and 750 | Stable for at least 6 months at -70°C |
| | 20 –5000 (VXVHPP) $R^2 > 0.998$ | ≤ 7.0 | -6.1 to 3.8 | 60, 500, 750, and 3750 | |
| VRT-127394 | 2 – 1000 (VX9HPP) $R^2 > 0.999$ | NA | 1.6 to 7.2 | 6.0, 250 and 750 | Stable for at least 6 months at -70°C |
| | 20 –5000 (VXVHPP) $R^2 > 0.997$ | ≤ 5.7 | -8.3 to 1.3 | 60, 500, 750, and 3750 | |
| midazolam | 0.1 - 100 $R^2 \geq 0.994$ | ≤ 7.2 | -2.3 to 4.5 | 0.3, 15.0, 70.0 and 200 (10-fold dilution) | Stable for at least 1356 days at -70°C. |
| 1'-hydroxymidazolam | 0.1 – 100 $R^2 > 0.996$ | ≤ 5.1 | -5.0 to 0.0 | 0.3, 15.0, 70.0 and 200 (10-fold dilution) | |
| Digoxin (plasma) | 0.1 – 10.0 $R^2 > 0.997$ | ≤ 2.9 | 1.7 to 3.3 | 0.3, 3.0 and 7.5 | Stable for at least 101 days at -70°C |
| Digoxin (urine) | 0.5 - 100 $R^2 > 0.998$ | ≤ 5.7 | -0.4 to 3.7 | 1.5, 30.0, and 75.0 | Stable for at least 49 days at -70°C |

**Results**

Pharmacokinetics

*IV Midazolam*

The effect of telaprevir on IV midazolam was investigated by comparing results on Day 1 (without telaprevir) and Day 17 (with telaprevir). The median plasma concentration versus time profiles for midazolam on Days 1 and 17 are shown in Figure 1. The pharmacokinetic parameters for midazolam on Days 1 and 17 are summarized in Table 1. The median apparent elimination half-life of midazolam increased approximately 4-fold when co-administered with telaprevir. The median clearance of midazolam decreased by approximately 6-fold in the presence of telaprevir while the exposure of midazolam ($AUC_{0-\infty}$) increased by more than 5-fold from in the

presence of telaprevir. Since the percent of area extrapolated from $AUC_{0\text{-tlast}}$ ($AUC_{0\text{-}24}$) to infinity was greater than 25% of the exposure from $AUC_{0\text{-tlast}}$ on Day 17, $AUC_{0\text{-tlast}}$ was used as the parameter for comparisons. Table 2 shows the midazolam $AUC_{0\text{-}24}$ comparison with and without telaprevir. These results show that co-administration of telaprevir has a significant effect on the disposition of midazolam when midazolam is administered intravenously.

**Figure 1** **Median Plasma Concentration versus Time Profile of Midazolam following Intravenous Administration Without (Day 1) and With (Day 17) Telaprevir**

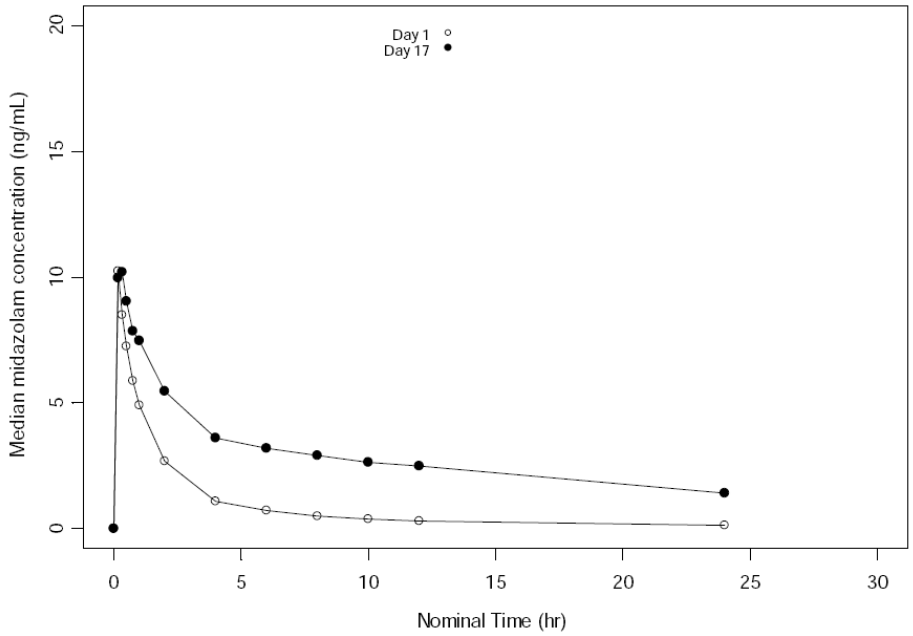



**Table 1** **Summary of Pharmacokinetic Parameters of Midazolam Following Intravenous Administration Without (Day 1) and With (Day 17) Telaprevir**

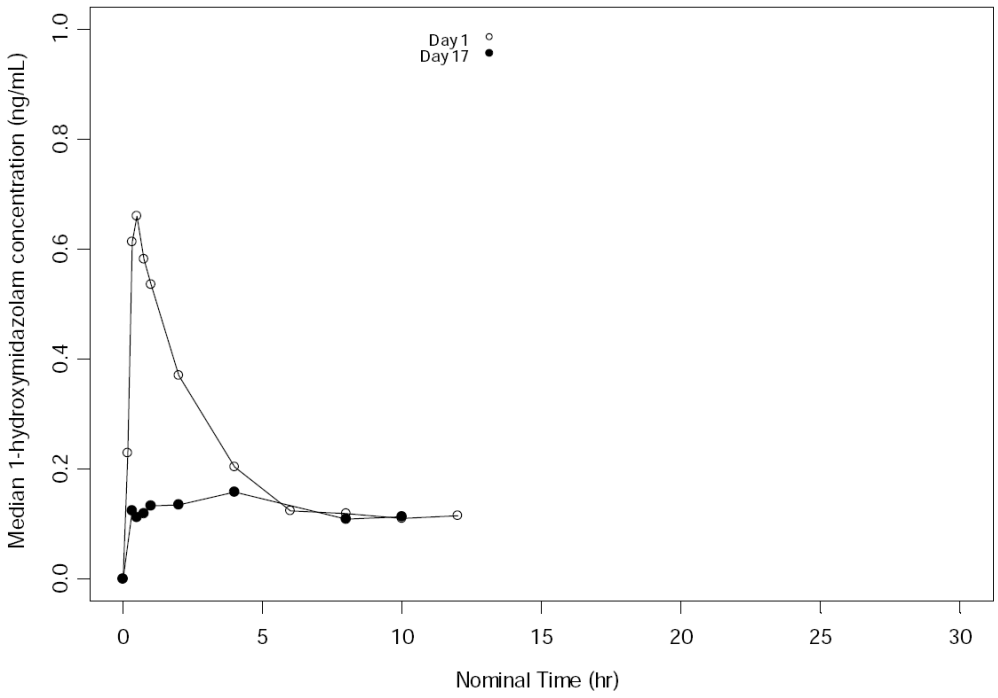
| Day | Parameter | $t_{½}$ (hr) | $C_{max}$ (ng/mL) | $AUC_{0\text{-tlast}}$ (ng*hr/mL) | $AUC_{0\text{-}\infty}$ (ng*hr/mL) | $V_z$ (L) | CL (L/hr) |
|---|---|---|---|---|---|---|---|
| 1 | N | 24 | 24 | 24 | 24 | 24 | 24 |
| | Mean | 4.05 | 19.05 | 21.95 | 23.42 | 134.99 | 23.98 |
| | SD | 1.60 | 37.06 | 12.76 | 13.04 | 49.81 | 5.98 |
| | Min | 1.35 | 7.11 | 13.44 | 13.89 | 27.59 | 6.09 |
| | Median | 4.16 | 10.24 | 18.90 | 20.99 | 149.45 | 23.83 |
| | Max | 6.61 | 192.00 | 79.63 | 82.11 | 212.62 | 35.99 |
| | % CV | 39.60 | 194.50 | 58.10 | 55.70 | 36.90 | 24.90 |
| 17 | N | 22 | 22 | 22 | 22 | 22 | 22 |
| | Mean | 17.10 | 22.36 | 75.37 | 115.00 | 109.55 | 4.74 |
| | SD | 6.84 | 42.91 | 19.50 | 38.41 | 34.50 | 1.35 |
| | Min | 7.75 | 6.13 | 52.03 | 66.76 | 54.56 | 2.14 |
| | Median | 16.27 | 11.05 | 77.70 | 113.23 | 110.76 | 4.42 |
| | Max | 31.96 | 203.00 | 124.37 | 233.44 | 176.93 | 7.49 |
| | % CV | 40.00 | 191.90 | 25.90 | 33.40 | 31.50 | 28.40 |

**Table 2 Geometric Least Square Means Ratio and 90% Confidence Intervals for Midazolam Exposure Following Intravenous Administration, Without and With the Administration of Telaprevir**

| Comparison | Parameter | GLS Mean Ratio (%) | 90% Confidence Interval |
|---|---|---|---|
| Midazolam without Telaprevir/ Midazolam with Telaprevir | $AUC_{0-24}$ | 339.5 | 304.4, 378.6 |

The effect of telaprevir on the pharmacokinetic profile of 1-hydroxymidazolam, the metabolite of midazolam, is shown in Figure 2. Due to the significant inhibitory effect of telaprevir on the metabolism of midazolam, no subjects had measurable concentrations of 1-hydroxymidazolam at all time points on Day 17. As a result, the AUC ratio of 1-hydroxymidazolam to midazolam on Day 17 could not be calculated and were not reported.

**Figure 2 Median Plasma Concentration versus Time Profile of 1-Hydroxymidazolam following Intravenous Administration Without (Day 1) and With (Day 17) Telaprevir**




*Oral Midazolam*

Midazolam was administered orally to subjects before (Day 3) and after (Day 19) treatment with telaprevir. The median plasma concentration versus time profile for midazolam on the two dosing occasions is shown in Figure 3 and the pharmacokinetic parameters of midazolam with and without the co-administration of telaprevir are summarized in Table 3.

**Figure 3 Median Plasma Concentration Versus Time Profile of Midazolam Following Oral Administration Without (Day 3) and With (Day 19) Telaprevir**

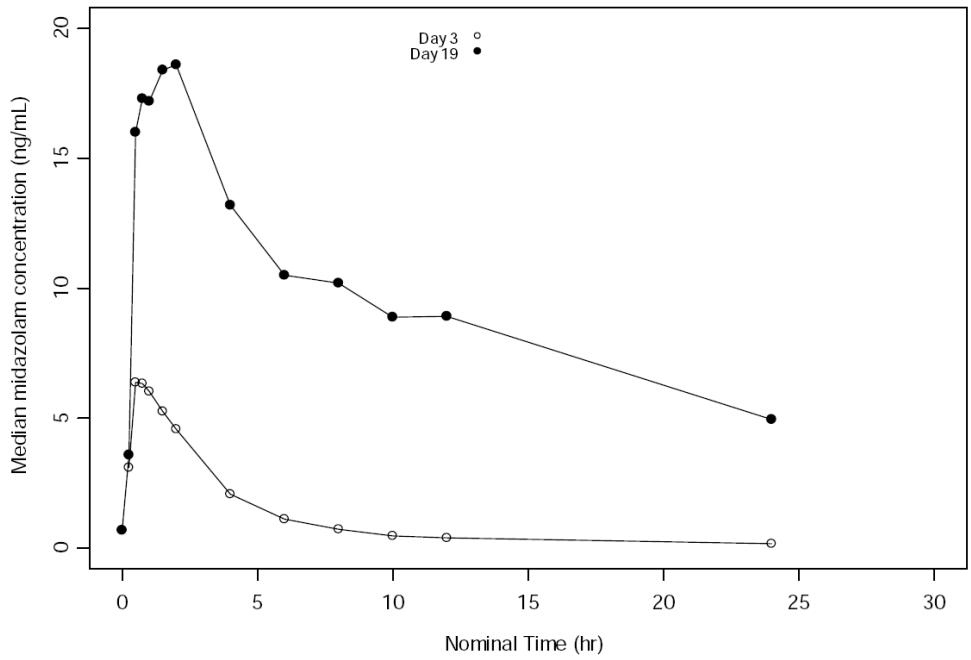



**Table 3 Summary of Pharmacokinetic Parameters of Midazolam Following Oral Administration Without (Day 3) and With (Day 19) Telaprevir**

| Day | Parameter | $t_{½}$ (hr) | $t_{max}$ (hr) | $C_{max}$ (ng/mL) | $AUC_{0\text{-}tlast}$ (ng*hr/mL) | $AUC_{0\text{-}\infty}$ (ng*hr/mL) | Vz/ F (L) | CL/ F (L/hr) |
|---|---|---|---|---|---|---|---|---|
| 3 | N | 23 | 23 | 23 | 23 | 23 | 23 | 23 |
| | Mean | 4.31 | 0.76 | 7.71 | 25.89 | 27.37 | 446.90 | 78.98 |
| | SD | 2.00 | 0.37 | 2.08 | 7.60 | 8.00 | 144.99 | 21.85 |
| | Min | 1.28 | 0.50 | 4.56 | 15.46 | 16.19 | 212.81 | 46.67 |
| | Median | 4.15 | 0.75 | 7.70 | 23.33 | 24.54 | 479.54 | 81.49 |
| | Max | 8.08 | 2.00 | 12.20 | 41.66 | 42.85 | 697.21 | 123.51 |
| | % CV | 46.40 | 48.90 | 27.00 | 29.40 | 29.20 | 32.40 | 27.70 |
| 19 | N | 21 | 21 | 21 | 21 | 21 | 21 | 21 |
| | Mean | 16.57 | 1.20 | 22.26 | 237.36 | 368.59 | 134.36 | 5.87 |
| | SD | 5.32 | 0.43 | 6.52 | 60.74 | 115.87 | 40.46 | 1.64 |
| | Min | 7.25 | 0.75 | 13.30 | 157.27 | 198.20 | 57.56 | 2.69 |
| | Median | 16.71 | 1.00 | 21.00 | 216.06 | 342.89 | 136.31 | 5.83 |
| | Max | 26.37 | 2.00 | 32.40 | 363.84 | 743.91 | 201.76 | 10.09 |
| | % CV | 32.10 | 35.80 | 29.30 | 25.60 | 31.40 | 30.10 | 27.90 |

The data show when midazolam was co-administered with telaprevir, midazolam $C_{max}$ increased approximately 3-fold; the median apparent elimination half-life ($t_{½}$) of midazolam increased 4-fold; and the overall exposure to midazolam ($AUC_{0\text{-}tlast}$) also increased by more than 9-fold. Since the percent of area extrapolated from $t_{last}$ to infinity was more than 25% of $AUC_{0\text{-}tlast}$ on Day 19 for most subjects, the estimate of the parameter $AUC_{0\text{-}\infty}$ was not expected to be accurate

and should be interpreted with caution. Comparing results from Day 3 with Day 19, the median apparent volume of distribution ($V_z/F$) of midazolam decreased by approximately 3.5-fold and clearance (CL/F) of midazolam decreased by approximately 14-fold. The GLS mean ratio and the 90% CI for oral midazolam before and after treatment with telaprevir are shown in Table 4. These results show that there is a significant effect of telaprevir on the pharmacokinetics of orally administered midazolam.

**Table 4 Geometric Least Square Means Ratio and 90% Confidence Intervals for Midazolam Exposure Following Oral Administration Without and With the Administration of Telaprevir**

| Comparison | Parameter | GLS Mean Ratio (%) | 90% Confidence Interval |
|---|---|---|---|
| Midazolam without Telaprevir/ Midazolam with Telaprevir | $AUC_{0-24}$ | 895.6 | 774.7, 1035.3 |
| | $C_{max}$ | 286.1 | 252.0, 324.7 |

The pharmacokinetics of 1-hydroxymidazolam, the primary metabolite of midazolam are summarized in Table 5.

**Table 5 Summary of Pharmacokinetic Parameters of 1-Hydroxymidazolam Following Oral Administration Without (Day 3) and With (Day 19) Telaprevir**

| Day | Parameter | $t_{½}$ (hr) | $t_{max}$ (hr) | $C_{max}$ (ng/mL) | $AUC_{0-tlast}$ (ng*hr/mL) | $AUC_{0-\infty}$ (ng*hr/mL) | $AUC_{0-24}$ (ng*hrmL) | AUC Ratio |
|---|---|---|---|---|---|---|---|---|
| 3 | N | 23 | 23 | 23 | 23 | 23 | 23 | 23 |
| | Mean | 3.35 | 0.92 | 3.12 | 9.47 | 10.20 | 10.02 | 0.40 |
| | SD | 2.06 | 0.40 | 1.62 | 4.21 | 4.57 | 4.30 | 0.20 |
| | Min | 1.49 | 0.50 | 1.25 | 4.27 | 4.80 | 4.77 | 0.19 |
| | Median | 2.73 | 0.75 | 2.67 | 8.41 | 8.75 | 8.69 | 0.35 |
| | Max | 11.33 | 1.52 | 8.49 | 21.30 | 22.64 | 22.47 | 1.11 |
| | % CV | 61.40 | 44.10 | 51.90 | 44.50 | 44.80 | 42.90 | 50.00 |
| 19 | N | 21 | 21 | 21 | 21 | 21 | 21 | 21 |
| | Mean | 14.41 | 1.36 | 0.42 | 3.33 | 6.22 | 4.01 | 0.02 |
| | SD | 12.21 | 0.44 | 0.18 | 2.12 | 4.54 | 1.83 | 0.01 |
| | Min | 4.80 | 0.75 | 0.21 | 1.13 | 2.01 | 1.95 | 0.01 |
| | Median | 9.53 | 1.50 | 0.33 | 2.47 | 4.45 | 3.18 | 0.02 |
| | Max | 57.94 | 2.00 | 0.87 | 9.13 | 21.29 | 9.13 | 0.03 |
| | % CV | 84.70 | 32.70 | 42.70 | 63.50 | 72.90 | 45.70 | 37.90 |

Note: AUC ratio was calculated as follows: $AUC_{0-24}$ 1-hydroxymidazolam/ $AUC_{0-24}$ midazolam

The data show when midazolam was co-administered with telaprevir, the median $C_{max}$ of 1-hydroxymidazolam was decreased by approximately 8-fold; the median $t_{1/2}$ of 1-hydroxymidazolam increased from 2.73 hr (Day 3) to 9.53 hr (Day 19); and the median total exposure to 1-hydroxymidazolam ($AUC_{0-\infty}$) decreased approximately 2-fold. The median AUC ratio of 1-hydroxymidazolam to midazolam decreased more than 17-fold from 0.35 (Day 3) to 0.02 (Day 19). These results indicate that telaprevir significantly decreases the conversion of midazolam to 1-hydroxymidazolam by inhibiting CYP3A4.

*Intestinal Versus Hepatic Effects of Telaprevir on Midazolam Pharmacokinetics*

Assuming the absorbed fraction ($F_{ABS}$) of midazolam to be 1 and unaffected by telaprevir coadministration, telaprevir significantly decreased the median first-pass intestinal metabolism ($E_G$) of oral midazolam (median of 0.57 on Day 3 and 0.01 on Day 19), while having a modest effect on the median pre-systemic hepatic elimination ($E_H$) of oral midazolam (median of 0.25 on Day 3 and 0.19 on Day 19). The median oral bioavailability of midazolam increased approximately 2.5-fold from 33% to 81%. However, since $AUC_{0-24}$ was used in the calculation of $F_{oral}$, these data should be interpreted with caution. The summary of pharmacokinetic parameters for midazolam is shown in Table 6.

**Table 6 Summary Statistics of Hepatic and Intestinal Extraction Ratios of Midazolam Following Oral Administration without (Day 3) and with (Day 19) Telaprevir**

| Day | Parameter | Hepatic Extraction Ratio[a] ($E_H$) | Oral Bioavailability[b] ($F_{oral}$) | Intestinal Extraction Ratio[c] ($E_G$) |
|---|---|---|---|---|
| 3 | N | 24 | 23 | 23 |
| | Mean | 0.25 | 0.32 | 0.58 |
| | SD | 0.04 | 0.09 | 0.11 |
| | Min | 0.19 | 0.07 | 0.39 |
| | Median | 0.25 | 0.33 | 0.57 |
| | Max | 0.34 | 0.45 | 0.92 |
| | CV% | 17.70 | 27.00 | 19.60 |
| 19 | N | 22 | 21 | 21 |
| | Mean | 0.18 | 0.81 | 0.05 |
| | SD | 0.08 | 0.08 | 0.07 |
| | Min | 0.02 | 0.65 | 0.00 |
| | Median | 0.19 | 0.82 | 0.01 |
| | Max | 0.34 | 0.97 | 0.23 |
| | CV% | 45.42 | 9.94 | 149.10 |

[a] Hepatic Extraction Ratio: $E_H = CL_{IV}/Q_p$, where $Q_p$ is the hepatic blood flow (25.3 and 25.5 mL/min/kg in males and females respectively)
[b] Oral Bioavailability: $F_{oral} = (AUC_{0-24, po} * Dose_{IV}) / (Dose_{po} * AUC_{0-24, IV})$
[c] Intestinal Extraction Ratio: $E_G = 1 - F_{oral} / (F_{ABS} * (1 - E_H))$

*Digoxin*

Digoxin was administered orally to subjects before (Day 3) and after (Day 19) treatment with telaprevir. The median plasma concentration versus time profile for digoxin on the 2 dosing occasions is shown in Figure 4 and the pharmacokinetic parameters of digoxin are summarized in Table 7.

**Figure 4 Median Plasma Concentration versus Time Profile of Digoxin Following Oral Administration Without (Day 3) and With (Day 19) Telaprevir**

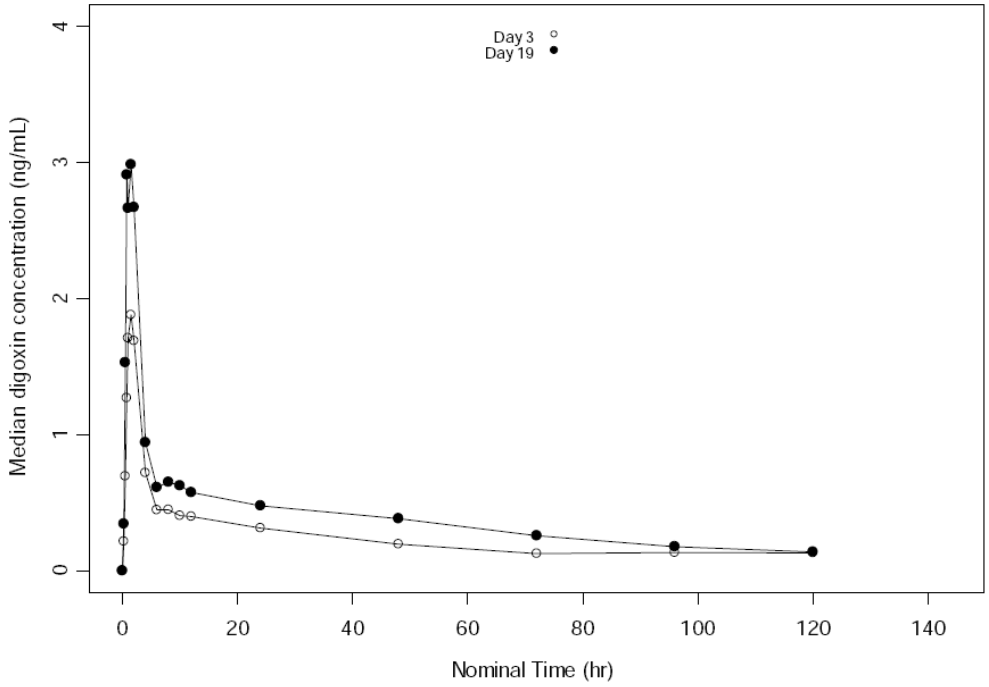



**Table 7 Summary of Pharmacokinetic Parameters of Digoxin Following Oral Administration Without (Day 3) and With (Day 19) Telaprevir**

| Day | Parameter | $t_{½}$ (hr) | $t_{max}$ (hr) | $C_{max}$ (ng/mL) | $AUC_{0\text{-}tlast}$ (ng*hr/mL) | $AUC_{0\text{-}\infty}$ (ng*hr/mL) | Vz/ F (L) | CL/ F (L/hr) |
|---|---|---|---|---|---|---|---|---|
| 3 | N | 23 | 23 | 23 | 23 | 23 | 23 | 23 |
| | Mean | 38.33 | 1.32 | 2.43 | 24.63 | 31.66 | 914.89 | 17.15 |
| | SD | 8.16 | 0.45 | 0.90 | 9.16 | 10.24 | 212.58 | 4.61 |
| | Min | 21.85 | 0.50 | 1.36 | 12.34 | 18.59 | 619.18 | 8.89 |
| | Median | 39.66 | 1.50 | 2.14 | 22.37 | 29.01 | 886.09 | 17.24 |
| | Max | 62.17 | 2.00 | 5.17 | 45.39 | 56.26 | 1391.84 | 26.89 |
| | % CV | 21.30 | 34.00 | 37.10 | 37.20 | 32.30 | 23.20 | 26.90 |
| 19 | N | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | Mean | 49.64 | 1.22 | 3.58 | 46.68 | 57.47 | 662.69 | 9.30 |
| | SD | 6.14 | 0.45 | 1.03 | 13.91 | 15.84 | 181.08 | 2.39 |
| | Min | 40.36 | 0.50 | 2.02 | 22.73 | 33.41 | 387.83 | 5.15 |
| | Median | 48.05 | 1.25 | 3.30 | 45.60 | 54.95 | 643.82 | 9.10 |
| | Max | 60.61 | 2.03 | 6.20 | 81.02 | 97.05 | 1031.04 | 14.96 |
| | % CV | 12.40 | 36.90 | 28.80 | 29.80 | 27.60 | 27.30 | 25.70 |

The GLS mean ratio and the 90% CI for orally administered digoxin with and without coadministration of telaprevir are shown in Table 8. The GLS mean ratios for $C_{max}$ and $AUC_{0\text{-}\infty}$ were 149.5 and 184.7, respectively, and above the 75-133% range, indicating the presence of an interaction between telaprevir and digoxin, when administered orally. Given the narrow therapeutic index of digoxin, the extent of the interaction is clinically significant.

**Table 8 Geometric Least Square Means Ratio (GLM ratio) and 90% Confidence Intervals for Digoxin Exposure Following Oral Administration Without and With the Administration of Telaprevir**

| Comparison | Parameter | GLS Mean Ratio (%) | 90% Confidence Interval |
|---|---|---|---|
| Digoxin without Telaprevir/ Digoxin with Telaprevir | $AUC_{0-\infty}$ | 184.7 | 170.2, 200.4 |
| | $C_{max}$ | 149.5 | 136.0, 164.5 |

The cumulative amount of digoxin excreted in the urine was determined over a 5-day period without (Day 3) and with (Day 19) the co-administration of telaprevir. The summary statistics of digoxin excretion in the urine is shown in Table 9. When coadministered with telaprevir, median Ae of digoxin over a 120 hour period was increased by approximately 1.4-fold; while the median renal clearance decreased by 16%, indicating that there is minimal effect of telaprevir on the P-gp in the kidney.

**Table 9 Summary Statistics of Urinary Excretion of Digoxin Administered Without (Day 3) and With (Day 19) Telaprevir**

| Day | Parameter | Cumulative Amount Excreted (μg) | Renal Clearance (mL/hr) |
|---|---|---|---|
| 3 | N | 23 | 23 |
| | Mean | 139.16 | 5.13 |
| | SD | 49.53 | 1.66 |
| | Min | 50.94 | 1.14 |
| | Median | 140.64 | 5.16 |
| | Max | 242.65 | 9.23 |
| | CV% | 35.60 | 32.32 |
| 19 | N | 20 | 20 |
| | Mean | 191.16 | 4.28 |
| | SD | 64.73 | 1.78 |
| | Min | 64.10 | 1.43 |
| | Median | 203.04 | 4.33 |
| | Max | 317.04 | 9.04 |
| | CV% | 33.90 | 41.52 |

*Telaprevir and VRT-127394*

Plasma samples to determine the trough concentrations of telaprevir and VRT-127394 were taken on Days 12 and 16 while intensive sampling was conducted following the administration of the first dose of telaprevir on Days 17 and 19 to determine the pharmacokinetics of telaprevir and VRT-127394 following co-administration of a single dose of midazolam (IV and oral) and digoxin. The pharmacokinetic parameters for telaprevir and VRT-127394 on Days 17 and 19 are summarized in Table 10. The data indicate that midazolam or digoxin has no effect on telaprevir pharmacokinetics.

**Table 10 Summary Statistics of Pharmacokinetic Parameters for Telaprevir and VRT-127394 on Day 17 and 19**

| Day | Analyte | Statistics | $t_{max}$ (hr) | $C_{max}$ (ng/mL) | $AUC_{0\text{-tlast}}$ (ng*hr/mL) | AUC Ratio[a] (%) |
|---|---|---|---|---|---|---|
| 17 | telaprevir | N | 22 | 22 | 22 | 22 |
| | | Mean | 3.30 | 3193.64 | 19780.27 | 61.71 |
| | | SD | 1.40 | 724.23 | 4509.54 | 2.12 |
| | | Min | 1.02 | 2200 | 12624.60 | 58.40 |
| | | Median | 2.92 | 3300 | 19307.33 | 61.70 |
| | | Max | 6.00 | 4530 | 27497.86 | 66.12 |
| | | % CV | 42.40 | 22.70 | 22.80 | 3.43 |
| 19 | telaprevir | N | 21 | 21 | 21 | 21 |
| | | Mean | 3.57 | 3087.62 | 19722.17 | 62.51 |
| | | SD | 1.25 | 582.79 | 4170.71 | 2.40 |
| | | Min | 2.00 | 2120 | 12063.31 | 58.62 |
| | | Median | 3.00 | 3060 | 20314.50 | 61.79 |
| | | Max | 6.00 | 4380 | 27092.16 | 67.16 |
| | | % CV | 34.90 | 18.90 | 21.10 | 3.84 |
| 17 | VRT-127394 | N | 22 | 22 | 22 | Not reported |
| | | Mean | 2.99 | 1775.23 | 12220.11 | |
| | | SD | 2.29 | 384.79 | 2515.42 | |
| | | Min | 0.00 | 995.00 | 7051.28 | |
| | | Median | 3.46 | 1730.00 | 11827.01 | |
| | | Max | 6.00 | 2370.00 | 15748.09 | |
| | | % CV | 76.50 | 21.70 | 20.60 | |
| 19 | VRT-127394 | N | 21 | 21 | 21 | Not reported |
| | | Mean | 3.76 | 1700.19 | 11880.11 | |
| | | SD | 2.21 | 450.37 | 2652.10 | |
| | | Min | 0.00 | 904.00 | 6072.46 | |
| | | Median | 4.00 | 1780.00 | 12773.02 | |
| | | Max | 8.00 | 3000.00 | 15150.56 | |
| | | % CV | 58.80 | 26.50 | 22.30 | |

[a] AUC ratio = 100 * $AUC_{0\text{-tlast}}$ telaprevir/($AUC_{0\text{-tlast}}$ telaprevir + $AUC_{0\text{-tlast}}$ VRT-127394)

Safety

During this study, 750-mg telaprevir q8h was generally well tolerated when administered alone and in combination with single doses of IV midazolam (0.5 mg) or oral midazolam (2 mg) and digoxin (0.5 mg). There were no serious or severe adverse events.

**Conclusion:**

- The pharmacokinetics of midazolam are affected significantly when co-administered with telaprevir. Telaprevir appears to have a stronger inhibitory effect on the intestinal CYP3A4 than hepatic CYP3A4.
- Telaprevir also appears to have an inhibitory effect on P-gp, as evidenced by a statistically significant increase in the exposure of digoxin, a model P-gp substrate.

**An Open-Label Phase 1 Study to Examine the Effect of Multiple Doses of Rifampin on Telaprevir and the Multiple-Dose Drug-Drug Interaction between Telaprevir and Efavirenz in Healthy Subjects**

**Individual Study Review—VX09-950-016**

**Objectives:**

- To evaluate the effect of steady-state rifampin on the single-dose pharmacokinetics of telaprevir.
- To evaluate the effect of steady-state efavirenz on the steady-state pharmacokinetics of telaprevir.
- To evaluate the effect of steady-state telaprevir on the steady-state pharmacokinetics of efavirenz.

**Study Rationale:** In vitro studies showed telaprevir was metabolized extensively by the CYP3A4 isozyme of cytochrome P450. This indicates the potential for drug-drug interactions when telaprevir is coadministered with drugs that are inducers of CYP3A4. Rifampin is the model CYP3A4 inducer and has been shown to decrease the levels of many drugs that are substrates of CYP3A4

**Study Population:** In Part 1, 16 subjects were planned, enrolled, and completed the study. All subjects were included in the pharmacokinetic analyses. In Part 2, 28 subjects were planned and enrolled; 20 subjects completed the study. All subjects who provided plasma samples on intensive pharmacokinetic sampling days were included in the pharmacokinetic analysis. Efavirenz is also known to induce CYP3A4 following repeated administration, which may influence the pharmacokinetics of telaprevir. Efavirenz is a human immunodeficiency virus type 1 (HIV-1) specific non-nucleoside reverse transcriptase inhibitor indicated to treat HIV-1 infection. Because HCV infection is present in a high percentage of the HIV-infected population, there is a need to examine the potential drug-drug interaction between telaprevir and efavirenz.

**Study Design:** This was an open-label Phase 1 study to examine the effect of multiple-dose rifampin on the pharmacokinetics of telaprevir (Part 1) and the effect of multiple-dose drug-drug interaction between telaprevir and efavirenz (Part 2) in healthy subjects.

Part 1 (telaprevir and rifampin): As shown in Table 1, subjects were treated with a single dose of telaprevir (750 mg) 30 minutes after the start of a meal or snack on Day 1 and Day 9, and with a daily dose of rifampin (600 mg) in the fasted state (approximately 3.5 hours after the start of breakfast) on Days 2 through 9.

**Table 1 Part 1 Study Drug Dose and Administration**

| | Study Days | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study Drug** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** |
| Oral telaprevir 750 mg | X | | | | | | | | X |
| Oral rifampin 600 mg qd | | X | X | X | X | X | X | X | X |

Part 2 (telaprevir and efavirenz): As shown in Table 2, subjects were treated with multiple doses of telaprevir (750 mg q8h) 30 minutes after the start of a meal or snack on Days 1 through 10 and Days 28 through 37, and with multiple doses of efavirenz (600 mg once daily) in the fasted state (approximately 3.5 hours after the start of breakfast) on Days 18 through 37.

**Table 2 Part 2 Study Drug Dose and Administration**

| | Study Days | | |
|---|---|---|---|
| **Study Drug** | **1 - 10** | **18 - 27** | **28 - 37** |
| Oral telaprevir 750 mg q8h | X | | X |
| Oral efavirenz 600 mg qd | | X | X |

**Formulation:**
Telaprevir: 250 mg tablets, batch #C0849004, (b) (4)
Rifampin: 300 mg capsules, batch #ML061794, Eon Labs, Laurelton, NY
Efavirenz: 600 mg tablets, batch #6L19305A, Bristol-Myers Squibb, Princeton, NJ

**Pharmacokinetic Sampling:**
Part 1: Telaprevir and VRT-127394 Plasma Sampling (4 mL blood sample)
- Days 1 and 9: 0 (predose), 0.5, 1, 2, 3, 3.5, 4, 6, 8, 10, 12, and 24 hours after the administration of telaprevir dose.

Part 1: Rifampin Plasma Sampling (4 mL blood sample)
- Day 9: 0 (predose), 1, 2, 3, 6, 8, 12, and 24 hours after the administration of the rifampin dose.
- Days 6, 7, and 8: Trough plasma samples were collected prior to the administration of the rifampin dose.

Part 2: Telaprevir and VRT-127394 Plasma Sampling (4 mL blood sample)
- Days 10 and 37: 0 (predose), 0.5, 1, 2, 3, 3.5, 4, 6, and 8 hours after the administration of the afternoon telaprevir dose.
- Days 7, 8, 34, and 35: Trough plasma pharmacokinetic samples were collected prior to the administration of the afternoon telaprevir dose.
- Days 9 and 36: Trough plasma pharmacokinetic samples were collected prior to the administration of the morning, afternoon, and night telaprevir doses.

Part 2: Efavirenz Plasma Sampling (4 mL blood sample)
- Days 27 and 37: 0 (predose), 1, 2, 3, 4, 5, 6, 8, 10, 12 and 24 hours after the administration of the efavirenz dose.
- Days 18, 21, 24, 25, 26, 34, 35, and 36: Trough plasma pharmacokinetic samples were collected prior to the administration of the efavirenz dose.

**Analytical Method:** VX-950 (telaprevir), VRT-127394, rifampin, and efavirenz human plasma samples were analyzed by validated LC/MS/MS methods. The standard curve and QC data indicated that the plasma assay methods for VX-950 (telaprevir), VRT-127394, rifampin, and efavirenz were precise and accurate as shown in the following table. The Applicant indicated that the storage stability longer than that of the study samples from collection to analysis.

**Table 3 Summary of Quality Control (QC) Results**

| Analyte | Linear range (ng/mL) | Between Run Precision (%CV) | Between Run Bias (% Deviation) | QC samples (ng/mL) | Validation sample for stability and conditions |
|---|---|---|---|---|---|
| telaprevir | 2 – 1000 (VX9HPP) $R^2 > 0.996$ | ≤ 5.0 | -5.9 to 2.2 | 6.0, 250 and 750 | Stable for at least 6 months at -70°C |
| | 20 –5000 (VXVHPP) $R^2 \geq 0.997$ | ≤ 3.7 | -4.0 to 2.2 | 60, 500, 750, and 3750 | |
| VRT-127394 | 2 – 1000 (VX9HPP) $R^2 > 0.992$ | ≤ 7.1 | -0.9 to 3.7 | 6.0, 250 and 750 | Stable for at least 6 months at -70°C |
| | 20 –5000 (VXVHPP) $R^2 > 0.994$ | ≤ 6.7 | -2.6 to 1.0 | 60, 500, 750, and 3750 | |
| rifampin | 50.0 - 35000 $R^2 \geq 0.998$ | ≤ 8.0 | -5.4 to 2.7 | 150, 12000 and 28000 | Stable for at least 747 days at -70°C. |
| efavirenz | 1 – 1000 $R^2 \geq 0.999$ | ≤ 4.3 | -10.6 to 0.3 | 3.00, 75.0, 750, and 5000 (10-fold dilution) | Stable for at least 72 days at -70°C. |

**Results**

Pharmacokinetics

*Effect of rifampin on the PK of Telaprevir and VRT-127394*

The effect of rifampin at steady-state on a single dose of orally administered telaprevir was investigated on Day 1 (telaprevir without rifampin) and Day 9 (telaprevir with steady-state rifampin). The pharmacokinetic parameters for telaprevir on Days 1 and 9 are shown in Table 4.

**Table 4 Summary of Pharmacokinetic Parameters of Telaprevir Following Oral Administration Without (Day 1) and With (Day 9) Rifampin**

| Day | Parameter | $t_{max}$ (hr) | Half Life (hr) | $C_{max}$ (ng/ml) | AUC $_{0\text{-last}}$ (hr*ng/ml) | $AUC_{0\text{-}\infty}$ (hr*ng/ml) | Vz/F (L) | CL/F (L/hr) |
|---|---|---|---|---|---|---|---|---|
| 1 | N | 16 | 16 | 16 | 16 | 16 | 16 | 16 |
| | Mean | 3.28 | 3.81 | 1899.06 | 10363.89 | 10586.30 | 537.41 | 97.90 |
| | SD | 1.05 | 0.82 | 940.12 | 5308.92 | 5512.16 | 429.76 | 70.41 |
| | Min | 2.00 | 2.68 | 324.00 | 2680.60 | 2756.62 | 199.96 | 30.47 |
| | Median | 3.25 | 3.65 | 2005.00 | 10317.06 | 10545.39 | 383.28 | 71.46 |
| | Max | 6.00 | 5.68 | 3760.00 | 23894.87 | 24617.64 | 1752.76 | 272.07 |
| | CV% | 31.86 | 21.48 | 49.50 | 51.23 | 52.07 | 79.97 | 71.92 |
| 9 | N | 16 | 16 | 16 | 16 | 16 | 16 | 16 |
| | Mean | 3.50 | 2.11 | 248.63 | 817.13 | 837.56 | 3415.58 | 1054.81 |
| | SD | 0.86 | 0.74 | 106.03 | 338.39 | 335.11 | 2446.59 | 498.65 |
| | Min | 1.00 | 1.28 | 117.00 | 287.19 | 298.92 | 957.39 | 495.81 |
| | Median | 4.00 | 1.90 | 246.00 | 812.86 | 837.88 | 2536.27 | 896.14 |
| | Max | 4.02 | 4.06 | 462.00 | 1500.02 | 1512.69 | 10815.02 | 2509.05 |
| | CV% | 24.59 | 34.84 | 42.65 | 41.4 | 40.01 | 71.63 | 47.27 |

Pharmacokinetic parameters for VRT-127394 were also analyzed on Days 1 and 9 and are presented in Table 5.

**Table 5 Summary of Pharmacokinetic Parameters of VRT-127394 Following Oral Administration Without (Day 1) and With (Day 9) Rifampin**

| Day | Parameter | $t_{max}$ (hr) | Half Life (hr) | $C_{max}$ (ng/ml) | $AUC_{0-\infty}$ (hr*ng/ml) | % total exposure attributable to telaprevir |
|---|---|---|---|---|---|---|
| 1 | N | 16 | 16 | 16 | 16 | 16 |
| | Mean | 4.58 | 4.45 | 486.14 | 4170.86 | 68.57 |
| | SD | 1.39 | 1.34 | 229.04 | 2161.80 | 2.98 |
| | Min | 3.00 | 2.77 | 87.20 | 985.39 | 63.87 |
| | Median | 4.00 | 4.02 | 510.50 | 4235.66 | 72.08 |
| | Max | 8.00 | 7.40 | 906.00 | 8493.23 | 76.16 |
| | CV% | 30.41 | 30.16 | 47.12 | 51.83 | 4.35 |
| 9 | N | 16 | 16 | 16 | 16 | 16 |
| | Mean | 3.91 | 2.70 | 42.68 | 193.00 | 76.82 |
| | SD | 0.94 | 0.74 | 21.76 | 65.96 | 3.46 |
| | Min | 1.00 | 1.26 | 17.10 | 74.42 | 74.45 |
| | Median | 4.00 | 2.88 | 35.35 | 178.19 | 80.38 |
| | Max | 6.00 | 4.14 | 111.00 | 369.34 | 87.28 |
| | CV% | 23.93 | 27.46 | 50.97 | 34.18 | 4.51 |

Note: The AUC Ratio was calculated by dividing the telaprevir $AUC_{0-\infty}$ by the sum of $AUC_{0-\infty}$ of telaprevir and VRT-127394 and expressed as percent

The geometric least squares ratio (GLS mean ratio) and the 90% confidence intervals (CI) of telaprevir and VRT-127394 for the orally administered telaprevir with and without rifampin are shown in Table 6. The data indicate that the administration of rifampin significantly reduces the exposure to telaprevir and VRT-127394. Rifampin and telaprevir should not be coadiministered.

**Table 6 Geometric Least Square Means Ratio and 90% Confidence Intervals for Telaprevir and VRT-127394 Exposure Following Single Dose Oral Administration of Telaprevir, Without and With the Administration of Rifampin**

| Comparison | Parameter | GLS Mean Ratio (%) | 90% Confidence Interval |
|---|---|---|---|
| Telaprevir with Rifampin/ Telaprevir without Rifampin | $AUC_{0-\infty}$ | 8.42 | 6.56, 10.81 |
| | $C_{max}$ | 13.98 | 10.77, 18.14 |
| VRT-127394 with Rifampin/ VRT-127394 without Rifampin | $AUC_{0-\infty}$ | 5.11 | 3.80, 6.88 |
| | $C_{max}$ | 9.20 | 6.83, 12.39 |

*Reviewer's Comment: rifampin is both an inducer of CYP3A4 and an inhibitor of OATP1B1. Rifampin significantly reduced both telaprevir and VRT-127394 concentrations indicated the effect of rifampin on telaprevir and VRT-127394 are mostly through CYP3A4 induction instead of OATP1B1 induction.*

*Effect of telaprevir on PK of Rifampin*

The pharmacokinetic parameters for rifampin on Day 9 are shown in Table 7. All pharmacokinetic parameters for rifampin are in the range published in the literature, indicating that telaprevir does not affect the pharmacokinetics of rifampin.

**Table 7 Summary of Pharmacokinetic Parameters of Rifampin (Day 9)**

| Day | Parameter | $t_{max}$ (hr) | Half life (hr) | $C_{max}$ (ng/ml) | $AUC_{0\text{-last}}$ (hr*ng/ml) | $AUC_{0\text{-}\infty}$ (hr*ng/ml) | $V_z/F$ (L) | CL/F (L/hr) |
|---|---|---|---|---|---|---|---|---|
| 9 | N | 16 | 16 | 16 | 16 | 16 | 16 | 16 |
| | Mean | 1.44 | 1.92 | 12751.25 | 51404.86 | 52285.64 | 34.69 | 13.00 |
| | SD | 0.51 | 0.45 | 4571.08 | 23511.39 | 23784.85 | 9.91 | 3.82 |
| | Min | 1.00 | 1.33 | 8230.00 | 33890.27 | 34242.34 | 17.75 | 5.00 |
| | Median | 1.03 | 1.96 | 10800.00 | 42456.23 | 43135.24 | 32.85 | 13.93 |
| | Max | 2.00 | 2.64 | 24900.00 | 119676.16 | 119942.63 | 52.60 | 17.52 |
| | CV% | 35.37 | 23.58 | 35.85 | 45.74 | 45.49 | 28.57 | 29.36 |

*Effect of Efavirenz on the PK of Telaprevir*

Steady-state pharmacokinetic parameters for telaprevir were determined without (Day 10) and with (Day 37) coadministration of efavirenz. The pharmacokinetic parameters of telaprevir are summarized in Table 8.

**Table 8 Summary of Pharmacokinetic Parameters of Telaprevir Following Oral Administration Without (Day 10) Efavirenz and With (Day 37) Efavirenz**

| Day | Parameter | $t_{max}$ (hr) | $C_{max}$ (ng/mL) | $C_{min}$ (ng/mL) | $AUC_{0\text{-}8}$ (hr*ng/mL) | CL/F (L/hr) |
|---|---|---|---|---|---|---|
| 10 | N | 25 | 25 | 25 | 24 | 24 |
| | Mean | 3.64 | 2477.60 | 1283.84 | 15274.84 | 52.82 |
| | SD | 1.14 | 632.09 | 451.97 | 4302.86 | 14.28 |
| | Min | 2.00 | 1650.00 | 716.00 | 9033.23 | 31.56 |
| | Median | 4.00 | 2360.00 | 1100.00 | 14245.79 | 52.66 |
| | Max | 6.00 | 3820.00 | 2340.00 | 23765.84 | 83.03 |
| | CV% | 31.23 | 25.51 | 35.20 | 28.17 | 27.04 |
| 37 | N | 21 | 21 | 21 | 21 | 21 |
| | Mean | 2.40 | 2297.24 | 744.72 | 11523.16 | 72.33 |
| | SD | 0.54 | 626.68 | 351.63 | 3662.77 | 28.70 |
| | Min | 2.00 | 942.00 | 95.10 | 4148.08 | 38.17 |
| | Median | 2.00 | 2210.00 | 671.00 | 10598.44 | 70.77 |
| | Max | 3.50 | 3490.00 | 1650.00 | 19647.99 | 180.81 |
| | CV% | 22.26 | 27.28 | 47.22 | 31.79 | 39.68 |

The pharmacokinetic parameters for VRT-127394 on Days 10 and 37 are summarized in Table 9.

**Table 9 Summary of Pharmacokinetic Parameters of VRT-127394 Following Oral Administration of Telaprevir Without (Day 10) Efavirenz and With (Day 37) Efavirenz**

| Day | Parameter | $t_{max}$ (hr) | $C_{max}$ (ng/mL) | Cmin (ng/mL) | $AUC_{0-8}$ (hr*ng/mL) | %total exposure attributable to telaprevir |
|---|---|---|---|---|---|---|
| 10 | N | 25 | 25 | 25 | 24 | 24 |
| | Mean | 4.02 | 1389.52 | 932.92 | 9485.04 | 61.69 |
| | SD | 1.19 | 392.04 | 346.57 | 2839.79 | 3.07 |
| | Min | 0.00 | 916.00 | 520.00 | 5748.28 | 55.95 |
| | Median | 4.00 | 1290.00 | 860.00 | 8991.59 | 61.91 |
| | Max | 6.00 | 2410.00 | 1730.00 | 16752.21 | 66.64 |
| | CV% | 29.70 | 28.21 | 37.15 | 29.94 | 4.97 |
| 37 | N | 21 | 21 | 21 | 21 | 21 |
| | Mean | 3.41 | 1041.38 | 506.04 | 6255.63 | 65.05 |
| | SD | 0.60 | 308.78 | 234.78 | 2127.91 | 3.97 |
| | Min | 2.00 | 312.00 | 46.80 | 1468.67 | 58.03 |
| | Median | 3.50 | 1030.00 | 460.00 | 5986.20 | 64.83 |
| | Max | 4.00 | 1870.00 | 1040.00 | 11898.58 | 73.85 |
| | CV% | 17.60 | 29.65 | 46.40 | 34.02 | 6.11 |

The GLS mean ratio and the 90% CI for orally administered telaprevir with and without coadministration of efavirenz are shown in Table 10. The data indicated that efavirenz lowers the $C_{min}$ of telaprevir by approximately 46%, $C_{max}$ by 9% and $AUC_{0-8}$ by 26%. The GLS mean ratio $C_{max}$ is within the 80-125% range, indicating that the $C_{max}$ of telaprevir is not affected by coadministration with efavirenz. Efavirenz lowers the $C_{min}$ of VRT-127394 by approximately 50%, $C_{max}$ by 27% and $AUC_{0-8}$ by 36%.

**Table 10 Geometric Least Square Means Ratio and 90% Confidence Intervals for Telaprevir and VRT-127394 Exposure Following Oral Administration of TelaprevirWithout and With the Administration of Efavirenz**

| Comparison | Parameter | GLS Mean Ratio (%) | 90% Confidence Interval |
|---|---|---|---|
| Telaprevir withEfavirenz/ Telaprevir without Efavirenz | $AUC_{0-8}$ | 73.96 | 65.20, 83.90 |
| | $C_{min}$ | 53.47 | 43.77, 65.32 |
| | $C_{max}$ | 91.32 | 81.45, 102.39 |
| VRT-127394 withEfavirenz/ VRT127394 without Efavirenz | $AUC_{0-8}$ | 63.79 | 54.90, 74.13 |
| | $C_{min}$ | 49.53 | 39.60, 61.95 |
| | $C_{max}$ | 73.12 | 64.47, 82.93 |

*Effect of Telaprevir on the PK of Efavirenz*

Efavirenz was administered orally to subjects without (Day 27) and with (Day 37) treatment with telaprevir. The pharmacokinetic parameters of efavirenz are summarized in Table 11.

**Table 11 Summary of Pharmacokinetic Parameters of Efavirenz Following Oral Administration Without (Day 27) Telaprevir and With (Day 37) Telaprevir**

| Day | Parameter | $t_{max}$ (hr) | $C_{max}$ (ng/mL) | $C_{min}$ (ng/mL) | $AUC_{0-24}$ (hr*ng/mL) | $CL_{ss}/F$ (L/hr) |
|---|---|---|---|---|---|---|
| 27 | N | 21 | 21 | 21 | 21 | 21 |
| | Mean | 2.72 | 3996.67 | 1641.91 | 57117.97 | 11.76 |
| | SD | 1.42 | 964.10 | 655.51 | 19574.46 | 4.04 |
| | Min | 1.00 | 2490.00 | 607.00 | 30426.53 | 6.06 |
| | Median | 2.00 | 3700.00 | 1650.00 | 56805.82 | 10.56 |
| | Max | 8.00 | 5860.00 | 3000.00 | 99077.81 | 19.72 |
| | CV% | 52.27 | 24.12 | 39.92 | 34.27 | 34.36 |
| 37 | N | 21 | 21 | 21 | 21 | 21 |
| | Mean | 2.82 | 3432.86 | 1635.71 | 53550.66 | 12.92 |
| | SD | 0.80 | 1018.87 | 738.16 | 20034.59 | 5.30 |
| | Min | 2.00 | 1690.00 | 554.00 | 21677.56 | 6.06 |
| | Median | 3.00 | 3370.00 | 1630.00 | 50288.62 | 11.93 |
| | Max | 4.92 | 4920.00 | 3330.00 | 98939.95 | 27.68 |
| | CV% | 28.31 | 29.68 | 45.12 | 37.41 | 40.99 |

The GLS mean ratio and the 90% CI for orally administered efavirenz before and after treatment with telaprevir are shown in Table 12. The GLS mean ratios for $AUC_{0-24}$, and $C_{min}$ are within the 80-125% range, indicating that telaprevir does not affect these pharmacokinetic parameters of efavirenz. However, $C_{max}$ is decreased by approximately 16%. The effect is not expected to be clinical significant

**Table 12 Geometric Least Square Means Ratio and 90% Confidence Intervals for Efavirenz Exposure Following Oral Administration, Without and With the Administration of Telaprevir**

| Comparison | Parameter | GLS Mean Ratio (%) | 90% Confidence Interval |
|---|---|---|---|
| Efavirenz with Telaprevir/ Efavirenz withpout Telaprevir | $AUC_{0-24}$ | 92.58 | 87.16, 98.34 |
| | Cmin | 97.66 | 93.70, 101.78 |
| | $C_{max}$ | 84.12 | 76.43, 92.58 |

*Circadian Effects on Telaprevir Concentrations*

Blood samples were obtained prior to the administration of telaprevir (Day 9) and prior to the coadministration of telaprevir and efavirenz (Day 36) before the morning, afternoon and evening doses to evaluate the circadian effect on the concentration of telaprevir. The mean plasma concentration for telaprevir on those days is summarized in Table 13. The GLS mean ratio and the 90% CI for predose plasma concentration telaprevir are shown in Table 14. The data show that there were no circadian effects on telaprevir concentrations except the morning on Day 36. On Day 36, telaprevir (q8h dosing) was administered approximately 3 hours before efavirenz (qd dosing). Therefore, the morning predose concentration of telaprevir may be expected to be less depressed by the effect of efavirenz than the afternoon and evening concentrations.

**Table 13 Summary of Predose Concentrations of Telaprevir Prior to Oral Administration of the Morning, Afternoon and Evening Dose**

| Day | Time | N | Mean | SD | Min | Median | Max | CV% |
|---|---|---|---|---|---|---|---|---|
| 9 | Morning | 25 | 1824.00 | 572.13 | 1060.00 | 1790.00 | 3350.00 | 31.37 |
| | Afternoon | 25 | 1704.00 | 588.04 | 837.00 | 1610.00 | 2850.00 | 34.51 |
| | Evening | 25 | 1629.20 | 426.36 | 1050.00 | 1420.00 | 2400.00 | 26.17 |
| 36 | Morning | 21 | 1038.67 | 433.09 | 210.00 | 1050.00 | 2260.00 | 41.70 |
| | Afternoon | 21 | 763.14 | 346.88 | 222.00 | 737.00 | 1700.00 | 45.45 |
| | Evening | 21 | 723.76 | 320.97 | 116.00 | 670.00 | 1350.00 | 44.35 |

**Table 14 Geometric Least Square Means Ratio and 90% Confidence Intervals for Telaprevir Predose Concentrations**

| Day | Comparison | GLS Mean Ratio (%) | 90% Confidence Interval |
|---|---|---|---|
| 9 | Afternoon/ Morning | 92.05 | 87.02, 97.37 |
| | Evening/ Morning | 90.27 | 85.34, 95.49 |
| | Evening/ Afternoon | 98.07 | 92.71, 103.74 |
| 36 | Afternoon/ Morning | 72.55 | 64.92, 81.07 |
| | Evening/ Morning | 68.20 | 61.03, 76.22 |
| | Evening/ Afternoon | 94.01 | 84.13, 105.06 |

Safety

Telaprevir was well tolerated in healthy adult subjects when administered as a single 750-mg dose alone or in combination with rifampin (600 mg qd; Part 1) or as 750 mg q8h for 10 days alone or in combination with efavirenz (600 mg qd; Part 2). There were no SAEs reported during the study.

**Conclusion:**

- Co-administration of telaprevir and rifampin resulted in decreased telaprevir exposure: AUC0-∞ of telaprevir was reduced by approximately 92% and Cmax was reduced by approximately 86%. Therefore, telaprevir should not coadministered with rifampin.
- Co-administration of telaprevir and efavirenz resulted in a 46% decrease in steady-state Cmin and a 26% decrease in steady-state AUC of telaprevir compared with telaprevir administered alone. Dose increase of telaprevir may be needed when telaprevir is coadministered with efavirenz. Telaprevir has not clinically significant effect on efavirenz PK.
- There did not appear to be a clinically relevant effect of the time of telaprevir administration (morning, afternoon, evening) on the pre-dose concentrations of telaprevir.

**An Open-Label Phase 1 Study in Healthy Subjects to Examine the Effects of Telaprevir (VX-950) on the Pharmacokinetics of 5-mg Amlodipine and 20-mg Atorvastatin (Caduet®)**

**Individual Study Review—VX07-950-018**

**Objectives:**

Primary:

- To evaluate the effect of telaprevir on a single dose of Caduet (5-mg amlodipine and 20-mg atorvastatin)

Secondary:

- To compare the pharmacokinetics of the ortho- and parahydroxylated metabolites of atorvastatin before and after the administration of 750-mg telaprevir q8h
- To determine the safety of 750-mg telaprevir q8h when coadministered with amlodipine and atorvastatin
- To determine the pharmacokinetics of telaprevir and VRT-127394 when coadministered with amlodipine and atorvastatin

**Study Rationale:** Amlodipine, a dihydropyridine calcium channel antagonist used to treat high blood pressure and angina or coronary artery disease, and atorvastatin, a hepatic hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase inhibitor used to lower high cholesterol and reduce the risk of heart attack and stroke, are both extensively metabolized by CYP3A4. Atorvastatin is extensively metabolized by cytochrome P450 3A4 to active ortho- and parahydroxylated derivatives and various beta-oxidation products. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. These drugs are frequently prescribed for patients with chronic HCV infection. Because telaprevir is a CYP3A4 inhibitor, telaprevir may reduce the metabolism of amlodipine and atorvastatin, resulting in increased plasma concentrations of amlodipine and atorvastatin.

**Study Population:** A total of 21 healthy subjects were enrolled, received at least 1 dose of study drug (Caduet or telaprevir). Seventeen subjects completed all dosing periods. Four subjects discontinued prematurely because of withdrawal of consent (2 subjects), an adverse event (1 subject), and other reasons (1 subject).

**Study Design:** This was an open-label, nonrandomized, single-center study. The dosing period consisted of 3 separate regimens: Caduet alone (Day 1), telaprevir alone (Days 11 through 16), and telaprevir with Caduet on Day 17 followed by telaprevir on Days 18 through 26. Telaprevir and Caduet were administered in fed state.

**Formulation:**

Telaprevir: 375 mg tablets, Batch No. 3060433R
Caduet: tablets containing 5-mg amlodipine and 20-mg atorvastatin per tablet, Batch No. 0304047

**Pharmacokinetic Sampling:** Blood/plasma samples were collected for the analysis of pharmacokinetics of telaprevir analytes (telaprevir and VRT-127394) and Caduet analytes (amlodipine, atorvastatin, and ortho- and parahydroxylated metabolites of atorvastatin). Single

pharmacokinetic samples were collected on Days 2, 3, 4, 6, 8, and 11 (Caduet analytes); Days 15 and 16 (telaprevir analytes); Days 18, 19, 20 (Caduet analytes); Days 22, 24, and 27 (Caduet and telaprevir analytes).

**Analytical Method:** VX-950 (telaprevir), VRT-127394, amlodipine, atorvastatin, and ortho- and parahydroxylated metabolites of atorvastatin human plasma samples were analyzed by validated LC/MS/MS methods. The standard curve and QC data indicated that the plasma assay methods for VX-950 (telaprevir), VRT-127394, amlodipine, atorvastatin, and ortho- and parahydroxylated metabolites of atorvastatin were precise and accurate as shown in the following table. The Applicant indicated that the storage stability longer than that of the study samples from collection to analysis.

**Table 1 Summary of Quality Control (QC) Results**

| Analyte | Linear range (ng/mL) | Between Run Precision (%CV) | Between Run Bias (% Deviation) | QC samples (ng/mL) | Validation sample for stability and conditions |
|---|---|---|---|---|---|
| telaprevir | 2 – 1000 (V9LHPP) $R^2 \geq 0.995$ | ≤ 6.6 | -4.2 to 3.9 | 6.0, 250, 750 and 8000 (10-fold dilution) | Stable for at least 6 months at -70°C |
| VRT-127394 | 2 – 1000 (V9LHPP) $R^2 > 0.992$ | ≤ 8.1 | -1.6 to 1.6 | 6.0, 250, 750 and 8000 (10-fold dilution) | Stable for at least 6 months at -70°C |
| amlodipine | 0.05 to 25.0 $R^2 \geq 0.996$ | ≤ 6.2 | 0.7 to 1.1 | 0.15, 2.00, and 18.0 | Stable for at least 50 days at -70°C |
| atorvastatin | 0.25 – 100 $R^2 \geq 0.996$ | ≤ 5.8 | -0.1 to 3.9 | 0.75, 20.0 and 75.0 | Stable for at least 219 days at -70°C |
| p-hydroxy atorvastatin | 0.25 – 100 $R^2 \geq 0.996$ | ≤ 4.7 | -4.3 to -2.1 | 0.75, 20.0 and 75.0 | |
| o-hydroxy atorvastatin | 0.25 – 100 $R^2 \geq 0.996$ | ≤ 4.1 | 2.0 to 3.3 | 0.75, 20.0 and 75.0 | |

**Results**

Pharmacokinetics

*Amlodipine*

The pharmacokinetic parameters estimated for amlodipine on Day 1 and Day 17 are summarized in Table 2. The geometric least square (GLS) mean ratio and its 90% confidence intervals for amlodipine with and without telaprevir coadministration are shown in Table 3. These results show that coadministration of telaprevir increased amlodipine concentrations significantly when both drugs are coadministered orally.

**Table 2 Summary of Pharmacokinetic Parameters of Amlodipine Following Oral Administration of Caduet Without Telaprevir (Day 1) and With Telaprevir (Day 17)**

| Day | | Half-life[A] (hr) | $T_{max}$ (hr) | $C_{max}$ (ng/mL) | $AUC_{last}$ (hr·ng/ML) | $AUC_{inf}$[a] (hr·ng/mL) | V/F[a] (L) | Cl/F[a] (L/hr) |
|---|---|---|---|---|---|---|---|---|
| DAY 1 (-TVR) | N | 21 | 21 | 21 | 21 | 21 | 21 | 21 |
| | Mean | 41.30 | 7.53 | 2.75 | 135.56 | 142.10 | 2190.61 | 38.01 |
| | SD | 8.20 | 1.66 | 0.74 | 36.71 | 37.44 | 521.46 | 11.81 |
| | Min | 26.90 | 6.00 | 1.58 | 67.36 | 72.32 | 1445.80 | 23.43 |
| | Median | 40.93 | 8.00 | 2.65 | 143.82 | 148.96 | 2082.84 | 33.57 |
| | Max | 56.73 | 12.00 | 4.02 | 206.53 | 213.44 | 3060.15 | 69.14 |
| | CV% | 19.90 | 22.10 | 27.10 | 27.10 | 26.30 | 23.80 | 31.10 |
| DAY 17 (+TVR) | N | 19 | 19 | 19 | 19 | 19 | 19 | 19 |
| | Mean | 95.06 | 11.14 | 3.55 | 345.87 | 425.31 | 1644.62 | 12.29 |
| | SD | 23.62 | 5.22 | 0.87 | 71.07 | 82.67 | 377.60 | 2.97 |
| | Min | 59.38 | 4.00 | 2.21 | 218.70 | 250.56 | 961.18 | 9.45 |
| | Median | 95.15 | 12.00 | 3.36 | 327.53 | 435.05 | 1711.37 | 11.49 |
| | Max | 143.45 | 23.85 | 5.17 | 463.15 | 529.02 | 2197.46 | 19.96 |
| | CV% | 24.80 | 46.90 | 24.40 | 20.50 | 19.40 | 23.00 | 24.20 |

[a] Numbers of subjects whose extrapolated component of $AUC_{inf}$ was over 25% were 0/21 and 5/19 for Day 1 and Day 17, respectively. Thus interpretation of these parameters should be made with caution.

**Table 3 Geometric Least Square Mean Ratios and 90% Confidence Intervals for Amlodipine Exposure Following Oral Administration Without and With Coadministration of Telaprevir**

| Parameter | N | Geometric Mean | | GLS Mean Ratio % | 90% CI Lower | 90% CI Upper |
|---|---|---|---|---|---|---|
| | | Day 1 | Day 17 | | | |
| $C_{max}$ | 19 | 2.73 | 3.46 | 126.77 | 121.15 | 132.64 |
| $AUC_{last}$ | 19 | 135.23 | 338.74 | 250.49 | 233.47 | 268.74 |
| $AUC_{inf}$ | 14 | 141.98 | 395.66 | 278.66 | 258.15 | 300.81 |

*Atorvastatin and its metabolites*

The PK parameters estimated from the noncompartmental analysis with imputed data for atorvastatin on Day 1 and Day 17 are summarized in Table 4. The GLS mean ratio and its 90% confidence intervals for atorvastatin with and without telaprevir coadministration are shown in Table 5. The data show that telaprevir increased atorvastatin Cmax and AUC by 10- and 8-fold when telaprevir and atorvastatin was coadministered.

**Table 4 Summary of Pharmacokinetic Parameters of Atorvastatin Following Oral Administration of Caduet Without Telaprevir (Day 1) and With Telaprevir (Day 17)**

| Day | | Half-life[A] (hr) | $T_{max}$ (hr) | $C_{max}$ (ng/mL) | $AUC_{last}$ (hr·ng/ML) | $AUC_{inf}$[a] (hr·ng/mL) | V/F[a] (L) | Cl/F[a] (L/hr) |
|---|---|---|---|---|---|---|---|---|
| DAY 1 (-TVR) | N | 21 | 21 | 21 | 21 | 21 | 21 | 21 |
| | Mean | 9.44 | 2.00 | 3.50 | 32.06 | 33.76 | 8983.67 | 684.53 |
| | SD | 2.64 | 1.21 | 1.93 | 13.54 | 13.58 | 3430.65 | 272.01 |
| | Min | 4.49 | 0.75 | 1.42 | 13.25 | 14.33 | 3424.43 | 292.19 |
| | Median | 9.75 | 1.50 | 3.02 | 28.15 | 30.18 | 9639.14 | 662.78 |
| | Max | 13.49 | 6.00 | 8.15 | 66.98 | 68.45 | 15189.94 | 1395.67 |
| | CV% | 28.00 | 60.60 | 55.30 | 42.20 | 40.20 | 38.20 | 39.70 |
| DAY 17 (+TVR) | N | 19 | 19 | 19 | 19 | 19 | 19 | 19 |
| | Mean | 6.75 | 2.90 | 38.45 | 275.77 | 276.99 | 838.14 | 83.83 |
| | SD | 1.55 | 0.79 | 20.03 | 115.77 | 115.65 | 404.78 | 32.72 |
| | Min | 4.99 | 1.50 | 10.80 | 124.70 | 125.96 | 252.23 | 34.69 |
| | Median | 6.17 | 3.00 | 40.70 | 265.47 | 266.47 | 826.66 | 75.06 |
| | Max | 9.95 | 4.02 | 79.20 | 575.61 | 576.51 | 1603.09 | 158.78 |
| | CV% | 22.90 | 27.40 | 52.10 | 42.00 | 41.80 | 48.30 | 39.00 |

[a] The terminal half-life was estimated using imputed data by replacing the first BQL after $C_{last}$ with half of the LLOQ. Thus interpretation of these parameters should be made with caution.

**Table 5 Geometric Least Square Means Ratio and 90% Confidence Intervals for Atorvastatin Exposure Following Oral Administration Without and With Coadministration of Telaprevir**

| Parameter | N | Geometric Mean | | GLS Mean Ratio % | 90% CI Lower | 90% CI Upper |
|---|---|---|---|---|---|---|
| | | Day 1 | Day 17 | | | |
| $C_{max}$ | 19 | 3.13 | 33.14 | 1059.73 | 874.18 | 1284.66 |
| $AUC_{last}$ | 19 | 30.80 | 255.29 | 828.79 | 720.36 | 953.54 |
| $AUC_{inf}$ | 19 | 32.59 | 256.64 | 787.53 | 683.80 | 906.99 |

Ortho-hydroxy Atorvastatin PK parameters are reported in Table 6. It should be noted that coefficients of variation (CV) for all parameters, $C_{max}$, $AUC_{last}$ and $AUC_{0-\infty}$ on Day 17 are quite large. Nonetheless, the median $C_{max}$ of ortho-hydroxy atorvastatin decreased with telaprevir coadministration by approximately 75%, and the median $AUC_{last}$ decreased approximately by 80%.

*Reviewer's comment: Atorvastatin and ortho-hydroxy atorvastatin are both OATP1B1 substrates. If telaprevir is a potent OATB1B1 inhibitor, we should see concentrations of both atorvastatin and ortho-hydroxy atorvastatin increased when atorvastatin is coadministered with telaprevir. Contrarily, the magnitude of the increase on atorvastatin concentrations by telaprevir is about the same as the magnitude of the decrease on ortho-hydroxy atorvastatin by telaprevir. These results indicate that the effect of telaprevir on atorvastatin is mostly through CYP3A inhibition.*

Most of the concentrations of para-hydroxy atorvastatin were below the LLOQ, especially for data from Day 1. Only 2 subjects showed detectable concentrations of para-hydroxy atorvastatin on Day 1. A noncompartmental analysis based on the data with imputation for the first BQL with half of the LLOQ, showed that the median $C_{max}$ of para-hydroxy atorvastatin increased with telaprevir coadministration from 0.42 ng/mL (Day 1) to 1.01 ng/mL, and the median $AUC_{last}$ increased from 8.33 hr·ng/mL to 17.49 hr·ng/mL. However, these results should be interpreted with caution

These results indicate a significant effect of telaprevir on the inhibition of atorvastatin metabolism.

**Table 6 Summary of Pharmacokinetic Parameters of Ortho-Hydroxy Atorvastatin Following Oral Administration of Caduet Without (Day 1) and With (Day 17) Telaprevir**

| Day | | Half-life[a] (hr) | $T_{max}$ (hr) | $C_{max}$ (ng/mL) | $AUC_{last}$ (hr·ng/ML) | $AUC_{inf}$[a] (hr·ng/mL) |
|---|---|---|---|---|---|---|
| DAY 1 (-TVR) | N | 21 | 21 | 21 | 21 | 21 |
| | Mean | 10.16 | 3.64 | 2.95 | 40.26 | 42.09 |
| | SD | 1.57 | 1.82 | 1.07 | 12.75 | 12.76 |
| | Min | 5.84 | 1.50 | 1.47 | 14.81 | 15.86 |
| | Median | 10.08 | 4.00 | 2.80 | 38.17 | 40.07 |
| | Max | 13.77 | 10.00 | 5.47 | 66.87 | 68.34 |
| | CV% | 15.40 | 49.90 | 36.20 | 31.70 | 30.30 |
| DAY 17 (+TVR) | N | 17 | 19 | 19 | 19 | 17 |
| | Mean | 8.53 | 5.43 | 1.04 | 10.41 | 12.64 |
| | SD | 2.36 | 2.83 | 1.44 | 10.40 | 10.50 |
| | Min | 3.50 | 3.00 | 0.30 | 0.55 | 6.73 |
| | Median | 8.90 | 4.00 | 0.72 | 7.45 | 9.08 |
| | Max | 13.23 | 12.00 | 6.77 | 46.79 | 47.43 |
| | CV% | 27.60 | 52.20 | 138.80 | 99.90 | 83.10 |

[a] Numbers of subjects whose extrapolated component of $AUC_{inf}$ was over 25% were 0/21 and 4/19 for Day 1 and Day 17, respectively. Furthermore, the AUC calculation was performed using imputed data by replacing the first BQL after $C_{last}$ with half of the LLOQ. Thus interpretation of these parameters should be made with caution.

*Telaprevir and VRT-127394*

The PK parameters for VX-950 and VRT-127394 on Day 17 are summarized in Table 7. These PK parameters of VX-950 and VRT-127394 on Days 17 were generally similar to the telaprevir steady-state estimates obtained from other studies in healthy volunteers.

**Table 7 Summary of Pharmacokinetic Parameters of VX-950 and VRT-127394 Following Oral Administration of Telaprevir on Day 17**

| Analyte | | $T_{max}$ (hr) | $C_{max}$ (ng/mL) | $AUC_{last}$ (hr·ng/mL) | $C_{min}$ (ng/mL) |
|---|---|---|---|---|---|
| VX-950 | N | 19 | 19 | 19 | 19 |
| | Mean | 2.66 | 3166.84 | 20470.55 | 1981.05 |
| | SD | 1.02 | 778.23 | 5317.30 | 660.03 |
| | Min | 1.00 | 2040.00 | 13663.79 | 1050.00 |
| | Median | 3.00 | 3090.00 | 19809.27 | 1960.00 |
| | Max | 4.02 | 5130.00 | 33740.62 | 3460.00 |
| | CV% | 38.2 | 24.6 | 26.0 | 33.3 |
| VRT-127394 | N | 19 | 19 | 19 | 19 |
| | Mean | 2.70 | 2075.79 | 14142.67 | 1460.74 |
| | SD | 1.48 | 643.42 | 4342.44 | 458.78 |
| | Min | 0.75 | 1210.00 | 8678.74 | 741.00 |
| | Median | 3.00 | 1940.00 | 13274.77 | 1510.00 |
| | Max | 6.00 | 3530.00 | 24397.30 | 2370.00 |
| | CV% | 54.6 | 31.0 | 30.7 | 31.4 |

Safety

While the overall highest frequency of subjects reporting adverse events occurred during the telaprevir-Caduet dosing period, also the longest dosing period, combination dosing did not result in any new or otherwise relevant safety findings. There were no deaths or SAEs reported during the study.

**Conclusion:**

- Coadministration of telaprevir significantly increases exposure (Cmax and AUC) of amlodipine and atorvastatin, and significantly decreases at least one of the active metabolites of atorvastatin, probably due to telaprevir inhibition of CYP3A isozyme.
- Amlodipine and atorvastatin should be used with caution (dose reduction or close monitoring for adverse events) when patients are receiving telaprevir concomitantly.
- There were insufficient data to conclude whether coadministration of these drugs significantly affects telaprevir exposure.

**An Open-Label Phase 1 Study to Examine the Effect of Telaprevir on the Pharmacokinetics of Zolpidem and Alprazolam in Healthy Subjects**

**Individual Study Review—VX09-950-019**

**Objectives:**

- To evaluate the effect of telaprevir at steady state on single-dose pharmacokinetics (PK) of zolpidem (5 mg PO) in healthy subjects
- To evaluate the effect of telaprevir at steady state on single-dose PK of alprazolam (0.5 mg PO) in healthy subjects

**Study Rationale:** Zolpidem and alprazolam are widely used in the HCV-infected patient population. Zolpidem is a short-acting (mean half-life of 2.6 hours) imidazopyridine hypnotic that is mainly metabolized by CYP3A4. Alprazolam is a benzodiazepine that also is almost exclusively metabolized by CYP3A4 with half-lif of 13 hours. Telaprevir is a CYP3A4 inhibitor, and thus there is a drug-drug interaction potential when telaprevir is coadministered with zolpidem and alprazolam

**Study Population:** A total of 40 healthy subjects (20 per group) were enrolled. A total of 19 subjects in Group 1 and 16 subjects in Group 2 completed the study. In Group 1, 1 subject prematurely discontinued because consent was withdrawn. In Group 2, 4 subjects prematurely discontinued because of adverse events (2 subjects), withdrawn consent (1 subject), and a positive drug screen (1 subject). The PK analyses included 20 subjects in Group 1 and 20 subjects in Group 2.

**Study Design:** This was an open-label, single-center, non-randomized, drug-drug interaction (DDI), crossover study. Subjects were enrolled in 2 groups. Dosing schemes are shown in Tables 1 and 2.

**Table 1 Dosing Schematic for Group 1**

| | Study Day | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Event | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 |
| Zolpidem | X | -- | -- | -- | X | -- | -- | -- | -- | -- | -- | -- | -- | -- | X | -- |
| Telaprevir | -- | -- | -- | -- | X | X | X | X | X | X | X | X | X | X | X | -- |

**Table 2 Dosing Schematic for Group 2**

| | Study Day | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Event | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
| Alprazolam | X | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | X | -- | -- | -- | -- |
| Telaprevir | -- | -- | -- | -- | -- | -- | X | X | X | X | X | X | X | X | X | X | X | X | X | X | -- |

Telaprevir (750 mg q8h PO), zolpidem (5 mg PO) and alprazolam were administered was administered in the fed state.

**Formulation:**
Telaprevir: 375 mg tablets, Batch No. 3060433R
Zolpidem: 5 mg tablets, Batch No. YK05T
Alprazolam: 0.5 mg tablets, Batch No. C070430

**Pharmacokinetic Sampling:**
**Group 1**:
Zolpidem (5 mg PO): Days 1, 5, and 15: 0 (predose), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, and 24 hours postdose
Telaprevir (750 mg q8h PO):
Days 5 and 15: 0 (predose), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 8 hours postdose
Days 13 and 14: immediately prior to breakfast and prior to morning dose of telaprevir
Day 16: 8 hours after the evening dose on Day 15 (immediately prior to breakfast and at the same time as the 24 hour zolpidem sample)
**Group 2**:
Alprazolam (0.5 mg PO):
Days 1 and 17: 0 (predose), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 48, 72, and 96 hours postdose.
Telaprevir (750 mg q8h PO):
Day 17: 0 (predose), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 8 hours postdose
Days 15 and 16: immediately prior to breakfast and prior to morning dose of telaprevir
Days 18, 19, 20, and 21: 8 hours after the evening dose on the day prior the sampling day (immediately prior to breakfast and at the same time as the alprazolam samples). On Days 18, 19 and 20, these samples will be collected immediately prior to breakfast and prior to the morning dose of telaprevir.

**Analytical Method:** VX-950 (telaprevir), VRT-127394, alprazolam, and zolpidem human plasma samples were analyzed by validated LC/MS/MS methods. The standard curve and QC data indicated that the plasma assay methods for X-950 (telaprevir), VRT-127394, alprazolam, and zolpidem were precise and accurate as shown in the following table. The Applicant indicated that the storage stability longer than that of the study samples from collection to analysis. However, alprazolam stability data were not reported.

**Table 2 Summary of Quality Control (QC) Results**

| Analyte | Linear range (ng/mL) | Between Run Precision (%CV) | Between Run Bias (% Deviation) | QC samples (ng/mL) | Validation sample for stability and conditions |
|---|---|---|---|---|---|
| telaprevir | 2 – 1000 (V9LHPP) $R^2$> 0.995 | ≤ 6.5 | -0.9 to 5.4 | 6.0, 250, 750, 8000 (10x dilution), and 8000 (10x dilution) | Stable for at least 6 months at -70°C |
| VRT-127394 | 2 – 1000 (V9LHPP) $R^2$ > 0.993 | ≤ 7.4 | -6.0 to -1.8 | 6.0, 250, 750, 8000 (10x dilution), and 8000 (10x dilution) | Stable for at least 6 months at -70°C |
| alprazolam | 0.05 to 25.0 $R^2$> 0.997 | ≤ 5.0 | -1.0 to 4.7 | 0.3, 5.0, and 75.0 | NA |
| zolpidem | 0.25 – 100 $R^2$ > 0.998 | ≤ 3.7 | -2.4 to 1.5 | 1.5, 25.0, 200 and 1250 (10x dilution) | Stable for at least 97 days at -70°C |

**Results**

Pharmacokinetic
*Group 1: Zolpidem*

The mean (SD) of zolpidem PK parameters generated from noncompartmental analysis are shown in Table 3. Subject 01-020 had an unusual high zolpidem concentration (11.7 ng/mL) at 24 hours time point (versus 1.15 ng/mL at previous time point of 16 hours) on Day 2. The sample was reassayed and the results were confirmed. The above concentration value was excluded from all PK analyses, which is acceptable.

**Table 3 Mean (SD) of Pharmacokinetic Parameters of Zolpidem Following Treatments**

| Treatment | | $AUC_{0-\infty}$ (ng*hr/mL) | $AUC_{0-last}$ (ng*hr/mL) | CL/F (L/hr) | $C_{max}$ (ng/mL) | $t_{1/2}$ (hr) | $t_{max}$* (hr) | Vz/F (L) |
|---|---|---|---|---|---|---|---|---|
| Zolpidem 5 mg Alone | N | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | MEAN | 368.21 | 342.91 | 18.00 | 58.03 | 4.32 | 2.77 | 95.92 |
| | SD | 217.63 | 173.92 | 10.16 | 18.61 | 1.85 | 0.50, 4.00 | 34.15 |
| Zolpidem 5 mg + Single Dose of Telaprevir 750 mg | N | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | MEAN | 399.28 | 376.30 | 14.86 | 55.7 | 4.80 | 3.00 | 93.94 |
| | SD | 191.12 | 163.19 | 5.65 | 12.57 | 1.43 | 1.00, 4.00 | 22.8 |
| Zolpidem 5 mg + Telaprevir 750 mg q8h for 10 Days | N | 19 | 19 | 19 | 19 | 18 | 19 | 18 |
| | MEAN | 221.13 | 198.25 | 32.85 | 33.28 | 3.37 | 3.00 | 141.57 |
| | SD | 187.92 | 129.44 | 18.71 | 10.55 | 1.24 | 1.00, 4.00 | 30.64 |

*median, minimum, maximum are reported for $t_{max}$

Statistical analysis results of effect of telaprevir on zolpidem exposure are presented in Table 4. The data show that a single dose of telaprevir increased zolpidem AUC by 14% (but not $C_{max}$) but the effect was not likely to be clinically relevant. However, multiple doses of telaprevir significantly decreased the zolpidem $C_{max}$ and $AUC_{0-\infty}$ by approximately 42% and 47%, respectively.

**Table 4 Statistical Analysis of Drug-Drug Interaction Effect of Telaprevir on Zolpidem Exposure**

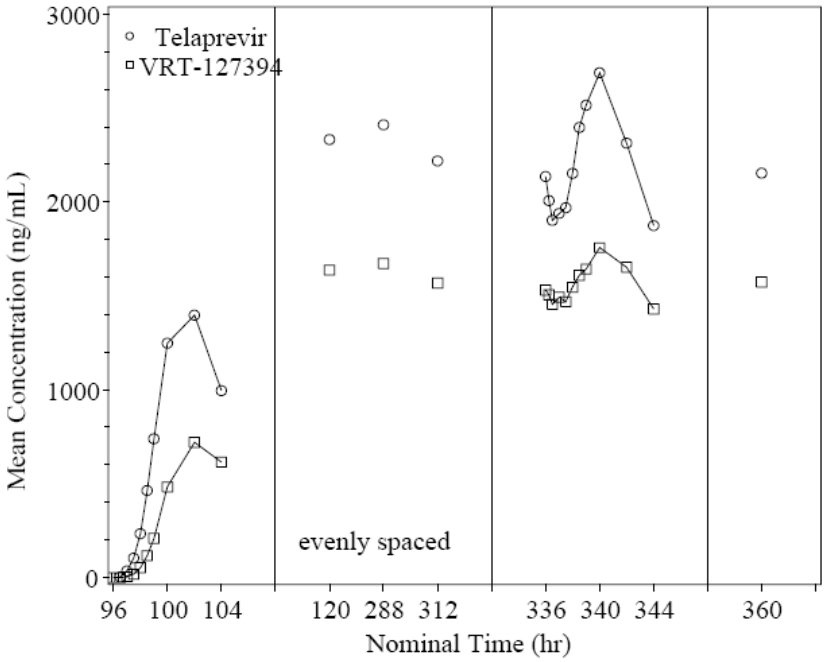
| Parameter | Treatment | Study Day | N | Least Square Means | Ratio* (%) | 90% Confidence Interval |
|---|---|---|---|---|---|---|
| $C_{max\ (ng/mL)}$ | Zolpidem Alone | 1 | 20 | 55.0 | 100 | N/A |
| | Zolpidem + Telaprevir (single dose) | 5 | 20 | 54.4 | 98.9 | 87.5, 112 |
| | Zolpidem + Telaprevir (multiple dose) | 15 | 19 | 32.1 | 58.4 | 51.5, 66.1 |
| $AUC_{0-\infty(hr*ng/mL)}$ | Zolpidem Alone | 1 | 20 | 318.7 | 100 | N/A |
| | Zolpidem + Telaprevir (single dose) | 5 | 20 | 364.1 | 114 | 95.9, 136 |
| | Zolpidem + Telaprevir (multiple dose) | 15 | 19 | 170.1 | 53.4 | 44.5, 64 |
| $AUC_{0-last\ (hr*ng/mL)}$ | Zolpidem Alone | 1 | 20 | 304.8 | 100 | N/A |
| | Zolpidem + Telaprevir (single dose) | 5 | 20 | 347.8 | 114 | 96.7, 135 |
| | Zolpidem + Telaprevir (multiple dose) | 15 | 19 | 169.4 | 55.6 | 46.9, 65.8 |

*Zolpidem 5-mg alone is the reference arm.

*Group 1: Telaprevir and VRT-127394*

Telaprevir and VRT-127394 mean plasma concentration time profiles are presented in Figure 1.

**Figure 1 Mean Telaprevir and VRT-127394 Plasma Concentration Time Profiles in Group 1**



The data show that telaprevir and VRT-127394 $C_{0h}$ concentrations were comparable at steady state when telaprevir was administered alone compared to when it was coadministered with a single dose of zolpidem.

The mean (SD) of PK parameters of telaprevir and VRT-127394 are presented in Table 5.

**Table 5 Mean (SD) of PK Parameters of VRT-127394 and VX-950 in Group 1**

| Analyte | Visit Number | Treatment | | $AUC_{0\text{-last}}$ (ng*hr/mL)[#] | $C_{max}$ (ng/mL) | $t_{max}$* (hr) | $C_{min}$ (ng/mL) |
|---|---|---|---|---|---|---|---|
| VRT-127394 | 5 | Zolpidem + Telaprevir (single dose) | N | 20 | 20 | 20 | |
| | | | MEAN | 2970.46 | 779.00 | 6.00 | N/A |
| | | | SD | 1445.32 | 331.16 | 4.00, 7.92 | |
| | 15 | Zolpidem + Telaprevir (multiple dose) | N | 19 | 19 | 19 | 19 |
| | | | MEAN | 12650.96 | 1827.89 | 4.00 | 1304.11 |
| | | | SD | 2458.15 | 334.01 | 0.00, 7.92 | 286.86 |
| Telaprevir | 5 | Zolpidem + Telaprevir (single dose) | N | 20 | 20 | 20 | |
| | | | MEAN | 6490.18 | 1644.95 | 4.00 | N/A |
| | | | SD | 2811.74 | 666.08 | 2.50, 7.92 | |
| | 15 | Zolpidem + Telaprevir (multiple dose) | N | 19 | 19 | 19 | 19 |
| | | | MEAN | 17939.93 | 2815.79 | 4.00 | 1753.16 |
| | | | SD | 3287.59 | 540.13 | 0.00, 6.00 | 412.41 |

*median, minimum, maximum is reported for $t_{max}$
[#]nominal tlast is 8 hours for $AUC_{0\text{-last}}$

The telaprevir and VRT-127394 exposures ($C_{max}$ and $AUC_{0\text{-last}}$) at Days 5 and 15 were similar to that in other Phase 1 studies. Therefore, zolpidem is unlikely to affect telaprevir and VRT-127394 pharmacokinetics.

*Group 2: Alprazolam*

The mean (SD) of PK parameters generated from noncompartmental analysis of alprazolam plasma concentration data are shown in Table 6.

**Table 6 Mean (SD) Pharmacokinetic Parameters of Alprazolam Following Treatments**

| Visit | Treatment | | $AUC_{0\text{-}\infty}$ (ng*hr/mL) | $AUC_{0\text{-last}}$ (ng*hr/m) | CL/F (L/hr) | $C_{max}$ (ng/mL) | $t_{1/2}$ (hr) | $t_{max}$* (hr) | Vz/F (L) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Alprazolam 0.5 mg Alone | N | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | | MEAN | 111.81 | 107.81 | 4.75 | 6.00 | 13.40 | 3.50 | 88.71 |
| | | SD | 30.04 | 29.1 | 1.18 | 1.27 | 2.94 | 0.50, 10.00 | 16.2 |
| 17 | Alprazolam 0.5 mg + telaprevir 750 mg q8h for 10 Days | N | 17 | 17 | 17 | 17 | 17 | 17 | 17 |
| | | MEAN | 154.98 | 146.63 | 3.61 | 5.86 | 18.70 | 3.00 | 90.81 |
| | | SD | 53.01 | 48.54 | 1.24 | 1.34 | 5.27 | 1.00, 9.95 | 19.42 |

*median, minimum, maximum are reported for $t_{max}$

Statistical analysis results of effect of telaprevir on zolpidem exposure are presented in Table 7.

**Table 7 Statistical Analysis of Drug-drug Interaction Effect of Telaprevir on Alprazolam Exposure**

| Parameters | Treatment | Study Day | N | Least Square Means | Ratio* | 90% CI |
|---|---|---|---|---|---|---|
| $C_{max}$ (ng/mL) | Alprazolam alone | 1 | 20 | 5.87 | 100 | N/A |
| | Alprazolam + Telaprevir | 17 | 17 | 5.70 | 97.1 | 91.6, 103 |
| $AUC_{0-\infty}$ (hr*ng/mL) | Alprazolam alone | 1 | 20 | 108.37 | 100 | N/A |
| | Alprazolam + Telaprevir | 17 | 17 | 146.80 | 135 | 123, 149 |
| $AUC_{0-last}$ (hr*ng/mL) | Alprazolam alone | 1 | 20 | 104.38 | 100 | N/A |
| | Alprazolam + Telaprevir | 17 | 17 | 139.55 | 134 | 121, 147 |

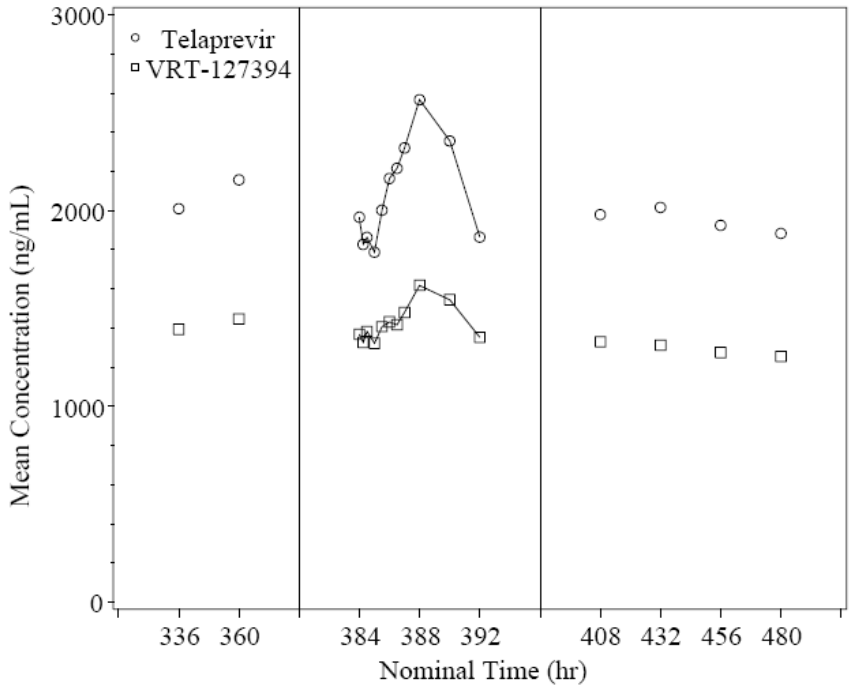
*alprazolam administered alone is the reference arm in denominator

The data show that multiple dose telaprevir increased the alprazolam exposure ($AUC_{0-\infty}$) by approximately 35%, while $C_{max}$ was unchanged. The results suggest that telaprevir tended to impact alprazolam metabolism but not absorption.

*Group 2: Telaprevir and VRT-127394*

Telaprevir and VRT-127394 mean plasma concentration time profiles are presented in Figure 2. The data show telaprevir and VRT-127394 $C_{0h}$ concentrations was comparable at steady state when telaprevir administered alone compared to when it was coadministered with a single dose of alprazolam.

**Figure 2 Mean Telaprevir and VRT-127394 Plasma Concentration Time Profiles in Group 2**




The mean (SD) PK parameters of telaprevir and VRT-127394 are presented in Table 8. The telaprevir and VRT-127394 exposures ($C_{max}$ and $AUC_{0\text{-last}}$) at Days 5 and 15 were similar to that in other Phase 1 studies. Therefore, alprazolam is unlikely to affect telaprevir and VRT-127394 pharmacokinetics.

**Table 8 Mean (SD) of Telaprevir and VRT-127394 PK Parameters for Group 2**

| Analyte | Visit | Treatment | | $AUC_{0\text{-last}}$ (ng*hr/mL)# | $C_{max}$ (ng/mL) | $t_{max}$* (hr) | $C_{min}$ (ng/mL) |
|---|---|---|---|---|---|---|---|
| VRT-127394 | 17 | Alprazolam + Telaprevir | N | 17 | 17 | 17 | 17 |
| | | | MEAN | 11654.54 | 1752.82 | 4.00 | 1212.82 |
| | | | SD | 3294.97 | 517.21 | 0.00, 6.00 | 401.52 |
| Telaprevir | | | N | 17 | 17 | 17 | 17 |
| | | | MEAN | 17427.12 | 2775.29 | 4.00 | 1657.12 |
| | | | SD | 4972.73 | 829.94 | 0.00, 6.00 | 530.46 |

*median, minimum, maximum is reported for $t_{max}$; nominal tlast was 8 hours for $AUC_{0\text{-last}}$

Safety

During the study, there were no deaths or SAEs reported. In Group 2, 2 subjects discontinued dosing during the telaprevir-alone dosing period (Days 14 and 15). The reasons were pharyngolaryngeal pain in 1 subject, and abnormal laboratory findings in 1 subject (increased blood creatine phosphokinase, increased blood lactate dehydrogenase, and increased transaminases). These adverse events, all mild or moderate in severity, were considered possibly related to study drug and resolved following the discontinuation of dosing.

Combination dosing with telaprevir and single doses of zolpidem or alprazolam was generally well tolerated and did not result in the occurrence of any new, significant safety findings.

**Discussion:**
Zolpidem is metabolized in vitro in human liver by CYP3A4 and, to a lesser extent, by CYP1A2 and CYP2D6. It was expected that zolpidem exposure would increase with coadministration of CYP3A4 inhibitor telaprevir. However, the exposure of zolpidem was decreased by 42% to 47% (Cmax and AUC0-∞, respectively) when a single dose of zolpidem was coadministered with multiple dose telaprevir. The in vitro studies indicate mild induction of CYP1A activity by telaprevir and VRT-127394. Therefore, the result suggests that after multiple dosing, telaprevir may induce the enzymes responsible, possibly CYP1A2, for zolpidem metabolism. In addition, induction of transports may have involved in telaprevir's induction effect.

**Conclusion:**
- Zolpidem AUC0-∞ (but not Cmax) increased 14% when zolpidem was coadministered with a single dose of telaprevir. The exposure of zolpidem was decreased by 42% to 47% (Cmax and AUC0-∞, respectively) when a single dose of zolpidem was coadministered with multiple dose telaprevir. Increasing the dose may be necessary in subjects experiencing lack of drug effect when zolpidem is coadministered with telaprevir.
- The exposure (AUC0-∞) of alprazolam was increased by 35% when a single dose of alprazolam was coadministered with telaprevir at the steady-state. Caution and/or dose adjustment of alprazolam is recommended when coadministered with telaprevir.

**A Phase I, Open-Label, Randomized, 2-Way Crossover Trial in 2 Parallel Panels of 20 Healthy Subjects Each to Investigate the Pharmacokinetic Interaction between Lopinavir/Ritonavir (LPV/Rtv) and Telaprevir, and between Atazanavir/Ritonavir (ATV/Rtv) and Telaprevir, All at Steady-State**

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**Individual Study Review—VX-950-TiDP24-C122**

**Objectives:**

- To determine the effect of steady-state concentrations of LPV/rtv 400/100 mg twice daily (b.i.d.) on the steady-state pharmacokinetics of telaprevir 750 mg every 8 hours (q8h) and to determine the effect of steady-state concentrations of telaprevir 750 mg q8h on the steady-state pharmacokinetics of LPV/rtv 400/100 mg b.i.d.;
- To determine the effect of steady-state concentrations of ATV/rtv 300/100 mg once daily (q.d.) on the steady-state pharmacokinetics of telaprevir 750 mg q8h and to determine the effect of steady-state concentrations of telaprevir 750 mg q8h on the steady-state pharmacokinetics of ATV/rtv 300/100 mg q.d.;
- To compare the steady-state pharmacokinetics of telaprevir 750 mg q8h versus telaprevir 750 mg every 12 hours (q12h), when coadministered with either steady-state LPV/rtv 400/100 mg b.i.d or with ATV/rtv 300/100 mg q.d..

**Study Rationale:** The combination of LPV/rtv or ATV/rtv inhibits CYP3A4 and P-glycoprotein (P-gp). Telaprevir is a substrate of both CYP3A4 and P-gp, and its pharmacokinetics might thus be altered during coadministration of these HIV protease inhibitors (PIs). Furthermore, inhibition of CYP3A4 by telaprevir could also affect the pharmacokinetics of the LPV and ATV, which are CYP3A4 substrates. The study aimed to assess the 2-way pharmacokinetic interaction between telaprevir at a dose of
750 mg q8h and LPV/rtv 400/100 mg b.i.d. or ATV/rtv 300/100 mg q.d. to provide guidance on dose recommendations for future combined administration of these drugs in the treatment of HCV/HIV co-infected patients.

**Study Population:** A total of 40 healthy subjects were selected and divided over 2 panels of 20 subjects each.

**Study Design:** This was a Phase I, open-label, randomized, 2-way crossover trial in 2 parallel panels of healthy subjects. Subjects in Panel 1will receive Treatment A and Treatment B and subjects in Panel 2 will receive Treatment C and Treatment D, in a randomized way:
Treatment A: Telaprevir 750 mg q8h on Days 1-9 and a morning dose on Day 10;
Treatment B: LPV/rtv 400/100 mg b.i.d. on Days 1 to 23 and a morning dose on Day 24 + Telaprevir 750 mg q8h on Days 11 to 20 + Telaprevir 750 mg q12h on Days 21 to 23 and a morning dose on Day 24;
Treatment C: Telaprevir 750 mg q8h on Days 1-9 and a morning dose on Day 10;
Treatment D: ATV/rtv 300/100 mg q.d. on Days 1 to 24 + Telaprevir 750 mg q8h on Days 11 to 20 + Telaprevir 750 mg q12h on Days 21 to 24

All treatments were administered under fed conditions, except for the intakes of LPV/rtv alone in Treatment B, which can be with or without food. Subsequent periods in a panel were separated by a washout period of at least 13 days.

**Formulation:**

| **Treatment** | Telaprevir | ATV (Reyataz) | ritonavir (Norvir) | LPV/rtv (Kaletra) |
|---|---|---|---|---|
| Concentration | 375 mg | 150 mg | 100 mg | 200/50 mg |
| Dosage Form | Tablet | Capsule | Capsule | Tablet |
| Usage | Oral | Oral | Oral | Oral |
| Batch Number | 3057618R | A105 | 52474VA | 47096VA |

**Pharmacokinetic Sampling:**
Blood samples for pharmacokinetic measurements were taken at the following time point:
Treatments A and C:

- on Days 1[a, b], 5[a], and 8[a] (morning predose) and Day 9[a] (predosec of all doses);
- on Day 10[a] at morning predose[c] and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, and 8 hours after study medication intake;
- at time of discontinuation or the following morning[a, b].

Treatments B and D:

- on Days 1[a, b] and 5[b] (morning predose) and Day 9[b] (predosec of all doses);
- on Day 10[b] at morning predosec and 0.5, 1, 2, 3, 4, 5, 6, 8 12, and 16 [Treatment D only] hours after study medication intake;
- on Day 11[a,b] at morning predose[c] and 2, 3, 4 and 5 hours after study medication intake);
- on Days 15[a,b], and Day 18[a,b] (morning predose), and Day 19[a,b] (predose of all
- doses);
- on Day 20 at morning predose[a,b, c] and 0.5[a,b], 1[a,b], 1.5[a], 2[a,b], 2.5[a], 3[a,b], 3.5[a], 4[a,b], 5[a,b], 6[a,b], 8[a,b], 12[b] and 16[b] [Treatment D only] hours after study medication intake;
- on Day 21[a,b] (Treatment D only) and Day 23[a,b],(predose of all doses);
- on Day 24 at morning predose[a,b], c and 0.5[a,b], 1[a,b], 1.5[a], 2[a,b], 2.5[a], 3[a,b], 3.5[a], 4[a,b], 5[a,b], 6[a,b], 8[a,b], 12[a,b], and 16[b] [Treatment D only] hours after study medication intake;
- on Day 25[b] (Treatment D only; 24 hours after last drug intake);
- at time of discontinuation or the following morning[a,b].

*a For determination of telaprevir and VRT-127394*
*b For determination of LPV/rtv (Panel 1; Treatment B) or ATV/rtv (Panel 2; Treatment D)*
*c Immediately before the intake of telaprevir*

**Analytical Method:** VX-950 (telaprevir), VRT-127394, lopinavir, atazanavir, and ritonavir human plasma samples were analyzed by validated LC/MS/MS methods. For several blood samples for the determination of ATV plasma concentrations, the storage period had exceeded the validated long-term stability period. The ATV plasma concentrations in these samples are reported as NR (Not Reported, stability period exceeded), which is acceptable. For telaprevir and VRT-127394, the freezer temperature was not indicated in the stability study. In addition, sample storage conditions were not specified.

| Analyte | Linear range (ng/mL) | Between Run Precision (%CV) | Between Run Bias (% Deviation) | QC samples (ng/mL) | Validation sample for stability and conditions |
|---|---|---|---|---|---|
| telaprevir | 5.0-10000 $R^2$> 0.999 | ≤ 4.9 | -0.8 to 9.1 | 13.6, 240, 7580, and 7680 | Stable for at least 563 days in a freezer |
| VRT-127394 | 10 – 20000 $R^2$ > 0.999 | ≤ 4.5 | -2.6 to 8.6 | 27.2, 480, 516, 15200, and 15400 | Stable for at least 387 days in a freezer |
| lopinavir | 10-20000 $R^2$ > 0.9998 | ≤ 3.8 | -1.3 to 3.0 | 27.2, 516, and 15200 | |
| atazanavir | 250 – 50000 $R^2$ > 0.996 | ≤ 7.3 | 0.2 to 4.3 | 750, 8000, and 40000 | Stable for at least 70 days at -20°C |
| ritonavir | 5-10000 $R^2$ > 0.999 | ≤ 3.6 | -2.4 to 3.8 | 13.6, 240, and 7580 | |

**Results:**

Pharmacokinetic

*LPV/RTV effect on telaprevir and VRT-127394 PK*

A summary list of key pharmacokinetic parameters the statistic analysis of telaprevir and VRT-127394 and are presented in Tables 1 and 2, respectively. The data show that LPV/rtv significantly reduced the exposure of telaprevir and VRT-127394.

**Table 1: Pharmacokinetic and statistic results of telaprevir after administration of telaprevir alone at 750 mg q8h (Treatment A, Day 10) and in combination with LPV/rtv at 400/100 mg b.i.d. (Treatment B, Day 20) and after administration of telaprevir at 750 mg q12h in combination with LPV/rtv at 400/100 mg b.i.d (Treatment B, Day 24)**

| *Pharmacokinetics of telaprevir* (mean ± SD, $t_{max}$: median [range]) | telaprevir q8h, Day 10 (reference) | telaprevir q8h + LPV/rtv, Day 20 (test 1) | telaprevir q12h + LPV/rtv, Day 24 (test 2) |
|---|---|---|---|
| n | 14[a] | 12 | 12 |
| $C_{0h}$, ng/mL | 2316 ± 674.2 | 1073 ± 378.4 | 981.8 ± 300.9 |
| $C_{min}$, ng/mL | 1886 ± 681.1 | 912.4 ± 334.0 | 683.8 ± 259.7 |
| $C_{max}$, ng/mL | 3496 ± 995.0 | 1586 ± 415.0 | 1368 ± 333.4 |
| $t_{max}$, h | 3.5 (3.0-6.0) | 4.0 (1.5-5.0) | 5.0 (1.5-5.0) |
| $AUC_{\tau}$, ng.h/mL[b] | 21040 ± 5906 | 9641 ± 2807 | 12000 ± 3463 |
| $C_{ss,av}$, ng/mL | 2630 ± 738.3 | 1206 ± 350.1 | 999.8 ± 288.6 |
| FI, % | 62.19 ± 15.28 | 58.33 ± 24.27 | 71.62 ± 19.42 |
| **LSmean ratio (90% CI), %** | | | |
| | - | **Test 1 vs reference** | **Test 2 vs reference** |
| n | - | 12 vs 14 | 12 vs 14 |
| $C_{min}$ | - | 47.60 (40.34 - 56.15) | 35.19 (29.20 - 42.41) |
| $C_{max}$ | - | 46.52 (41.34 - 52.34) | 39.43 (36.19 - 42.95) |
| $AUC_{8h}$ | - | 46.07 (40.83 - 51.98) | - |
| $C_{ss,av}$ | - | - | 37.59 (34.15 - 41.38) |

[a] n=13 for $C_{0h}$

[b] τ=8h for reference and test 1, τ=12h for test 2

**Table 2; Pharmacokinetic and Statistic Results of VRT-127394 After Administration of Telaprevir Alone at 750 mg q8h (Treatment A, Day 10) and in Combination With LPV/rtv at 400/100 mg b.i.d. (Treatment B, Day 20) and After Administration of Telaprevir at 750 mg q12h in Combination With LPV/rtv at 400/100 mg b.i.d (Treatment B, Day 24)**

| *Pharmacokinetics of VRT-127394* (mean ± SD, $t_{max}$: median [range]) | telaprevir q8h, Day 10 (reference) | telaprevir q8h + LPV/rtv, Day 20 (test 1) | telaprevir q12h + LPV/rtv, Day 24 (test 2) |
|---|---|---|---|
| n | 14[a] | 12 | 12 |
| $C_{0h}$, ng/mL | 1755 ± 450.4 | 933.1 ± 260.9 | 789.8 ± 206.0 |
| $C_{min}$, ng/mL | 1439 ± 443.1 | 751.5 ± 187.6 | 585.7 ± 170.9 |
| $C_{max}$, ng/mL | 2234 ± 591.5 | 1049 ± 239.3 | 890.8 ± 179.1 |
| $t_{max}$, h | 3.5 (1.0-6.0) | 4.0 (0.0-6.0) | 5.0 (0.0-6.0) |
| $AUC_{\tau}$, ng.h/mL[b] | 14710 ± 3583 | 7198 ± 1675 | 8764 ± 1866 |
| $C_{ss,av}$, ng/mL | 1839 ± 447.9 | 900.3 ± 208.8 | 730.3 ± 155.5 |
| FI, % | 43.88 ± 13.89 | 33.31 ± 14.28 | 42.95 ± 21.42 |
| **LSmean ratio (90% CI), %** | | | |
| | - | **Test 1 vs reference** | **Test 2 vs reference** |
| n | - | 12 vs 14 | 12 vs 14 |
| $C_{min}$ | - | 54.17 (46.68 - 62.86) | 41.65 (35.83 - 48.43) |
| $C_{max}$ | - | 50.97 (46.31 - 56.11) | 43.15 (40.49 - 45.98) |
| $AUC_{8h}$ | - | 51.86 (46.66 - 57.64) | - |
| $C_{ss,av}$ | - | - | 41.68 (38.77 - 44.81) |

[a] n=13 for $C_{0h}$

[b] τ=8h for reference and test 1, τ=12h for test 2

*Telaprevir effect on LPV/RTV PK*

As shown in Tables 3 and 4, telaprevir did not affect the exposure to LPV or ritonavir, as expressed by $C_{max}$ and $AUC_{12h}$, although the $C_{min}$ of LPV was increased by 14% and 25% after coadministration with telaprevir 750 mg q8h or q12h, respectively.

**Table 3: Pharmacokinetic and Statistic Results of Lopinavir after Administration of LPV/rtv Alone at 400/100 mg b.i.d. (Treatment B, Day 10) in Combination With Telaprevir at 750 mg q8h (Treatment B, Day 20) and in Combination With Telaprevir at 750 mg q12h (Treatment B, Day 24)**

| *Pharmacokinetics of lopinavir* (mean ± SD, $t_{max}$: median [range]) | LPV/rtv, Day 10 (reference) | LPV/rtv + telaprevir q8h, Day 20 (test 1) | LPV/rtv + telaprevir q12h, Day 24 (test 2) |
|---|---|---|---|
| n | 19 | 12 | 12 |
| $C_{0h}$, ng/mL | 7223 ± 2820 | 8308 ± 1940 | 7974 ± 2251 |
| $C_{min}$, ng/mL | 6433 ± 2703 | 6562 ± 1831 | 7033 ± 1862 |
| $C_{max}$, ng/mL | 12470 ± 3055 | 11730 ± 3132 | 11850 ± 2772 |
| $t_{max}$, h | 4.0 (2.0-6.0) | 4.0 (2.0-6.0) | 4.0 (2.0-6.0) |
| $AUC_{12h}$, ng.h/mL | 109900 ± 33500 | 108700 ± 23670 | 109300 ± 23210 |
| $C_{ss,av}$, ng/mL | 9161 ± 2791 | 9061 ± 1971 | 9109 ± 1934 |
| FI, % | 71.08 ± 24.65 | 57.06 ± 15.62 | 53.82 ± 19.93 |
| **LSmean ratio (90% CI), %** | | | |
| | - | **Test 1 vs reference** | **Test 2 vs reference** |
| n | - | 12 vs 19 | 12 vs 19 |
| $C_{min}$ | - | 114.1 (95.92 - 135.6) | 125.2 (109.6 - 143.1) |
| $C_{max}$ | - | 95.64 (87.00 - 105.1) | 98.32 (93.72 - 103.2) |
| $AUC_{12h}$ | - | 105.9 (95.96 - 116.8) | 107.6 (99.82 - 116.0) |

**Table 4**: **Pharmacokinetic and Statistic Results of Ritonavir after Administration of LPV/rtv Alone at 400/100 mg b.i.d. (Treatment B, Day 10) in Combination With Telaprevir at 750 mg q8h (Treatment B, Day 20) and in Combination With Telaprevir at 750 mg q12h (Treatment B, Day 24)**

| *Pharmacokinetics of ritonavir* (mean ± SD, $t_{max}$: median [range]) | LPV/rtv, Day 10 (reference) | LPV/rtv + telaprevir q8h, Day 20 (test 1) | LPV/rtv + telaprevir q12h, Day 24 (test 2) |
|---|---|---|---|
| n | 19 | 12 | 12 |
| $C_{0h}$, ng/mL | 216.5 ± 128.1 | 254.4 ± 117.8 | 276.5 ± 178.3 |
| $C_{min}$, ng/mL | 166.0 ± 102.0 | 145.0 ± 64.21 | 161.7 ± 74.88 |
| $C_{max}$, ng/mL | 1063 ± 596.1 | 924.2 ± 538.6 | 1003 ± 488.1 |
| $t_{max}$, h | 4.0 (2.0-5.0) | 4.0 (3.0-5.0) | 4.0 (3.0-5.0) |
| $AUC_{12h}$, ng.h/mL | 5435 ± 2621 | 4885 ± 1858 | 5001 ± 1992 |
| $C_{ss,av}$, ng/mL | 452.9 ± 218.4 | 407.4 ± 155.1 | 416.7 ± 166.0 |
| FI, % | 200.4 ± 48.18 | 184.4 ± 47.24 | 202.3 ± 73.81 |
| **LSmean ratio (90% CI), %** | | | |
| | - | **Test 1 vs reference** | **Test 2 vs reference** |
| n | - | 12 vs 19 | 12 vs 19 |
| $C_{min}$ | - | 102.7 (85.90 - 122.8) | 113.9 (95.71 - 135.6) |
| $C_{max}$ | - | 92.59 (82.54 - 103.9) | 100.5 (86.34 - 117.0) |
| $AUC_{12h}$ | - | 104.7 (95.70 - 114.5) | 104.3 (91.01 - 119.6) |

*ATV/RTV effect on telaprevir and VRT-127394 PK*

Tables 5 and 6 summarize the key pharmacokinetic parameters of telaprevir and VRT-127394 for Treatment C and Treatment D, respectively. The data show that telaprevir concentrations (Cmin, Cmax and AUC) reduced by 15%- 21% when telaprevir was coadministered with ATV/RTV. The effect of ATV/RTV on VRT-127394 is at the similar magnitude.

**Table 5: Pharmacokinetic and Statistic Results of Telaprevir after Administration of Telaprevir Alone at 750 mg q8h (Treatment C, Day 10) and in Combination with ATV/rtv at 300/100 mg q.d. (Treatment D, Day 20) and After Administration of Telaprevir at 750 mg q12h in Combination with ATV/rtv at 300/100 mg q.d. (Treatment D, Day 24)**

| *Pharmacokinetics of telaprevir* (mean ± SD, $t_{max}$: median [range]) | telaprevir q8h, Day 10 (reference) | telaprevir q8h + ATV/rtv, Day 20 (test 1) | telaprevir q12h + ATV/rtv, Day 24 (test 2) |
|---|---|---|---|
| n | 17 | 14 | 14 |
| $C_{0h}$, ng/mL | 2141 ± 464.5 | 1736 ± 379.5 | 1680 ± 430.8 |
| $C_{min}$, ng/mL | 1785 ± 453.3 | 1506 ± 283.6 | 1260 ± 287.9 |
| $C_{max}$, ng/mL | 3242 ± 711.4 | 2478 ± 382.7 | 2624 ± 527.9 |
| $t_{max}$, h | 3.0 (2.5-5.0) | 3.25 (2.0-5.0) | 3.75 (2.0-5.0) |
| $AUC_{\tau}$, ng.h/mL[a] | 19930 ± 4056 | 15500 ± 2153 | 22550 ± 4613 |
| $C_{ss,av}$, ng/mL | 2491 ± 507.0 | 1939 ± 268.5 | 1879 ± 384.4 |
| FI, % | 58.62 ± 15.46 | 50.55 ± 18.43 | 72.78 ± 16.66 |
| **LSmean ratio (90% CI), %** | | | |
| | - | **Test 1 vs reference** | **Test 2 vs reference** |
| n | - | 14 vs 17 | 14 vs 17 |
| $C_{min}$ | - | 85.39 (74.58 - 97.77) | 71.21 (61.68 - 82.21) |
| $C_{max}$ | - | 78.76 (74.25 - 83.54) | 81.31 (72.56 - 91.10) |
| $AUC_{8h}$ | - | 80.48 (76.21 - 84.98) | - |
| $C_{ss,av}$ | - | - | 76.32 (69.25 - 83.92) |

[a] τ=8h for reference and test 1, τ=12h for test 2

**Table 6: Pharmacokinetic and Statistic Results of VRT-127394 After Administration of Telaprevir Alone at 750 mg q8h (Treatment C, Day 10) and in Combination With ATV/rtv at 300/100 mg q.d. (Treatment D, Day 20) and After Administration of Telaprevir at 750 mg q12h in Combination with ATV/rtv at 300/100 mg q.d. (Treatment D, Day 24)**

| *Pharmacokinetics of VRT-127394* (mean ± SD, $t_{max}$: median [range]) | telaprevir q8h, Day 10 (reference) | telaprevir q8h + ATV/rtv, Day 20 (test 1) | telaprevir q12h + ATV/rtv, Day 24 (test 2) |
|---|---|---|---|
| n | 16[b] | 14 | 14 |
| $C_{0h}$, ng/mL | 1664 ± 365.5 | 1428 ± 303.5 | 1246 ± 287.2 |
| $C_{min}$, ng/mL | 1386 ± 340.5 | 1180 ± 236.7 | 1039 ± 208.6 |
| $C_{max}$, ng/mL | 2026 ± 455.4 | 1659 ± 221.5 | 1620 ± 321.2 |
| $t_{max}$, h | 3.75 (0.0-5.0) | 4.0 (0.0-5.0) | 4.0 (0.5-8.0) |
| $AUC_{\tau}$, ng.h/mL[a] | 13780 ± 3016 | 11270 ± 1605 | 15980 ± 3292 |
| $C_{ss,av}$, ng/mL | 1722 ± 377.0 | 1409 ± 199.2 | 1332 ± 274.3 |
| FI, % | 37.10 ± 14.46 | 35.17 ± 15.28 | 43.68 ± 15.67 |
| **LSmean ratio (90% CI), %** | | | |
| | - | **Test 1 vs reference** | **Test 2 vs reference** |
| n | - | 14 vs 16[b] | 14 vs 16[b] |
| $C_{min}$ | - | 85.71 (74.77 - 98.25) | 73.27 (62.43 - 86.01) |
| $C_{max}$ | - | 86.26 (81.45 - 91.35) | 80.80 (72.51 - 90.05) |
| $AUC_{8h}$ | - | 85.44 (80.33 - 90.88) | - |
| $C_{ss,av}$ | - | - | 78.24 (70.77 - 86.50) |

[a] τ=8h for reference and test 1, τ=12h for test 2
[b] n=17 for $C_{0h}$ and $C_{min}$

*Telaprevir and VRT-127394 effect on ATV/RTV PK*

As shown in Table 7, mean ATV $C_{0h}$, $C_{min}$, $C_{ss,av}$ and $AUC_{24h}$ were higher when ATV/rtv q.d. was administered in combination with telaprevir (q8h and q12h) compared to ATV/rtv q.d. administered alone. However, $C_{max}$ was lower. No dose adjustment is necessary for ATV when it is coadministered with telaprevir.

**Table 7: Pharmacokinetic and Statistic Results of Atazanavir after Administration of ATV/rtv Alone at 300/100 mg q.d. (Treatment D, Day 10), in Combination With Telaprevir at 750 mg q8h (Treatment D, Day 20) and in Combination With Telaprevir at 750 mg q12h (Treatment D, Day 24)**

| *Pharmacokinetics of atazanavir* (mean ± SD, $t_{max}$: median [range]) | ATV/rtv, Day 10 (reference) | ATV/rtv + telaprevir q8h, Day 20 (test 1) | ATV/rtv + telaprevir q12h, Day 24 (test 2) |
|---|---|---|---|
| n | 7[a] | 11 | 14 |
| $C_{0h}$, ng/mL | 1026 ± 519.1 | 1759 ± 571.3 | 1712 ± 603.5 |
| $C_{min}$, ng/mL | 832.1 ± 377.0 | 1520 ± 475.6 | 1557 ± 540.4 |
| $C_{max}$, ng/mL | 5104 ± 1139 | 4423 ± 819.2 | 4094 ± 750.0 |
| $t_{max}$, h | 3.0 (2.0-5.0) | 3.0 (2.0-4.0) | 3.0 (1.0-4.0) |
| $AUC_{24h}$, ng.h/mL | 46880 ± 14460 | 56400 ± 14550 | 58870 ± 12990 |
| $C_{ss,av}$, ng/mL | 1954 ± 602.6 | 2351 ± 605.9 | 2453 ± 541.1 |
| FI, % | 228.0 ± 51.19 | 127.9 ± 26.12 | 106.8 ± 28.73 |
| **LSmean ratio (90% CI), %** | | | |
| | - | **Test 1 vs reference** | **Test 2 vs reference** |
| n | - | 11 vs 7 | 14 vs 7 |
| $C_{min}$ | - | 185.0 (140.3 - 244.0) | 192.7 (150.7 - 246.6) |
| $C_{max}$ | - | 84.53 (73.25 - 97.55) | 79.95 (69.57 - 91.88) |
| $AUC_{24h}$ | - | 117.4 (96.71 - 142.5) | 127.4 (109.4 - 148.3) |

[a] n=8 for $C_{0h}$

As shown in Table 8, there is no clinically significant effect of telaprevir on ritonavir.

**Table 8: Pharmacokinetic Results of Ritonavir after Administration of ATV/rtv Alone at 300/100 mg q.d. (Treatment D, Day 10) in Combination with Telaprevir at 750 mg q8h (Treatment D, Day 20) and in Combination with Telaprevir at 750 mg q12h (Treatment D, Day 24)**

| *Pharmacokinetics of ritonavir* (mean ± SD, $t_{max}$: median [range]) | ATV/rtv, Day 10 (reference) | ATV/rtv + telaprevir q8h, Day 20 (test 1) | ATV/rtv + telaprevir q12h, Day 24 (test 2) |
|---|---|---|---|
| n | 16[a] | 14 | 14 |
| $C_{0h}$, ng/mL | 57.06 ± 36.87 | 53.24 ± 48.10 | 54.95 ± 36.40 |
| $C_{min}$, ng/mL | 41.20 ± 29.01 | 38.19 ± 30.77 | 43.32 ± 25.26 |
| $C_{max}$, ng/mL | 1526 ± 524.3 | 1316 ± 479.1 | 1228 ± 392.9 |
| $t_{max}$, h | 4.0 (2.0-5.0) | 4.0 (2.02-4.0) | 4.0 (3.0-5.0) |
| $AUC_{24h}$, ng.h/mL | 9401 ± 3142 | 7859 ± 2930 | 7846 ± 2705 |
| $C_{ss,av}$, ng/mL | 391.7 ± 130.9 | 327.5 ± 122.2 | 326.9 ± 112.7 |
| FI, % | 384.2 ± 69.84 | 394.7 ± 75.72 | 369.5 ± 72.84 |
| **LSmean ratio (90% CI), %** | | | |
| | - | **Test 1 vs reference** | **Test 2 vs reference** |
| n | - | 14 vs 16 | 14 vs 16 |
| $C_{min}$ | - | 94.98 (78.84 - 114.4) | 115.5 (98.56 - 135.4) |
| $C_{max}$ | - | 86.73 (73.81 - 101.9) | 82.66 (73.90 - 92.45) |
| $AUC_{24h}$ | - | 85.83 (75.63 - 97.40) | 86.70 (77.52 - 96.97) |

[a] n=17 for $C_{0h}$

Safety

Telaprevir 750 mg q8h alone is generally safe and well tolerated. The most common individual events reported during administration of telaprevir alone and considered at least possibly related to telaprevir were headache, pruritus, and diarrhea. The type of AEs observed during coadministration of telaprevir and ATV/rtv or LPV/rtv was consistent with the safety profile of the individual drugs. During administrations including ATV/rtv, events related to hyperbilirubinemia were observed (i.e., increased blood bilirubin and ocular icterus); this was expected, as these are known side effects of ATV.

**Discussion:** As telaprevir is a substrate of CYP3A4, combination with CYP3A4 inhibitors such as LPV/rtv or ATV/rtv was expected to result in increased exposure to telaprevir. In the current trial, however, exposure to telaprevir (administered either q8h or q12h) was decreased during combination with these boosted HIV protease inhibitors. The mechanism of this effect remains to be established.

**Conclusion:** LPV/rtv or ATV/rtv can significantly reduce telaprevir exposure, and that dose adjustment of telaprevir may be necessary if these drugs are coadministered.

### 3.3 Pharmacometrics Review

# Office of Clinical Pharmacology: Pharmacometric review

| | |
|---|---|
| **Application Number** | NDA 201917 |
| **Submission Number (Date)** | 23 Nov 2010 |
| **Drug Name** | Telaprevir |
| **Proposed Indication** | In combination with peginterferon alfa and ribavirin, for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease, including cirrhosis, who are treatment naïve or who have been previously treated, including prior null responders, partial responders, and relapsers |
| **Clinical Division** | DAVP |
| **Primary CP Reviewer** | Shirley K. Seo, Ph.D. |
| **Primary PM Reviewer** | Jiang Liu, Ph.D. & Kevin M. Krudys, Ph.D. |
| **Secondary CP Reviewer** | Sarah M. Robertson, Pharm.D. |
| **Secondary PM Reviewer** | Pravin R. Jadhav, Ph.D. |
| **Applicant** | Vertex |

## 1 Summary of Findings

## 1.1 Key Review Questions

The purpose of this review is to address the following key questions.

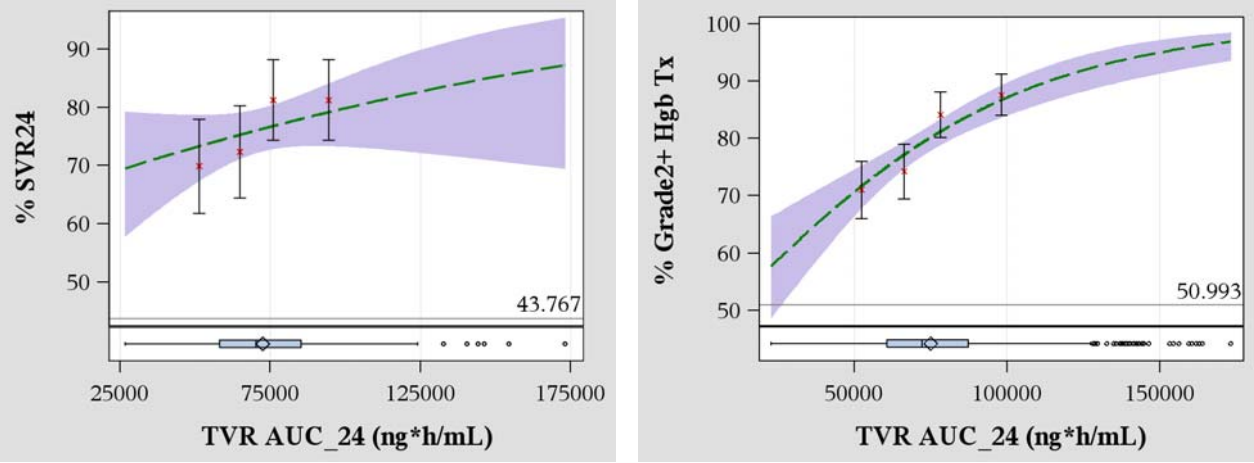
### 1.1.1 Does telaprevir exposure-response for efficacy and safety support 750 mg q8h dose?

Yes. The 750 mg q8h telaprevir (TVR) dose in combination with PEG-IFN and RBV was consistently superior to the standard of care (SOC) in all of the Phase 2 and Phase 3 clinical trials. The exposure-response relationship indicated that the exposure range obtained with the 750 mg q8h TVR dosing seemed to balance between efficacy and safety in combination with PEG-IFN and ribavirin (RBV). And a higher dose of TVR is clearly not desired due to the much stronger exposure-Hgb toxicity relationship compared to the exposure-efficacy relationships (Figure 1).

- The relationships between TVR exposure and all efficacy endpoints [SVR (sustained viral response), RVR (rapid viral response), eRVR (extended rapid viral response), VBT (viral breakthrough), and relapse – please refer to the study reports for the definitions] were shallow, and statistically non-significant. SVR24P defined as undetectable HCV RNA at the end of treatment (EOT) visit and at 24 weeks after the last planned dose of study treatment without any confirmed detectable in between was the primary efficacy endpoint in the pivotal trials. As shown in Figure 1 (left), higher TVR exposure was weakly associated with increased SVR24P.

- However, higher TVR exposure was significantly associated with increased risk of anemia and Hgb toxicity event defined as Hgb < 10 g/dL or any decrease from baseline > 3.5 g/dL (Figure 1, right). From a multivariate logistic analysis, the odd ratio of Hgb toxicity for doubling the TVR exposure is 2.4 (95% CI: 1.6, 3.6) after adjusting for PEG-IFN and RBV exposure.
- The exposure-response relationship between Hgb toxicity and RBV exposure is steepest compared to the relationship with respect to TVR or PEG-IFN exposure. Therefore, using dose reduction of RBV to manage Hgb toxicity and anemia is reasonable (Figure 10).

**Figure 1. Higher Telaprevir Exposure Was Weakly Associated with Increased SVR (Left [a]), but Was Significantly Associated with Increased Risk of Hgb Tox (Right [b])**




[a] Exposure-SVR analysis was conducted in the pooled naïve patients with T12/PR (RGT or 48 WK).
[b] Exposure-Hgb Tx was conducted in the pooled patients with T12/PR. Grade 2+ Hgb Tx was defined as Hgb < 10 g/dL or any decrease from baseline > 3.5 g/dL.

### 1.1.2 Does telaprevir 8-week treatment provide similar benefit as the 12-week treatment in selected sub-populations?

No, 8-weeks of telaprevir treatment (shorter) does not provide advantage ove 12 weeks of treatment (longer) in selected subpopulation. Although in subgroup analyses treatment naïve patients with low baseline HCV RNA levels (<80000 IU/mL) may seem to achieve similar SVR with the shorter (8-week) TVR treatment compared to the 12-week TVR treatment, the breakthrough rate was higher with shorter duration.

- Both TVR 8-week (T8/PR) and 12-week (T12/PR) treatment achieved significantly higher SVR in treatment naïve patients compared to SOC.
- In the overall naïve population, the proportion of patients achieving SVR was numerically higher in T12/PR compared to T8/PR, but the proportion of patients with Grade 3 rash ESI was also higher in T12/PR (Table 7 and Figure 2).
- Proportion achieving SVR in T8/PR was comparable to T12/PR among patients with low baseline HCV RNA levels (HCV RNA < 800,000 IU/mL) (Table 8 and Figure 3).

- However, the cumulative viral breakthrough rate was higher with T8/PR (5.8%: 21/364) compared to that with T12/PR (2.8%: 10/363) during PEG-IFN/RBV treatment. In patients with patients with low baseline HCV RNA levels (<80000 IU/mL), the cumulative viral breakthrough rate was 4.7% (4/85) in the T8/PR group versus the 1.2% (1/82) in the T12/PR group.
- On the other hand, shorter duration of telaprevir resulted in lower proportion (6% vs. 9%) of patients with Grade 3 Rash.

**Figure 2. Proportion of Patients Achieving SVR Was Numerically Higher in T12/PR Compared to T8/PR (Left), but Proportion of Patients with Grade 3 Rash ESI Was Also Higher in T12/PR (Right) [Study 108]**

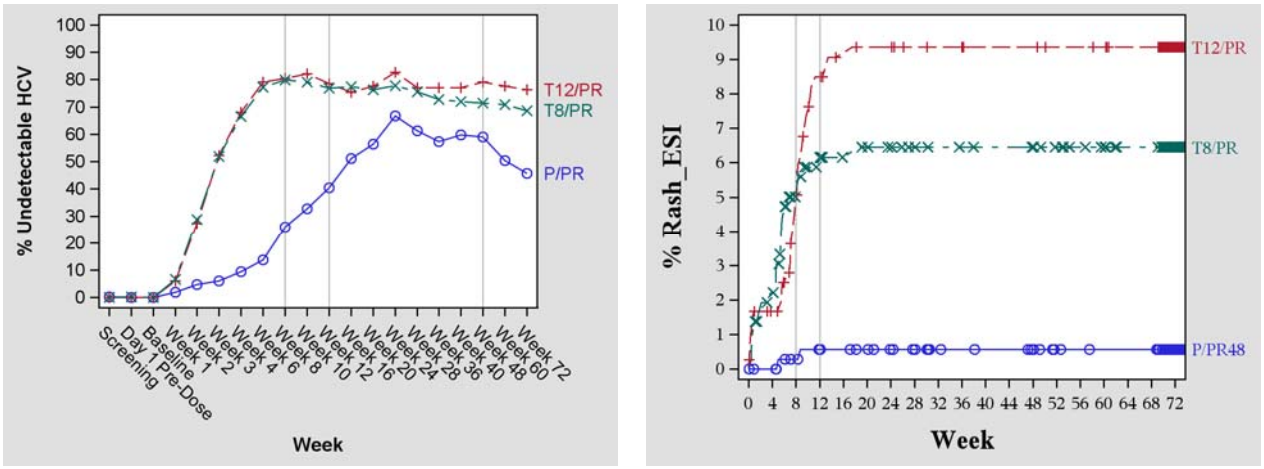
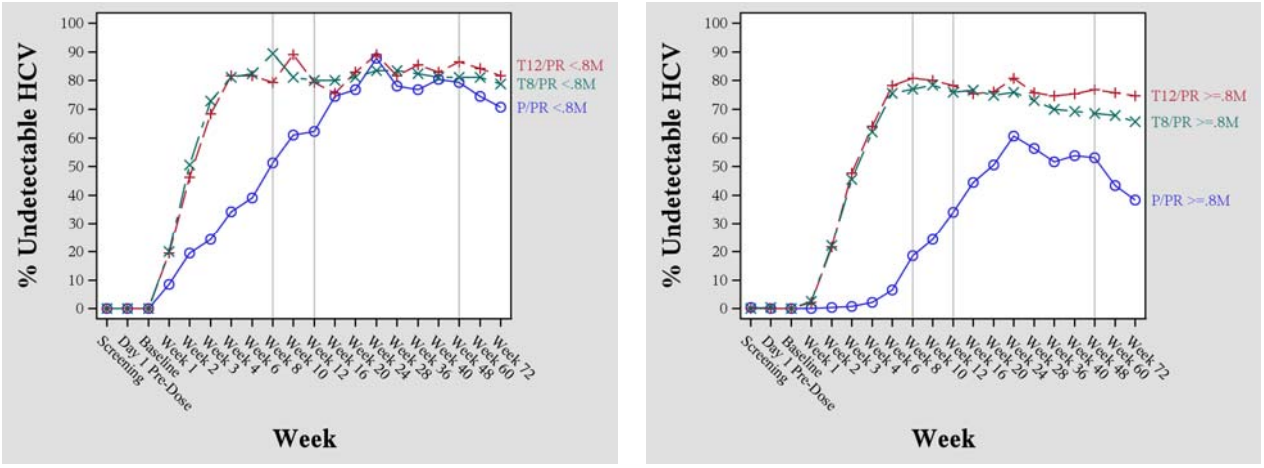



**Figure 3. Proportion Achieving SVR in T8/PR Was Comparable to T12/PR Among Patients with Low Baseline HCV RNA Levels (Left: Baseline HCV RNA < 800,000 IU/mL (total number of patients per group= 82 (T12/PR) 85 (T8/PR) 82 (PR)), Right: Baseline HCV RNA >= 800,000 IU/mL (total number of patients per group= 281 (T12/PR) 279 (T8/PR) 279 (PR))) [Study 108]**

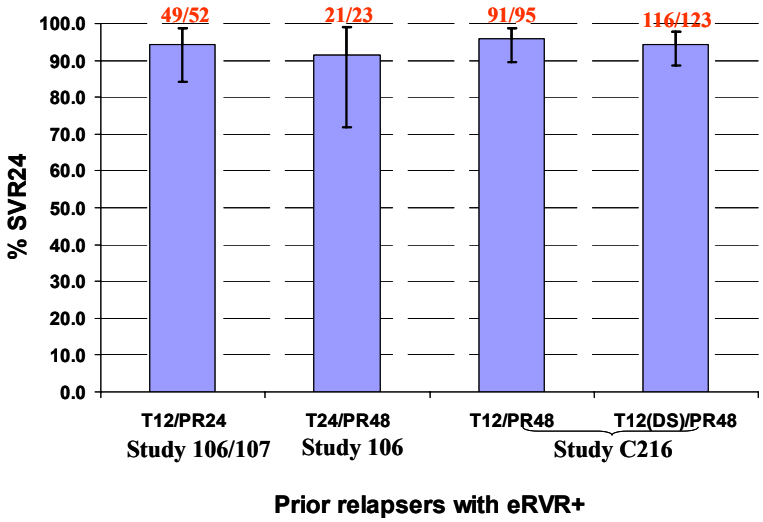


### 1.1.3 Is the proposed response-guided Peg-IFN/RBV treatment for the prior treatment relapse patients reasonable?

Yes, the response-guided Peg-IFN/RBV treatment duration for prior relapse patients is reasonable:

- The SVR rates for prior relapse patients who achieve eRVR were high (>90%) with short (24 weeks) or long (48 weeks) Peg-IFN/RBV duration based on cross-trial comparison (Figure 4).
- Prior relapse patients are a subset within treatment naïve population who are suitable for RGT (Figure 12-Figure 13). The data suggests that longer treatment with peg-IFN/RBV may not provide incremental benefit in patients who achieve eRVR.
- Data from treatment naïve and experienced population can be bridged to derive dosing recommendations for prior relapse patients (Figure 14).

**Figure 4. SVR Rates Among Cohorts of Prior Relapse Subjects Achieving eRVR in Phase 2 and Phase 3 Telaprevir Trials**




T12(DS)/PR48 is the treatment with 4-week delayed start of TVR.
The Y-error bars are the 95% Fisher Exact Confidence Limits for each treatment group.

### 1.1.4 Is the response-guided Peg-INF/RBV treatment for the prior treatment failure (partial and null responders) patients reasonable?

Yes, the response-guided Peg-IFN/RBV treatment duration for partial or null responder patients seems also reasonable:

- The SVR rates for patients who achieve eRVR were similar (Partial responders~62-77% and null responders~62-71%) for each group with short (24 weeks) or long (48 weeks) Peg-IFN/RBV duration based on cross-trial comparison (Figure 15). The data suggests that longer treatment with peg-IFN/RBV may not provide incremental benefit in patients who achieve eRVR.

- Partial and null responder patients are a potential subset within treatment naïve population who are accepted for RGT (Figure 12-Figure 13).
- Data from treatment naïve and experienced population can be bridged to derive dosing recommendations for partial and null responders (Figure 14).

### 1.1.5 Is the proposed (b) (4) virologic stopping rule at Week 4 and Week 12 of treatment reasonable?

No. Patients with HCV RNA > 1000 IU/mL (b) (4) at Week 4 or 12 should discontinue TVR and PEG-IFN/RBV treatment.
The Applicant has proposed patients with HCV RNA (b) (4) at week 4 should discontinue TVR and 12 should discontinue all treatment which are different from the criteria (> 1000 IU/mL) applied in the pivotal trials for the treatment naïve patients. As shown in Table 1, in the pivotal trials:

- There were about 2% of treatment naïve patients with >1000 IU/mL HCV RNA at Week 4, and none of these patients achieved SVR even through the PEG-IFN/RBV treatment was continued. Therefore, there is limited benefit to continue PEG-IFN/RBV treatment in subjects with >1000 IU/mL HCV RNA at Week 4.
- There were about 4% of treatment naïve patients with >1000 IU/mL HCV RNA at Week 12, and none of these patients achieved SVR even through the PEG-IFN/RBV treatment was continued. Therefore, there is limited benefit to continue PEG-IFN/RBV treatment in subjects with >1000 IU/mL HCV RNA at Week 12.
- Further, there were about 2% of treatment naïve patients with 100-1000 IU/mL HCV RNA at Week 4. Among these patients, 26% achieved SVR. Therefore, TVR/PEG-IFN/RBV treatment should be continued in subjects with 100-1000 IU/mL HCV RNA at Week 4, especially when there is no other better choice available.
- About 1% of treatment naïve patients had HCV RNA levels between 100 and 1000 IU/mL at Week 12. Among these patients, 25% achieved SVR. Therefore, PEG-IFN/RBV treatment can be continued in subjects with 100-1000 IU/mL HCV RNA at Week 12.

For prior treatment failure patients in Study C216, there were approximate 2% patients with 100-1000 IU/mL HCV RNA at Week 4 and 1% at Week 12. Harmonizing the stopping rules (>1000 IU/mL HCV RNA) as suggested in the treatment naïve patients is reasonable.

**Table 1. Observed Percentages of Treatment-Naïve Patients with T12/PR Who Met Alternative Criteria of Stopping Rules and Their Outcomes**

| | | Met the stopping rule: HCV RNA >1000 IU/mL at WK 4 | | HCV RNA 100-1000 IU/mL at WK4 | |
|---|---|---|---|---|---|
| **Study** | **N** | n1 (% of N) | SVR: n1' (% of n1) | n2 (% of N) | SVR: n2' (% of n2) |
| **108** | **363** | 7 (1.9%) | 0 (0.0%) | 11 (3.0%) | 5 (45.5%) |
| **111** | **540** | 9 (1.7%) | 0 (0.0%) | 8 (1.5%) | 0 (0.0%) |

| | | | | | |
|---|---|---|---|---|---|
| **Total** | **903** | 16 (1.8%) | 0 (0.0%) | 19 (2.1%) | 5 (26.3%) |

| | | Met the stopping rule: HCV RNA >1000 IU/mL at WK 12 | | HCV RNA 100-1000 IU/mL at WK12 | |
|---|---|---|---|---|---|
| **Study** | **N** | n1 (% of N) | SVR: n1' (% of n1) | n2 (% of N) | SVR: n2' (% of n2) |
| **108** | **363** | 15 (4.1%) | 0 (0.0%) | 4 (1.1%) | 2 (50%) |
| **111** | **540** | 19 (3.5%) | 0 (0.0%) | 8 (1.5%) | 1 (12.5%) |
| **Total** | **903** | 34 (3.8%) | 0 (0.0%) | 12 (1.3%) | 3 (25%) |

## 1.2 Recommendations

- Based on the outcome from the pivotal trials and the exposure-response relationships for efficacy and safety, the 750 mg q8h telaprevir dose is recommended for approval.
- Response-guided Peg-IFN/RBV treatment duration for prior relapse patients is recommended.
- Response-guided Peg-IFN/RBV treatment duration for partial and null responder patients is also recommended.
- Patients with HCV RNA > 1000 IU/mL (instead of (b) (4) as proposed by the Applicant) at Week 4 or 12 should discontinue telaprevir and PEG-IFN/RBV treatment.

### 1.3 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

## 2 Pertinent regulatory background

This is the original submission (NDA 201917) that the Applicant is seeking approval of telaprevir (TVR) in combination with peginterferon alfa (PEG-IFN) and ribavirin (RBV), for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease, including cirrhosis, who are treatment naïve or who have been previously treated, including prior null responders, partial responders, and relapsers.

TVR is a member of a new class of direct-acting antiviral agents, the HCV NS3•4A protease inhibitors. Currently, no drugs in this pharmacological class nor any other HCV direct-acting antiviral agents are marketed.

TVR has additive antiviral activity when combined with Peg-IFN/RBV. In subjects with genotype 1 CHC, TVR for 12 weeks, in combination with Peg-IFN/RBV for 24 or 48 weeks, resulted in significantly higher SVR rates than treatment with 48 weeks of Peg-IFN/RBV alone. There are a total of 40 completed clinical studies and 3 ongoing studies. The primary efficacy and safety data in support of telaprevir comes from 3 Phase 3 and 5 Phase 2 studies:

— Treatment-naïve population

  - 2 Phase 3 studies (108: pivotal study and 111: uncontrolled supportive study)

- 3 Phase 2 studies (104, 104EU, and C208: uncontrolled)

— Prior treatment-failure population

- 1 Phase 3 study (C216: pivotal study)
- 2 Phase 2 studies (106, 107: uncontrolled)

# 3 Results of Applicant's Analysis

## 3.1 Analysis method

The PD endpoints examined for efficacy were RVR, eRVR, SVR and VBT. The PD endpoints examined for safety were incidence of Grade 3 or higher rash SSC, and incidence of Grade 2 or higher hemoglobin (Hgb) decrease. PK/PD relationships were explored using graphical analysis followed by logistic regression modeling and clinical utility analysis.
Study data were not pooled for efficacy analyses due to differing study populations (treatment-naïve and treatment-failure populations) and differing study designs, including different stratification factors, treatment regimens, treatment durations, and virologic stopping rules. For each study, data across the different T/PR arms were pooled together. Models were built for each endpoint by initially fitting a full model (a model containing all exposure measures for the 3 compounds as predictors). Final model selection was based on AIC value.

## 3.2 Explore the exposure-response relationship

### 3.2.1 Exposure-response analyses in early phase studies

Final logistic regression model selected based on AIC varied across the 3 studies, with the exception of the model selected for the incidence of viral breakthrough. Possible explanations for the differences in results between studies include the small sample sizes, weak relationships between exposure and endpoint, and differences in study design (e.g., stopping rules and rash management plans). In all 3 studies, VBT was correlated with both TVR and Peg-IFN-alfa-2a exposure, and Hgb toxicity was consistently associated with the RBV exposure. All other endpoints were relatively weakly correlated with the TVR exposure (Table 2).

**Table 2. Summary of Final Multivariate Logistic Regression Model in Phase 2b Trials**

| Response Variable | Study 104 | Study 104EU | Study 106 |
|---|---|---|---|
| RVR | ~ PEGDay 29 | ~ Cmin,ss + RBV Day 29 | ~ Cmin,ss + PEG Day 29 |
| eRVR | ~ PEGDay 29 | ~ Cmin,ss + RBV Day 29 | ~ Cmin,ss + PEG Day 29 |
| SVR | ~ RBV Day 29 | ~ 1 | ~ Cmin,ss + PEG Day 29 |
| Viral Breakthrough (vBT) | ~ Cmin,ss + PEG Day 29 | ~ Cmin,ss + PEG Day 29 | ~ Cmin,ss + PEG Day 29 |
| Relapse | ~ PEG Day 29 | ~ 1 | ~ RBV Day 29 |
| Rash SSC (grade 3+) | ~ Cmin,ss + PEG Day 29 | ~ Cmin,ss | ~ 1 |
| Hemoglobin (grade 2+) | ~ PEG Day 29 + RBV Day 29 | ~ Cmin,ss + RBV Day 29 | ~ Cmin,ss + PEG Day 29 + RBV Day 29 |

*Source: the Applicant's report, Summary of Clinical Pharmacology Studies, Table 87 on page 110.*

### 3.2.2 Exposure-response analyses in pivotal trials

#### 3.2.2.1 Exposure-response analyses in the pivotal treatment naïve trial (Study 108)

The number of subjects in the PK/PD Analysis Dataset who met each of the PD endpoints is summarized, by treatment group, in Table 3.

**Table 3. PK/PD Analysis Population Summary by Treatment Group (Study 108)**

| | Treatment Group | | |
|---|---|---|---|
| **PD Endpoint** | **T8/PR n (%)** | **T12/PR n (%)** | **Total n (%)** |
| All Subjects | 313 (100) | 306 (100) | 619 (100) |
| RVR | 217 (69.3) | 217 (70.9) | 434 (70.1) |
| eRVR | 185 (59.1) | 192 (62.7) | 377 (60.9) |
| SVR | 223 (71.2) | 240 (78.4) | 463 (74.8) |
| Viral breakthrough[a] | 5 (1.98) | 12 (4.55) | 17 (3.29) |
| Rash[b] | 9 (2.88) | 13 (4.25) | 22 (3.55) |
| Hemoglobin[c] | 241 (77.0) | 247 (80.7) | 488 (78.8) |

eRVR: extended rapid viral response; RVR: rapid viral response; SVR: sustained viral response.

[a] Statistics include only subjects who had undetectable HCV RNA at Week 12 or experienced viral breakthrough by Week 12.

[b] Rash events were special search category (SSC) Grade 3 or higher

[c] Hemoglobin toxicity Grade 2 or higher

*Source: the Applicant's report, vx07-950-108-csr-body.phd, Table 66 on page 177.*

Logistic exposure-response models were built for each PD endpoint by initially fitting a full model (a model containing all 3 drug exposure measures as predictors). Step-wise model selection, using both backward elimination and forward addition, was then performed to identify the predictors that provided the best model fit according to the AIC (Table 4). It should be noted that, in many cases, the change in AIC value with the addition or removal of a drug exposure measure as a predictor is small. This implies the correlation between this drug exposure and the PD endpoint is weak.

**Table 4. PK/PD Analysis Population Summary by Treatment Group (Study 108)**

| Response Variable | Model | AIC |
|---|---|---|
| RVR | ~ Cavg,ss + PEG29 | 747.50 |
| | - Cavg,ss | 748.77 |
| | + RBV29 | 749.17 |
| | - PEG29 | 753.46 |
| eRVR | ~ Cavg,ss | 828.25 |
| | + PEG29 | 828.75 |
| | + RBV29 | 829.70 |
| | - Cavg,ss | 830.44 |
| SVR | ~ Cavg,ss + PEG29 | 697.70 |
| | - PEG29 | 698.33 |
| | + RBV29 | 698.95 |
| | - Cavg,ss | 698.95 |
| Viral Breakthrough | ~ Cavg,ss + PEG29 | 124.54 |
| | - Cavg,ss | 124.72 |
| | + RBV29 | 126.28 |
| | - PEG29 | 146.63 |
| Grade 3+ Rash SSC | ~ 1 | 192.04 |
| | + PEG29 | 193.62 |
| | + Cavg,ss | 193.63 |
| | + RBV29 | 193.74 |
| Grade 2+ Hemoglobin Toxicity | ~ Cavg,ss + PEG29 + RBV29 | 545.96 |
| | - PEG29 | 547.48 |
| | - Cavg,ss | 550.82 |
| | - RBV29 | 619.33 |

AIC: Akaike Information Criterion; $C_{avg,ss}$: average model-predicted telaprevir plasma concentration at steady state; eRVR: extended rapid viral response; PEG29: Day 29 measured Peg-IFN-alfa-2a serum concentration; RBV29: Day 29 measured ribavirin plasma concentration; RVR: rapid viral response; SVR: sustained viral response.

*Source: the Applicant's report, vx07-950-108-csr-body.phd, Table 67 on page 184.*

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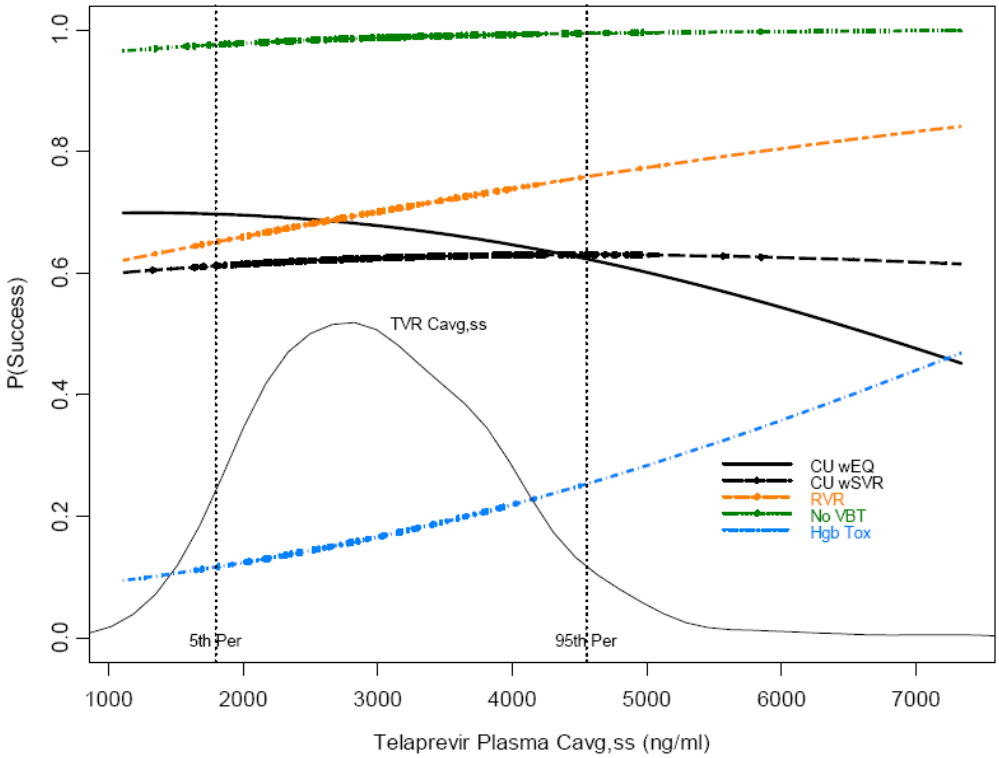
Probability curves with TVR exposure as the independent variable were used to create a clinical utility curve for TVR conditioned upon the median concentrations of PEG-IFN and RBV. Two weighting schemes (equal weighting or a weighted scheme based on SVR) were used in the clinical utility analyses (see the Applicant's report, vx07-950-108-csr-body.phd for details). Clinical utility analysis seemed to indicate that the exposure range obtained with the 750-mg q8h TVR dosing regimen provided a reasonable balance between safety (Hgb toxicity) and efficacy (RVR and the prevention of VBT) (Figure 5).

**Figure 5. Clinical Utility Curve of Telaprevir**



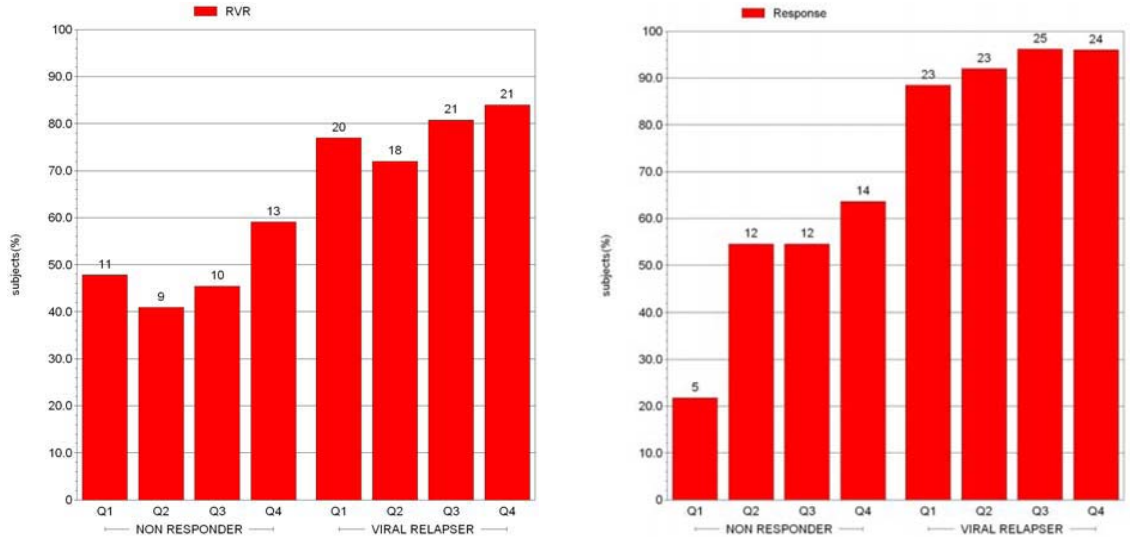

Note: Probability of RVR (RVR), no viral breakthrough (No VBT), Grade 2 or higher hemoglobin toxicity (Hgb Tox) and the resulting clinical utility curves (CU wEQ = ((P(RVR)+P(No VBT))/2) – P(Hgb)); CU wSVR= ((0.81×P(RVR)+0.77×P(No VBT))/2) – 0.24×P(Hgb)) as predicted by logistic regression modeling as a function of model-predicted TVR Cavg,ss. The probabilities for RVR and no VBT were conditioned with the median Day 29 Peg-IFN-alfa-2a serum concentration. The probability for hemoglobin toxicity was conditioned around the median Day 29 Peg-IFN-alfa-2a serum concentration and median Day 29 RBV plasma concentration. The distribution of model-predicted TVR Cavg,ss is also included, with the 5th and 95$^{th}$ percentiles indicated by the dashed vertical lines.

*Source: the Applicant's report, vx07-950-108-csr-body.phd, Figure 21 on page 186.*

### 3.2.2.2 Exposure-response analyses in the pivotal prior treatment failure trial (Study C216)

Efficacy responses by quartile ranges of drug exposures were explored. A lower SVR rate was observed in the lowest quartile of exposure, particularly in the prior non-responder population. These observations are consistent with the outcome of the logistic regression analysis. The TVR AUC was a significant predictor of SVR (p=0.019) but not of RVR (p=0.138). Neither the concentration of PEG-IFN nor that of RBV was significantly associated with SVR or RVR (Figure 6).

**Figure 6. RVR (Left) and SVR24P (Right) by Telaprevir AUC Quartile (Study C216)**




*Source: the Applicant's report, vx-950-C216-csr-body.phd, Figure 59-60 on page 294.*

Exposure to TVR was comparable between subjects who experienced a rash SSC event versus those without rash SSC events. For hemoglobin toxicity, however, higher exposure to TVR was observed in subjects with grade 3 treatment-emergent hemoglobin toxicity compared to those with grade 1 or 2 toxicity (Table 5).

**Table 5. Mean (± SD) Telaprevir AUC by Rash SSC Severity Grade and Hemoglobin Toxicity Grade (Study C216)**

| | Rash SSC | | Hemoglobin toxicity | |
|---|---|---|---|---|
| | $AUC_{sh}$ (h*ng/mL) | n | $AUC_{sh}$ (h*ng/mL) | n |
| None | 29432 ± 7859 | 94 | 38360 ± 9398 | 3 |
| Grade 1 | 30938 ± 9986 | 74 | 25912 ± 7342 | 27 |
| Grade 2 | 29579 ± 8365 | 19 | 27463 ± 6784 | 43 |
| Grade 3 | 30768 ± 4266 | 4 | 31442 ± 8741 | 114 |
| Grade 4 | NA | - | 40272 ± 15236 | 4 |

NA: not assessable

*Source: the Applicant's report, vx-950-C216-csr-body.phd, Figure 59-60 on page 295.*

*Reviewer's comments: The Applicant's analyses have the following limitation:*

- *Differences in the TVR durations (i.e., 8, 12 or 24 weeks) were not taken into account in the Applicant's analyses. This may confound the exposure-response relationships.*
- *Analyses did not consider the effect of baseline characteristics (such as, viral load, subject demographics, disease states, and laboratory parameters).*
- *In all trials, all subjects in the active treatment groups were received a triple combination therapy of telaprevir, RBV, and Peg-IFN-alfa-2a. Based on these trial designs, it is difficult to completely tease out the relative contributions of each component to a clinical response due to the potential interactions among components.*

- *Only the 750-mg q8h telaprevir dose was tested in the trials. For the extrapolation purpose, the correlations identified in this study may be limited by the range of telaprevir exposures resulting from this regimen.*
- *The number of subjects in each quartile of exposure is relatively small (i.e., 22 to 26 subjects) in the prior treatment failure trial for establishing a solid exposure-response relationship in this population.*

# 4 Reviewer's Analysis

## 4.1 Introduction

This is the original submission of telaprevir (TVR), a member of a new class of direct-acting antiviral agents, the HCV NS3•4A protease inhibitors. The Applicant is seeking approval of TVR in combination with peginterferon alfa (PEG-IFN) and ribavirin (RBV), for the treatment of genotype 1 chronic hepatitis C. Based on the trial design, it is difficult to completely tease out the contributions of each component in the combination to a clinical response and optimize the dosing regimen for each component separately. During the course of the review, a number of efficacy and safety events appeared to be associated with TVR treatment in combination with PEG-IFN and RBV. A thorough review of the dosing strategy and exposure-response relationships for efficacy and safety is performed.

### 4.2 Objectives

Analysis objectives are:

1. to assess the 750 mg q8h TVR dose based on the exposure-response relationship for efficacy and safety
2. to assess the 12-week TVR treatment duration and explore whether there are sub-populations can be benefited from the shorter 8-week TVR treatment
3. to evaluate the response-guided Peg-IFN/RBV treatment for the prior treatment relapse patients
4. to evaluate alternative virologic stopping rule criteria at Week 4 and 12

### 4.3 Methods

#### 4.3.1 Data Sets

Data sets used are summarized in Table 6.

**Table 6. Analysis Data Sets**

| Study Number | Name | Link to EDR |
|---|---|---|
| vx07-950-108 | adhc.xpt | \\cdsesub1\evsprod\NDA201917\0004\m5\datasets\vx07-950-108\analysis\adhc.xpt |
| vx07-950-108 | adsl.xpt | \\cdsesub1\evsprod\NDA201917\0004\m5\datasets\vx07-950-108\analysis\adsl.xpt |
| iss-phase- | ppad.xpt | \\cdsesub1\evsprod\NDA201917\0005\m5\datasets\iss-phase-2and3\analysis\ppad.xpt |

| | | |
|---|---|---|
| 2and3 | | |
| vx-950-pkpd | pkpd.xpt | \\cdsesub1\evsprod\NDA201917\0024\m5\datasets\vx-950-pkpd\analysis\pkpd.xpt |
| vx07-950-108 | mb.xpt | \\cdsesub1\evsprod\NDA201917\0019\m5\datasets\vx07-950-108\listings\mb.xpt |
| vx08-950-111 | mb.xpt | \\cdsesub1\evsprod\NDA201917\0021\m5\datasets\vx08-950-111\listings\mb.xpt |
| vx-950-tidp24-c216 | mb.xpt | \\cdsesub1\evsprod\NDA201917\0021\m5\datasets\vx-950-tidp24-c216\listings\mb.xpt |
| vx05-950-104 | mb.xpt | \\cdsesub1\evsprod\NDA201917\0024\m5\datasets\vx05-950-104\listings\mb.xpt |
| vx05-950-104eu | mb.xpt | \\cdsesub1\evsprod\NDA201917\0024\m5\datasets\vx05-950-104eu\listings\mb.xpt |
| vx06-950-106 | mb.xpt | \\cdsesub1\evsprod\NDA201917\0024\m5\datasets\vx06-950-106\listings\mb.xpt |
| vx06-950-107 | mb.xpt | \\cdsesub1\evsprod\NDA201917\0027\m5\datasets\vx06-950-107\listings\mb.xpt |
| vx-950-tidp24-c208 | mb.xpt | \\cdsesub1\evsprod\NDA201917\0027\m5\datasets\vx-950-tidp24-c208\listings\mb.xpt |

### 4.3.2 Software

SAS, R, and NONMEM were used for the reviewer's analyses.

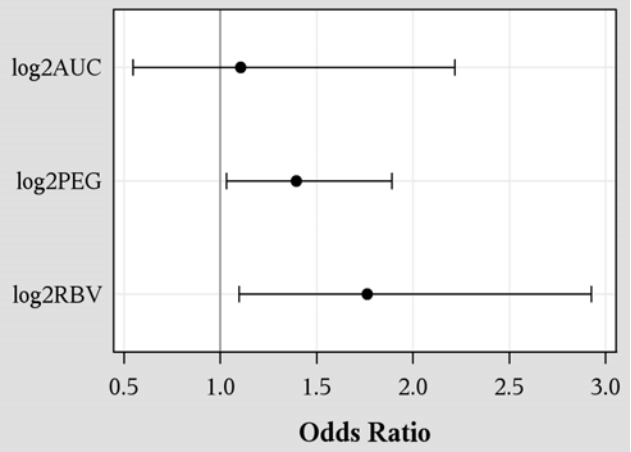
### 4.3.3 Models and Results

To avoid the potential confounding effect from different TVR regimens, the reviewer's analyses focused only on T12/PR treatments.

#### 4.3.3.1 Exposure-Response relationship for efficacy

The exposure-response analyses for efficacy mainly focused on the treatment naïve population. Multivariate logistic regression modeling and graphic visualization were used to explore the effects of drug exposures and baseline characteristics on the clinical outcomes. Base on these analyses, the relationships between TVR exposure and all efficacy endpoints (SVR24, RVR, eRVR, VBT, and relapse) were shallow, and statistically non-significant. As shown in Figure 1, higher TVR exposure was only weakly associated with increased SVR. Multivariate logistic analyses indicated that RBV exposure was significantly correlated with eRVR and SVR (Figure 7). However, this correlation between RBV exposure and SVR did not exist in the sub-group of patients who achieved RVR which accounted for approximate 70% of TVR treatment population (Figure 8).

**Figure 7. Effect of RBV Exposure on SVR [in the Treatment Naïve Patients with T12/PR]**



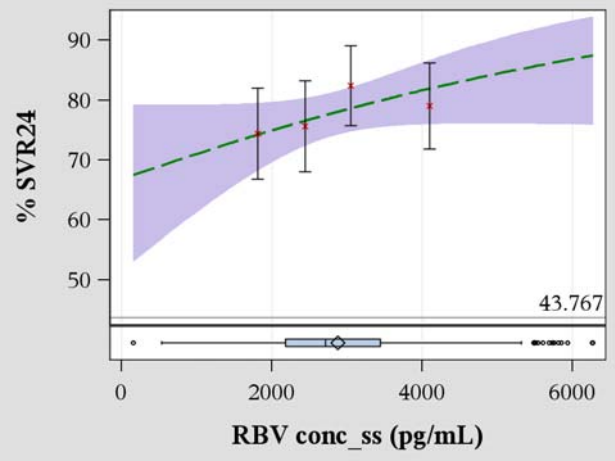
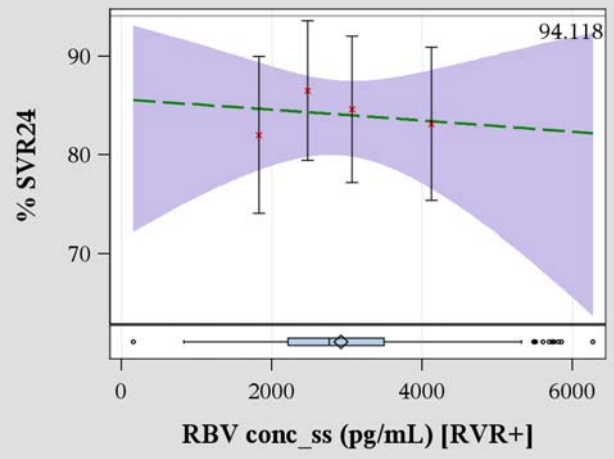
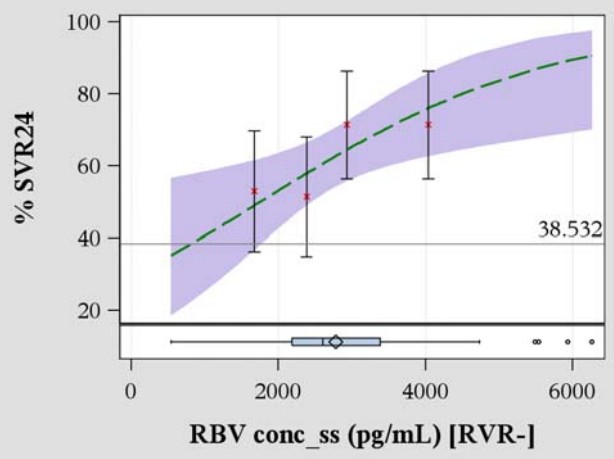




**Figure 8. Correlation between SVR and RBV Exposure by RVR Status (Left: RVR+ and Right: RVR -) [in the Treatment Naïve Patients with T12/PR]**




#### 4.3.3.2 Exposure-Response relationship for safety

The exposure-response analyses for safety mainly focused on the pooled population with a 12-week TVR treatment combined with PEG-IFN/RBV. Multivariate logistic regression modeling and graphic visualization were used to explore the effects of drug exposures and baseline characteristics on the clinical safety outcomes. Base on these analyses, the relationship between rash toxicity and all drug (TVR, PEG-IFN, and RBV) exposures were shallow, and statistically non-significant (Figure 9). However, higher TVR exposure was significantly associated with increased risk of Hgb toxicity (Figure 1). From a multivariate logistic analysis, the odd ratio of Hgb toxicity for doubling the TVR exposure is 2.4 (95% CI: 1.6, 3.6) after adjusting for PEG-IFN and RBV exposure. The exposure-response relationship between Hgb toxicity and RBV exposure is steepest compared to the relationship with respect to TVR or PEG-IFN exposure, with the odd ratio for doubling the RBV exposure as 5.2 (95% CI: 3.6, 7.5) [Figure 10].

**Figure 9. Correlations between Rash Toxicity and Drug Exposures Were Shallow [in Pooled Population with 12-week Telaprevir Combined with PEG-IFN/RBV]**

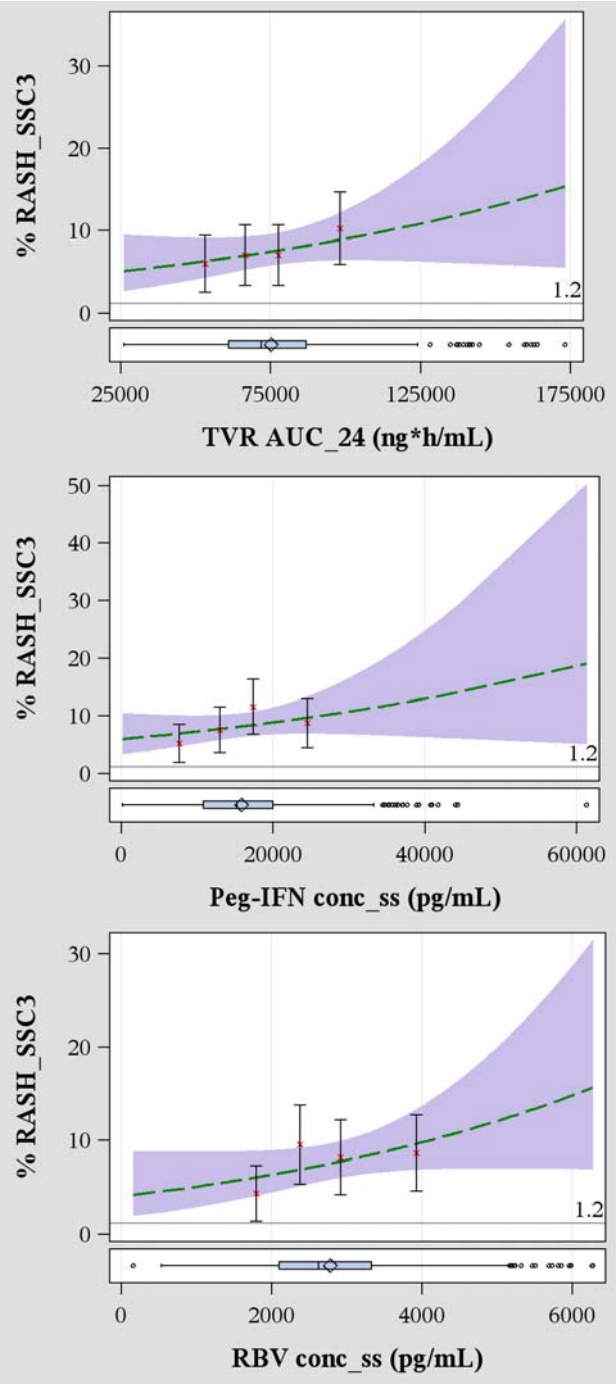
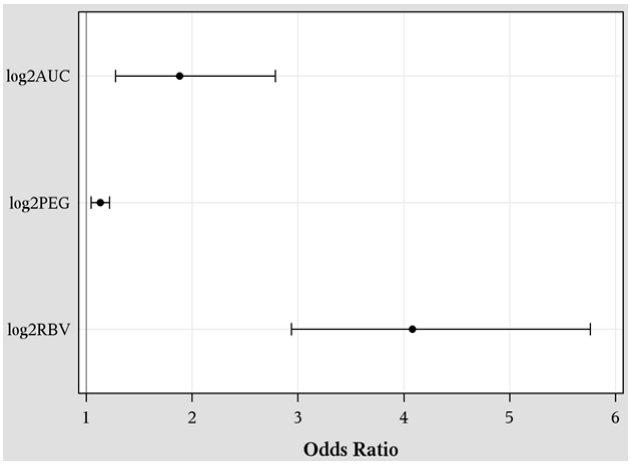
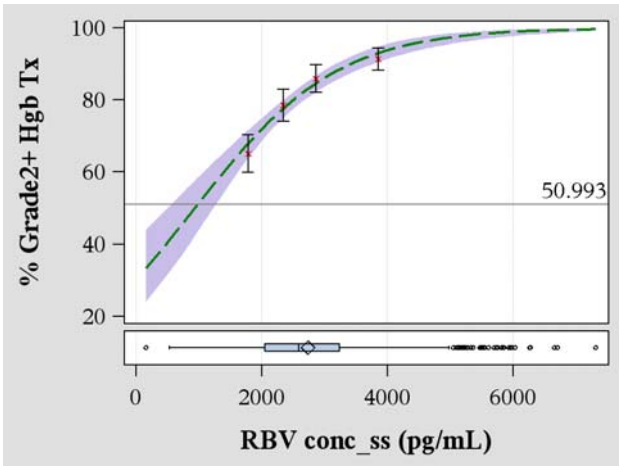


**Figure 10. Effect of RBV Exposure on Hgb Toxicity**

**[in Pooled Population with 12-week Telaprevir Combined with PEG-IFN/RBV]**




#### 4.3.3.3 Telaprevir 8-week versus 12-week treatment duration

For treatment naïve patients (Study 108), both TVR 8-week (T8/PR) and 12-week (T12/PR) treatment in combination with PEG-IFN/RBV achieved significantly higher SVR compared to the standard of care treatment (SOC). In the overall naïve population, the proportion of patients achieving SVR was numerically (6%) higher in T12/PR compared to T8/PR, but the proportion of patients with Grade 3 rash ESI was also higher (2.5%) in T12/PR (Table 7 and Figure 2).

**Table 7. Proportion of Patients Achieving SVR Was Numerically Higher in T12/PR Compared to T8/PR, but Proportion of Patients with Grade 3 Rash ESI Was Also Higher in T12/PR (Study 108)**

| | T8/PR | T12/PR | P/PR |
|---|---|---|---|
| Variable n (%) | N=364 | N=363 | N=361 |
| SVR24 | 250 (68.7) | 271 (74.7) | 158 (43.8) |
| Grade 3 rash ESI | 13 (3.6) | 22 (6.1) | 2 (0.6) |

To explore whether there are some sub-populations can be benefited from the shorter 8-week TVR treatment, subgroup analyses by patient's baseline characteristics (i.e., baseline HCV RNA value, liver disease status, race, HCV genotype) or virologic early response (RVR or eRVR) status were conducted. The proportion of patients achieving SVR with the T8/PR treatment was comparable to that with the T12/PR treatment among patients with baseline HCV RNA levels less than 800,000 IU/mL (Table 8 and Figure 3), which suggests that treatment naïve patients with low baseline HCV RNA levels (HCV RNA < 800,000 IU/mL) may consider to adopt the shorter (8-week) TVR regimen to reduce safety risks (e.g., rash, Hgb toxicity, and anemia) without any substantial lose of efficacy in comparison to the 12-week treatment as proposed by the Applicant.

**Table 8. SVR Rate by Patient's Baseline or Early Response Characteristics (Study 108)**

| Baseline/Early response Characteristics | T8/PR | | T12/PR | | Pbo/PR48 | |
|---|---|---|---|---|---|---|
| | N | n (%) | N | n (%) | N | n (%) |
| Total | 364 | 250 (68.7) | 363 | 271 (74.7) | 361 | 158 (43.8) |
| Baseline HCV RNA (IU/mL) | | | | | | |
| <800000 | 85 | 67 (78.8) | 82 | 64 (78.0) | 82 | 57 (69.5) |
| ≥800000 | 279 | 183 (65.6) | 281 | 207 (73.7) | 279 | 101 (36.2) |
| Liver Disease Status | | | | | | |
| Cirrhosis | 26 | 11 (42.3) | 21 | 13 (61.9) | 21 | 7 (33.3) |
| No cirrhosis | 338 | 239 (70.7) | 342 | 258 (75.4) | 340 | 151 (44.4) |
| Race | | | | | | |
| Caucasian | 315 | 220 (69.8) | 325 | 244 (75.1) | 318 | 147 (46.2) |
| Black | 40 | 23 (57.5) | 26 | 16 (61.5) | 28 | 7 (25.0) |
| Genotype | | | | | | |
| 1a | 210 | 138 (65.7) | 213 | 152 (71.4) | 208 | 85 (40.9) |
| 1b | 151 | 111 (73.5) | 149 | 118 (79.2) | 151 | 73 (48.3) |
| RVR status | | | | | | |
| RVR+ | 242 | 188 (77.7) | 246 | 206 (83.7) | 34 | 32 (94.1) |
| RVR- | 122 | 62 (50.8) | 117 | 65 (55.6) | 327 | 126 (38.5) |
| eRVR status | | | | | | |
| eRVR+ | 207 | 171 (82.6) | 212 | 189 (89.2) | 29 | 28 (96.6) |
| eRVR- | 157 | 79 (50.3) | 151 | 82 (54.3) | 332 | 130 (39.2) |

However, the cumulative viral breakthrough (defined as an more than 1-log10 increase in on-treatment HCV RNA compared to the lowest recorded on-treatment value or an on-treatment HCV RNA level of >100 IU/mL in a subject who had undetectable HCV RNA at a prior time point) rate was higher with T8/PR (5.8%: 21/364) compared to that with T12/PR (2.8%: 10/363) during PEG-IFN/RBV treatment. In patients with patients with low baseline HCV RNA levels (<80000 IU/mL), the cumulative viral breakthrough rate was 4.7% (4/85) in the T8/PR group versus the 1.2% (1/82) in the T12/PR group.

#### 4.3.3.4 Response-guided Peg-IFN/RBV treatment for the prior treatment relapsers

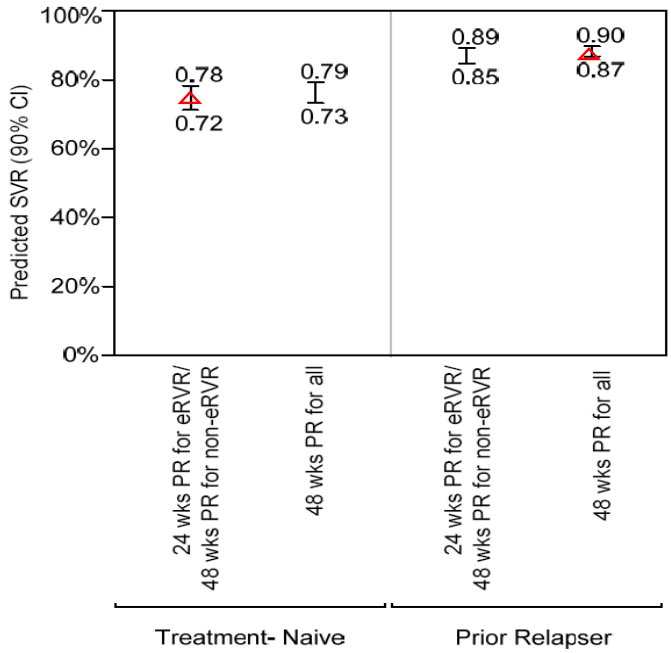
In the pivotal clinical trial for prior treatment failure patients (Study C216), only the 48-week Peg-IFN/RBV treatment duration was tested. This trial design was not able to evaluate the response-guided Peg-IFN/RBV treatment for any subgroup of the prior treatment failure patients directly. However, the response-guided Peg-IFN/RBV treatment (RGT) was tested in a Phase 2 trial (Study 107) where patients were assigned to short and long duration base on eRVR status. The 24-week Peg-IFN/RBV treatment duration was also tested in another Phase 2 trial (Study 106). Data from pivotal study in treatment experienced patients (Study C216) was also used to gain insights into SVR rates among prior relapse patients who achieved eRVR. A cross-study comparison between 24-week and 48-week PEG-IFN/RBV duration was conducted among the prior relapse patients treated with TVR who achieved eRVR. It was found that:

- The SVR rates were high in prior relapsers (~90%), irrespective of Peg-IFN/RBV duration (24- or 48-week) [Figure 4].

- Within the Phase 2 trial (Study 106) where treatment was randomized, longer PEG-IFN/RBV treatment (T24/PR48) did not seem to provide additional benefit compared to shorter treatment (91% SVR with T24/PR48 vs. 89% with T12/PR24).

To support the proposed labeling recommendation, the Applicant conducted a retrospective viral dynamic simulation analysis of prior relapsers who achieved eRVR. The viral dynamic model incorporated the presence of viral variants of differing TVR resistance profiles and fitness, and the variability in subject responses to PR treatment. The model produced reasonable matches to the observed clinical outcomes in Phase 2 and Phase 3 studies. Results of viral dynamic modeling analyses predict limited virological benefit of extending PR duration to longer than 24 weeks for treatment-naïve subjects and for prior relapsers with eRVR (Figure 11).

**Figure 11. Viral Dynamic Predicted SVR Rates by Prior PR Response, Comparing Response-Guided T12/PR24-48 Regimen With T12/PR48**




*Source: the Applicant's report, Summary of Clinical Pharmacology Studies, Figure 19 on page 133.*

To further confirm that response-guided Peg-IFN/RBV treatment duration for prior relapse patients is acceptable, we conducted additional analyses to bridge knowledge from treatment naïve population to prior treatment experienced patients.

**Prior relapse patients are a subset within treatment naïve population**

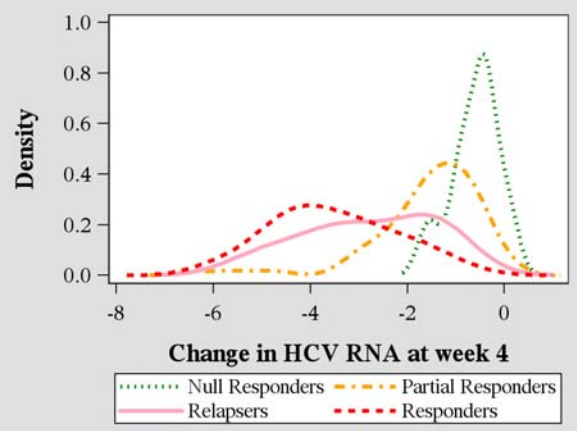
The high rates (>90%) of SVR in prior relapse subjects who achieved eRVR suggested strong response to triple regimen in this subgroup. Mechanistically, we would expect lack of virologic resistance to PegIFN/RBV and emerging genetic evidence that response to PegIFN is dependent, in large part, on host factors (eg. *IL28B*) and not the virus. If so, prior relapse patients should

respond to triple therapy regimen very much like a subset of treatment naïve population that would relapse if treated with pegIFN/RBV.

To further support the lack of potential resistance to pegIFN/RBV, we compared the distribution of mean change in HCV RNA at week 4 of treatment in the control PR48 arm of Study 108 (treatment naïve subjects) according to their ultimate treatment outcome to a similar week 4 HCV RNA measurement in subjects in the PR48 and the delayed start T12/PR48 arms of Study C216 (treatment experienced). Figure 12a shows the distribution of Week 4 HCV RNA change by end of treatment status for treatment naïve patients in the PR48 arm. Figure 12b shows the same distribution of Week 4 HCV RNA change for treatment experienced patients by response to prior treatment. The Week 4 response to PegIFN/RBV within each subgroup is similar suggesting that the previous exposure to PegIFN/RBV has not changed the patient's responsiveness to PegIFN/RBV. Therefore, it is clear that treatment naïve population already contains the distribution of these subgroups.

**Figure 12. Distribution of Change in HCV RNA at Week 4 in Cohorts receiving PegIFN/RBV**

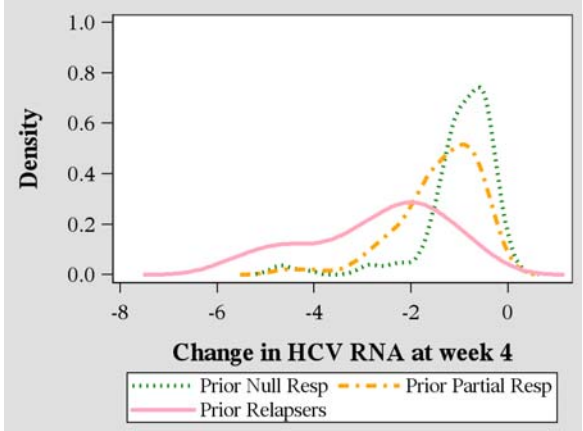
a. Treatment naïve subjects receiving PR48 according to final treatment outcome (Study 108)




Log change in HCV RNA at week 4

| | Mean | Q1 | Median | Q3 |
|---|---|---|---|---|
| Relapsers | -2.8 | -3.6 | -2.9 | -1.5 |
| Partial Responders | -1.6 | -2.0 | -1.4 | -0.9 |
| Null Responders | -0.6 | -0.9 | -0.5 | -0.4 |

b. Treatment experienced subjects receiving PR according to prior response to treatment (Study C216)



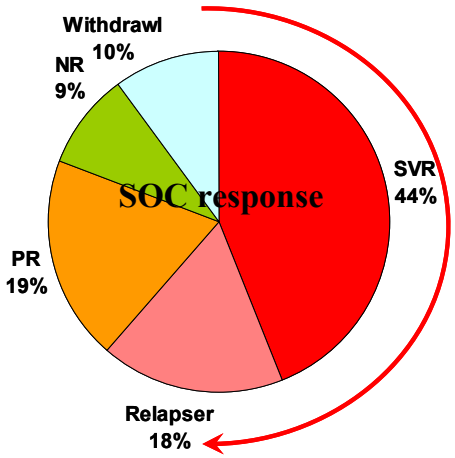

Log change in HCV RNA at week 4

| | Mean | Q1 | Median | Q3 |
|---|---|---|---|---|
| Relapsers | -2.7 | -3.6 | -2.4 | -1.7 |
| Partial Responders | -1.4 | -1.8 | -1.3 | -0.8 |
| Null Responders | -1.0 | -1.2 | -0.9 | -0.5 |

**Data from treatment naïve and experienced population can be bridged to derive dosing recommendations for prior relapse patients**

Based on the data provided above, any treatment naïve population can be theoretically divided into potential responder, relapser, partial responder, and null responder subgroups based on the response to SOC although this response is not known at the time treatment is initiated. Figure 13 demonstrates the distribution at baseline of the potential subgroups in the naïve population, The distribution was derived from the observed outcome with SOC from Study 108.

**Figure 13. Distribution of the outcome with SOC from Study 108 with arrow indicating direction of decreasing effectiveness for therapies**



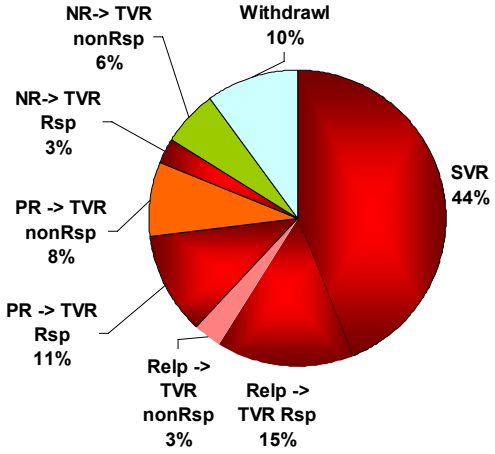

Because patients were randomized, patients that will potentiall fail are already represented in the overall treatment naïve population. If the argument is true, the expected results for prior experienced patients with TVR triple regimen can be derived from the overall treatment naïve population with the same TVR triple regimen, and vice versa.

To demonstrate that knowledge from prior experienced patients inform about response among naïve population, the observed SVR rate for each of the prior failure groups from Study C216 was applied to derive the expected SVR rate for the overall naïve population with T/PR in Study 108. The predicted SVR (73%) for treatment naïve patients using data from treatment experienced patients matched closely to the overall actual SVR rate observed with T/PR in Study 108 (75%) [Figure 14]. Moreover, using the same approach, the SVR rate with T/PR for the naïve patients with eRVR+ in Study 108 was derived to be 92%, which also matched closely the observed 88-92% SVR rate with T/PR for the naïve patients with eRVR in Study 108 and Study 111. If the information about treatment naïve patients was not contained in the treatment experienced group, it would not be possible to derive expected response in one population using another population.

**Figure 14. Data from prior experienced patients (C216 trials) inform about response among naïve patients**

| Naïve population | % with SOC | TVR response % Within group | SVR % Overall |
|---|---|---|---|
| Responders | 44 | 100[a] | 44 |
| Relapsers | 18 | 86[b] | 15 |
| Partial Responders | 19 | 57[b] | 11 |
| Null Responders | 9 | 31[b] | 3 |
| Total SVR rate | | | 73 |

[a] based on the response to SOC
[b] observed response rate the pivotal clinical trial for prior treatment failure patients (Study C216)




In conclusion, the results of above analyses indicate that knowledge from prior experienced patients informs about response among naïve patients, and vice versa. The baseline prior response characteristics to SOC reflect the same patients' potential response characteristics to SOC before the treatment actually start (i.e., naïve population is a combination of the potential responder, relapser, partial responder, and null responder subgroups to SOC). Because Study 111 indicates that RGT should be applied in the naïve population, baseline prior relapsers (same as the potential prior relapsers who are a subgroup of naïve population which responses to the T/PR second best) should also receive the same RGT regimen.

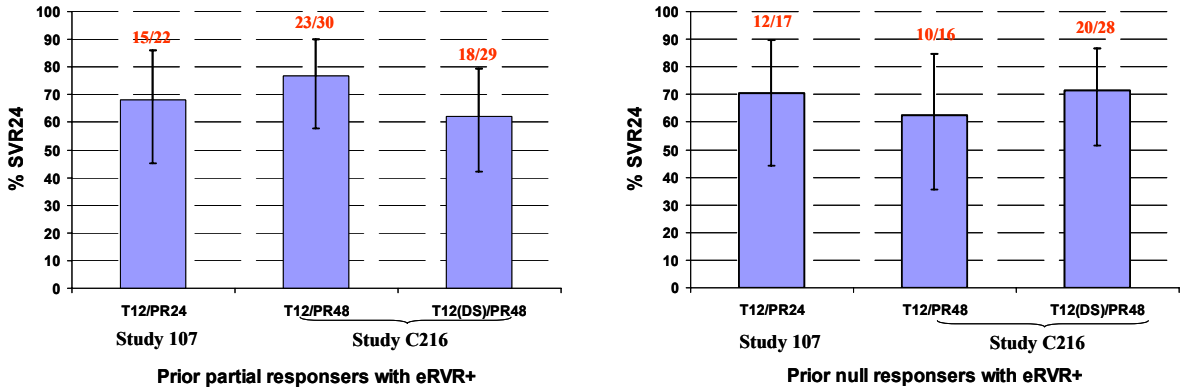
#### 4.3.3.5 Response-guided PEG-IFN/RBV treatment for the prior treatment partial responders and null responders

Similar arguments as above for the prior relpapsers can be applied to prior partial and null responders: i.e., baseline prior partial and null responders who are same as the potential prior and null responders respectively represented as unknown subgroups of naïve population should also receive the same dosing regimen as their corresponding potential subgroups in the naïve population.
A cross-study comparison between 24-week and 48-week PEG-IFN/RBV duration was conducted among the prior partial or null responders treated with TVR who achieved eRVR. It was found that:

- The SVR rates were 62-77% in prior partial responders, irrespective of Peg-IFN/RBV duration (24- or 48-week) [Figure 15 left].
- The SVR rates were 62-71% in prior null responders, irrespective of Peg-IFN/RBV duration (24- or 48-week) [Figure 15 right].
- Study 106 did not differentiate null responders and partial responders. For the overall non-responders, the SVR rates were 68% irrespective of Peg-IFN/RBV duration (24- or 48-week).

The limited clinical data support the same RGT regimen should also be applied to prior partial and null responders.

**Figure 15. SVR Rates Among Cohorts of Prior Partial Responders (Left) and Null Responders (Right) achieving eRVR in Phase 2 and Phase 3 Telaprevir Trials**




T12(DS)/PR48 is the treatment with 4-week delayed start of TVR.
The Y-error bars are the 95% Fisher Exact Confidence Limits for each treatment group.

### 4.3.3.6 Virologic stopping rule criteria at Week 4 and 12

TVR stopping rules were instituted during the clinical development program to avoid unnecessary exposure in patients who were not likely to achieve SVR, and to curtail potential evolution of TVR-resistant HCV variants that could occur with continued TVR treatment. In Phase 3 trials for treatment naïve patients (Studies 108 and 111), TVR dosing was discontinued in subjects with >1000 IU/mL HCV RNA at Week 4. In Phase 3 Study C216 for prior treatment failure patients, TVR dosing was discontinued in subjects with >100 IU/mL HCV RNA at Week 4, Week 6, or Week 8. In addition, patients discontinue treatment at Week 12 in all studies if they do not have EVR in all studies. However, the Applicant proposed a different stopping rule in the label:

(b) (4)

The reviewer performed independent analyses to evaluate alternative virologic stopping rule criteria at Week 4 and 12. As shown in Table 1, in the pivotal trials:

- There were about 2% of treatment naïve patients with >1000 IU/mL HCV RNA at Week 4, and none of these patients achieved SVR even through the PEG-IFN/RBV treatment was continued. Therefore, there is limited benefit to continue PEG-IFN/RBV treatment in subjects with >1000 IU/mL HCV RNA at Week 4.
- There were about 4% of treatment naïve patients with >1000 IU/mL HCV RNA at Week 12, and none of these patients achieved SVR even through the PEG-IFN/RBV treatment was continued. Therefore, there is limited benefit to continue PEG-IFN/RBV treatment in subjects with >1000 IU/mL HCV RNA at Week 12.
- Further, there were about 2% of treatment naïve patients with 100-1000 IU/mL HCV RNA at Week 4. Among these patients, 26% achieved SVR. Therefore, TVR/PEG-

IFN/RBV treatment should be continued in subjects with 100-1000 IU/mL HCV RNA at Week 4, especially when there is no other better choice available.

- About 1% of treatment naïve patients had HCV RNA levels between 100 and 1000 IU/mL at Week 12. Among these patients, 25% achieved SVR. Therefore, PEG-IFN/RBV treatment can be continued in subjects with 100-1000 IU/mL HCV RNA at Week 12.

For prior treatment failure patients in Study C216, there were approximate 2% patients with 100-1000 IU/mL HCV RNA at Week 4 and 1% at Week 12. Harmonizing the stopping rules (>1000 IU/mL HCV RNA) as suggested in the treatment naïve patients is reasonable.

- There were 18 out of 266 (6.8%) subjects met the HCV RNA > 100 IU/mL stopping criteria at Week 4. Among them, there were 7 out of 266 (2.6%) patients with HCV RNA 100-1000 IU/mL and 1 out of these 7 subjects (14.3%) achieved SVR.
- There were 2 out of 266 (0.8%) subjects had HCV RNA level 100-1000 IU/mL at week 12, none had SVR.

## 5 Listing of Analyses Codes and Output Files

| File Name | Description | Location in \\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\ |
|---|---|---|
| PKPD4.sas | ER analysis | \Telaprevir_NDA201917_JL\ER_Analyses\ |
| VR_108.sas | PPK ER analysis and bootstrap for AR | \Telaprevir_NDA201917_JL\ER_Analyses\ |
| quartilePlot_logistic_v2.sas | ER plotting | \Telaprevir_NDA201917_JL\ER_Analyses\ |

# Appendix - Population PK Analyses of Telaprevir by Dr. Kevin Krudys

## 6 Summary of Findings

### 6.1 Key Review Questions

The purpose of this review is to address the following key questions.

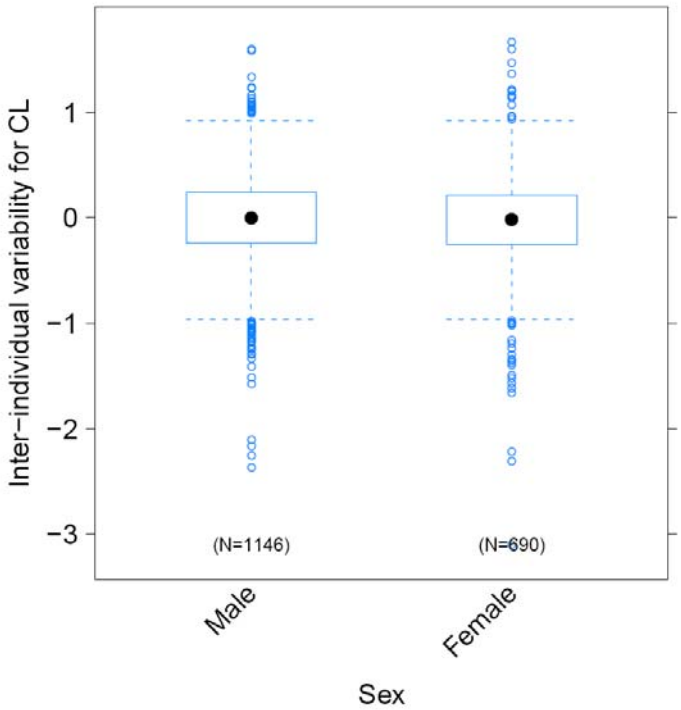
#### 6.1.1 Are the pharmacokinetic statements in the label supported by the population pharmacokinetic analysis submitted by the Applicant?

##### 6.1.1.1 Gender

The population pharmacokinetic analysis supports the following proposed labeling language, (b) (4)

The Applicant did not include gender in the full covariate model because gender was moderately correlated with weight with a correlation coefficient absolute value greater than 0.45. Furthermore, inter-individual variability in clearance (after adjusting for weight) did not show a relationship with gender (Figure 16).

**Figure 16. Relationship between Inter-individual Variability in CL/F and Gender**

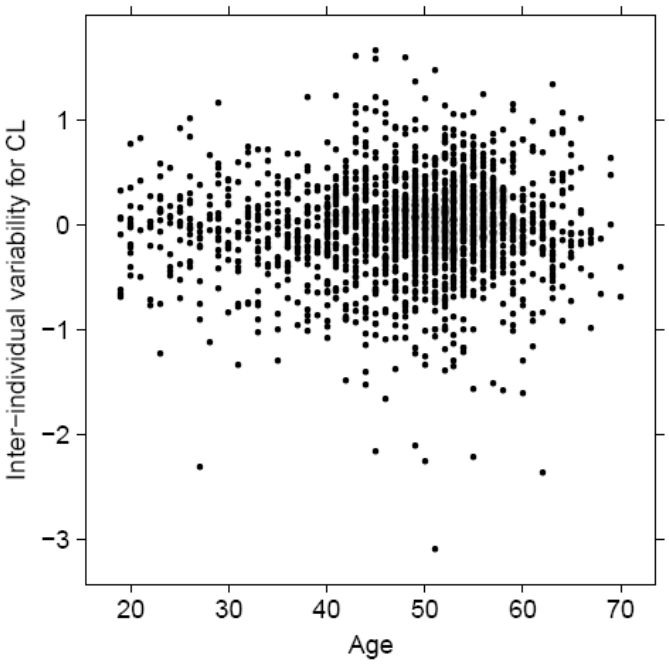



##### 6.1.1.2 Age

The population pharmacokinetic analysis supports the following proposed labeling language, (b) (4)

The results of the Applicant's analysis indicated that distributions of CL/F estimates for subjects at the extremes of the age range in the population lie entirely within 20% of the typical reference value, with confidence intervals overlapping the null value. Furthermore, there was no relationship between inter-individual variability in CL/F estimates and age (Figure 17).

**Figure 17. Relationship between Inter-individual Variability in CL/F and Age**




#### 6.1.1.3 Race

The population pharmacokinetic analysis supports the following proposed labeling language, "*Population pharmacokinetic analysis of telaprevir in HCV-infected subjects indicated that race had no apparent effect on the exposure to telaprevir.*"

The results of the Applicant's analysis indicated that distribution of CL/F estimates for subjects of race other than Caucasian lies entirely within 20% of the reference value. The mean effect of non-Caucasian race in the pharmacokinetic model was approximately 7%.

## 7 Results of Applicant's Analysis

The Applicant conducted a population pharmacokinetic analysis to:

1. Characterize the pharmacokinetics of telaprevir in adults with genotype 1 hepatitis C virus infection
2. Evaluate the effects of covariates on telaprevir exposure
3. Obtain individual estimates of telaprevir exposure to be used in exposure-response analysis

The dataset consisted of plasma concentrations from four Phase 2 studies (104, 104EU, 106 and C208) and three Phase 3 studies (108, 111 and C216). In all studies, telaprevir was administered in tablet formulation under fed conditions in combination with Peg-IFN-alfa-2a or Peg-IFN-alfa-2b, and with or without ribavirin. The schedule of PK assessments varied between trials, with a combination of frequent and sparse sampling schedules. Records for which concentrations were missing or below the limit of quantification (BLQ) (1.14%) were removed from the database. Further details of the dataset are provided in Table 9.

**Table 9. Summary of Data Included in the Population Pharmacokinetic Analysis**

| **Study** | **104** | **104EU** | **106** | **C208** | **108** | **111** | **C216** |
|---|---|---|---|---|---|---|---|
| Number of subjects | 175 | 239 | 339 | 82 | 641 | 173 | 191 |
| Number of PK samples | 2442 | 3455 | 2071 | 1437 | 2842 | 736 | 1468 |
| Treatment history | naive | naive | failure | naive | naive | naïve | failure |
| Telaprevir dose regimen | 1250 mg loading dose; 750 mg q8h | 1250 mg loading dose; 750 mg q8h | 1125 mg loading dose; 750 mg q8h | 750 mg q8h or 1125 mg q12h | 750 mg q8h | 750 mg q8h | 750 mg q8h |
| Telaprevir formulation | 250 mg tablet | 250 mg tablet | 375 mg tablet | 375 mg tablet | 375 mg tablet | 375 mg tablet | 375 mg tablet |
| Timing of PK assessments | Days 1, 4, 8, 15, 22, 29, 43, 51, 57 and 85 | Days 1, 4, 8, 15, 22, 29, 43, 51, 57 and 85 | Day 1; Wks 2, 4, 8, 12, 16, 24 | Days 1, 2, 3, 4, 8; Wks 2, 3, 4, 8, 12 | Day 1; Wks 1, 2, 4, 8, 12 | Day 1; Wks 1, 2, 4, 8, 12 | Wks 1, 2, 5, 6, 8, 12, 16 |

## 7.1 Pharmacokinetics Structural Model

The selection of a one compartment model as the structural model was informed by population pharmacokinetic analysis of earlier studies. The model was parameterized in terms of absorption rate constant ($k_a$), apparent clearance (CL/F) and apparent volume of distribution (V/F). Earlier in the drug development program, a time dependent $k_a$ was used to describe Day 1 absorption to account for an observed difference in telaprevir kinetics between Day 1 and steady-state. In the current analysis, the Applicant explored three absorption models; 1) first-order, 2) sequential zero- then first-order and 3) Weibull-type. Although a Weibull-type absorption model for Day 1 followed by first-order absorption for subsequent doses appeared to provide the best fit, the first-order absorption model for all doses provided better stability and was chosen for the final structural model. An additional study level covariate on the bioavailability term was used to stabilize the model and account for inter-study differences. Inter-individual variability was modeled using an exponential error model. A covariance between CL/F and V/F was included and V/F and $k_a$ shared a random effect parameter. Residual variability was parameterized with

additive and proportional error model terms for each of the two assays used (b) (4) .

*Reviewer's Comments: The structural model provides a reasonable description of telaprevir pharmacokinetics. The model tended to over-predict observed concentration within the first two hours post-dose, especially on Day 1. This is most likely due to the use of the first-order absorption model. Estimates of CL/F were unaffected by the choice of absorption model and therefore this misspecification is unlikely to affect covariate analysis or individual estimates of exposure. Shrinkage on CL/F (10%) and V/F (34%) was moderate, supporting the use of individual exposure estimates in exposure-response analysis. The term describing the effect of study on bioavailability suggests a 25% difference between different studies. The Applicant does not provide an explanation for this potential source of this variation even though the difference appears to be significant. Model predictive performance was also supported by a visual predictive check.*

## 7.2 Pharmacokinetics Covariate Model

The effects of covariates (Table 10) on telaprevir pharmacokinetics were evaluated using the full model estimation approach. Continuous covariates were modeled using a power function normalized by the median value of the covariate.

**Table 10. Summary of Covariates Included in the Covariate Model**

| Parameter | Covariate | Rationale |
|---|---|---|
| CL/F | AGE | Clinical interest |
| | RACE | Clinical interest |
| | WGT | Prior knowledge of weight effect on CL/F from exploratory analyses done in Studies 104 and 104EU. |
| | NRBV | To account for the potential effect of the concomitant administration of RBV on telaprevir PK. |
| V/F | WGT | To stabilize the model and physiological plausibility |
| F1 | FORM | Prior knowledge of potential difference in exposure following single 750-mg dose in the fed state with 250-mg and 375-mg tablets from Study 010 |
| | GRPB | To account for differences in the observed concentration data between studies |

*Source: Pharmacokinetics Study Report G190, P-19, Table 7-1.*

A summary of the covariates in the population is presented in Table 11.

**Table 11. Summary of Baseline Covariates**

| Covariate | Statistic | Value |
|---|---|---|
| Age (yr) | Mean (SD) | 48.05 (9.78) |
| | Range | 19 – 70 |
| Weight (kg) | Mean (SD) | 80.10 (17.33) |
| | Range | 42.6 – 152 |
| Gender | Male | 1146 |

| | | |
|---|---|---|
| | Female | 690 |
| Race | White | 1614 |
| | Black | 149 |
| | Asian | 27 |
| | Other | 46 |
| Formulation | 250 mg | 412 |
| | 375 mg | 1424 |
| Ribavirin | Yes | 1647 |
| | No | 189 |

Parameter estimates of the covariate model are presented in Table 12 and Table 13.

**Table 12. Parameter Estimates of the Covariate Model (Fixed Effects)**

| Model Parameter | Parameter Description | Units | Estimate | Standard Error | %RSE |
|---|---|---|---|---|---|
| θ1 | Volume of Distribution (TVV), V/F | L | 252 | 13.5 | 5.36 |
| θ 2 | Clearance (TVCL), CL/F | L/hr | 32.4 | 0.336 | 1.04 |
| θ 3 | Absorption Rate Constant (TVKA) | $hr^{-1}$ | 0.230 | 0.0125 | 5.43 |
| θ 4 | Study Group on F1 | NA | 1.23 | 0.025 | 2.03 |
| θ 5 | Scaling factor of ETA1 on KA | NA | 0.191 | 0.0534 | 28.0 |
| θ 6 | Covariate for weight on V/F | NA | 0.625 | 0.0973 | 15.6 |
| θ 7 | Covariate for weight on CL/F | NA | 0.489 | 0.0337 | 6.89 |
| θ 8 | Covariate for age on CL/F | NA | -0.00398 | 0.0230 | 578 |
| θ 9 | Covariate for race on CL/F | NA | 1.07 | 0.0219 | 2.05 |
| θ 10 | Covariate for no RBV on CL/F | NA | 1.09 | 0.0264 | 2.42 |
| θ 11 | Covariate for formulation on F1 | NA | 1.01 | 0.0178 | 1.76 |

*Source: Pharmacokinetics Study Report G190, P-34, Table 8-5*

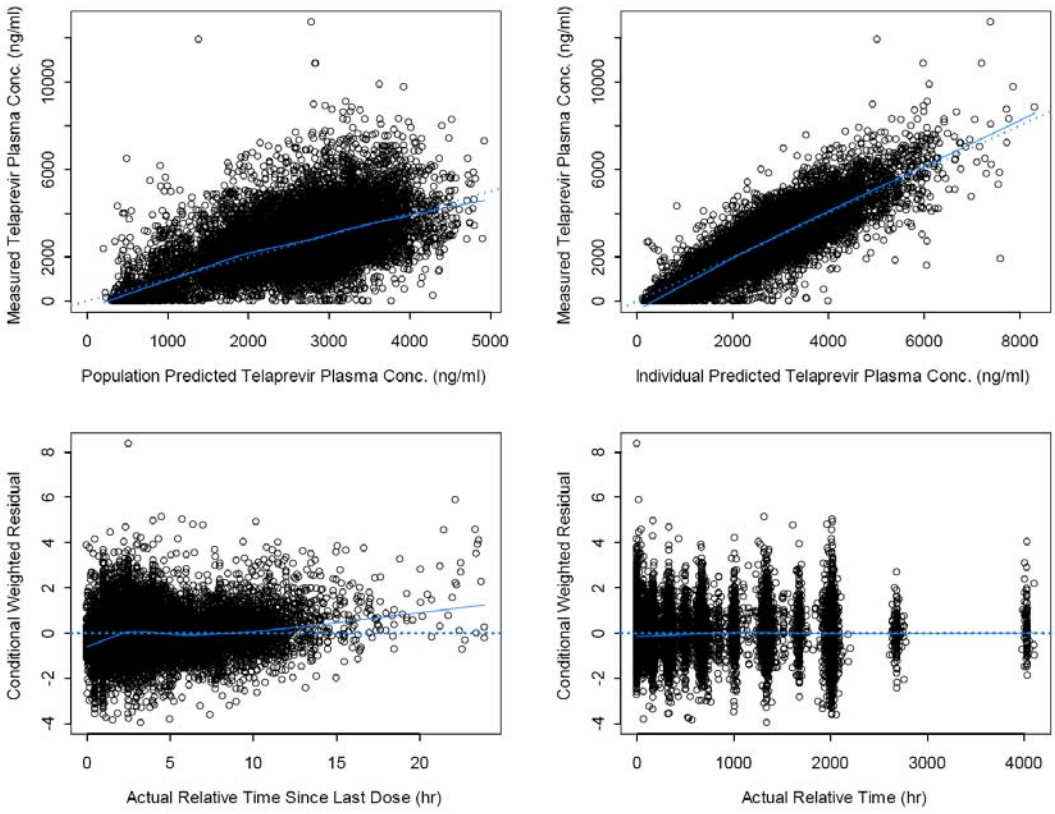
**Table 13. Parameter Estimated of the Covariate Model (Random Effects)**

| Model Parameters | Parameter Description | Estimate | Standard Error | %RSE | %CV |
|---|---|---|---|---|---|
| $\Omega_{1,1}$ | IIV in V/F and KA | 0.522 | 0.0701 | 13.4 | 72.2 |
| $\Omega_{2,2}$ | IIV in CL/F | 0.0740 | 0.00347 | 4.7 | 27.2 |
| $\Omega_{2,1}$ | Cov(V/F,CL/F) | 0.0548 | 0.00828 | 15.1 | NA |
| **Residual Variability** | **Parameter Description** | **Estimate** | **Standard Error** | **%RSE** | **%RV** |
| $\sigma_1$ | Proportional error (Covance) | 0.180 | 0.0562 | 31.2 | 18.0 |
| $\sigma_2$ | Proportional error (PRA) | 0.160 | 0.0785 | 49.1 | 16.0 |
| $\sigma_3$ (ng/mL) | Additive Error (Covance) | 547 | 143 | 26.1 | NA |
| $\sigma_4$ (ng/mL) | Additive Error (PRA) | 596 | 245 | 41.1 | NA |

*Source: Pharmacokinetics Study Report G190, P-34-35, Table 8-6*

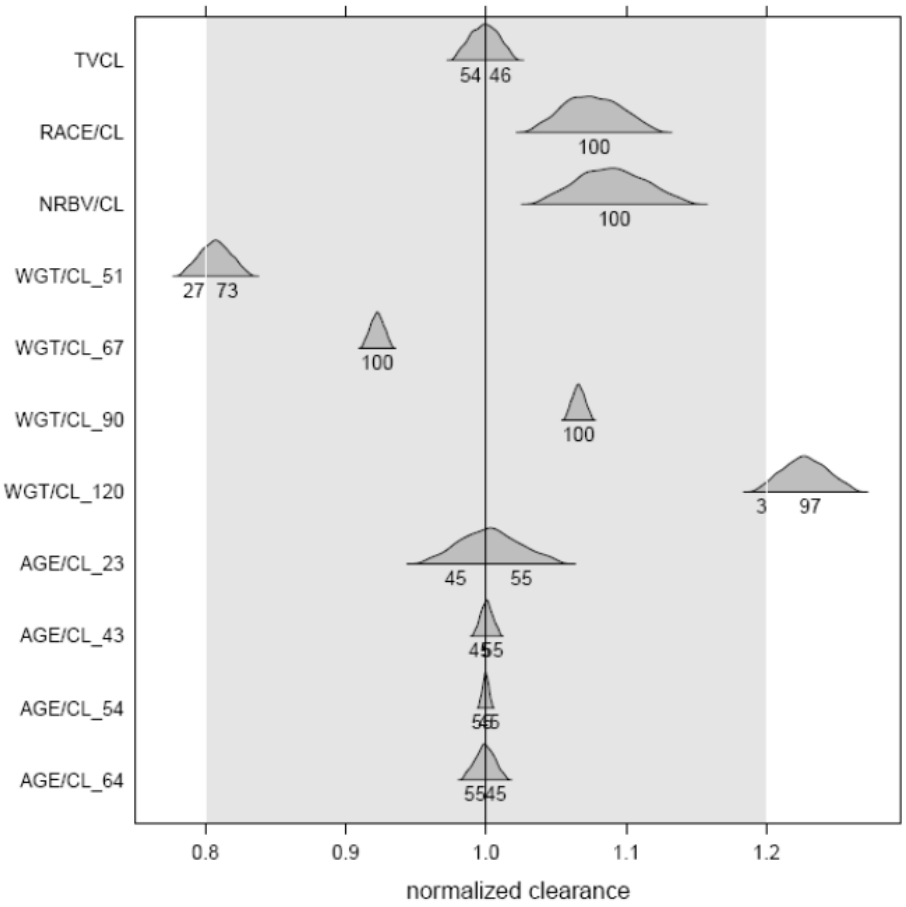
Basic goodness-of-fit plots for the full covariate model are provided in Figure 18.

**Figure 18. Basic Goodness-of-Fit Plots for the Full Covariate Model**




The potential clinical relevance of different covariates on telaprevir exposure was explored by evaluating CL/F at the range (0.025 and 0.975 quantiles) of covariate values observed in the database. The reference subject used for comparison was Caucasian with median covariate values, dosed with the 375 mg tablet with concomitant Peg-IFN and ribavirin and belonging to study Group A. The results are presented in Figure 19.

**Figure 19. Covariate Effects on Clearance**




Source: Appendix 13.15 and Appendix 13.17
Distributions of the normalized CL/F values from the non-parametric bootstrap of the full covariate model. The reference CL/F used was the point estimate from the full covariate model of a typical male, Caucasian subject of median age and weight, who received concomitant administration of ribavirin. Normalized distributions of CL/F subjects are shown for subjects of race other than Caucasian (RACE/CL), subjects who did not receive RBV (NRBV), subjects at the 2.5% quantile of weight (51kg, WGT/CL_51), subjects at the 25% quantile of weight (67kg, WGT/CL_67), subjects at the 75% quantile of weight (90kg, WGT/CL_90), subjects at the 97.5% quantile of weight (WGT/CL_120), subjects at the 2.5% quantile of age (23yrs, AGE/CL_23), subjects at the 25% quantile of age (43yrs, AGE/CL_43), subjects at the 75% quantile of age (54yrs, AGE/CL_54), and subjects at the 97.5% quantile of age (64yrs, AGE/CL_64).

*Source: Pharmacokinetics Study Report G190, P-39, Figure 8-8*

The results indicate that the effect of age (23 to 64 years), race and ribavirin administration fall within 20% of the reference value. The model predicts a 27% probability of CL/F being less than 0.8 of the reference value in subjects at the 0.025 quantile of weight (51 kg). Likewise, the model predicts a 97% probability of CL/F being greater than 1.2 of the reference value in subjects at the 0.975 quantile of weight (120 kg).

*Reviewer's Comment: The covariate model provides a reasonable description of the effects of covariates on telaprevir exposure. The clinical significance of the effect of weight on telaprevir exposure is explored in Dr. Liu's exposure-response review.*

## 3.4 Pharmacogenomics Review

| | |
|---|---|
| NDA Number | 201,917 |
| **Submission Date** | November 23, 2010 |
| **Applicant Name** | Vertex |
| **Drug Name** | Telaprevir |
| **Proposed Indication** | Treatment of chronic hepatitis C (CHC) genotype 1 infection |
| **Primary Reviewer** | Shashi Amur, Ph.D. |
| **Secondary Reviewer** | Michael Pacanowski, Pharm.D., M.P.H |

## 1 Background

The current submission is a NDA for telaprevir, an inhibitor of the hepatitis C virus (HCV) non-structural protein 3-4A (NS3-4A) serine protease. The proposed indication is for the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peg-interferon alpha and ribavirin (PR), in adult patients with compensated liver disease, including cirrhosis, who are treatment naïve or who have been previously treated, including prior null responders, partial responders, and relapsers.

A polymorphism that is approximately 3 kilobases from the *IL28B* gene (encoding interferon-lambda 3; hereafter referred to as "*IL28B* genotype") is a strong predictor of sustained virologic response (SVR) in patients receiving PR therapy, such that carriers of the variant alleles have lower SVR rates.1 Genotyping for rs12979860 was performed on 527/662 (80%) subjects from whom DNA samples were collected in trial C216, a Phase 3 trial in subjects who failed PR treatment. DNA samples were also collected from several clinical trials for case-control association studies of human leukocyte antigen (HLA) alleles or *ABCB1* (P-glycoprotein) and rash. Genotyping data from all these trials were submitted at the request of the Agency (correspondence dated December 15, 2010). Following the original NDA submission, the Agency became aware that *IL28B* genotyping had also been performed in trials 104 (Phase 2, 60%), 106 (Phase 2, 52%), and 108 (Phase 3, 42%) for the purpose of assay validation under the IND; these data were submitted to the NDA at the Agency's request on January 10, 2011. The proposed label does not discuss the influence of *IL28B* genotype or HLA alleles on the efficacy or safety of telaprevir/PR.

The purpose of this review is to evaluate 1) the influence of *IL28B* genotype on response to telaprevir/PR and to PR treatment in subjects naïve to or who failed prior PR treatment, 2) the relationship between HLA alleles and rash in subjects treated with telaprevir/PR, and 3) whether information related to the impact of *IL28B* genotype on telaprevir/PR clinical outcomes should be addressed in the label. This review does not evaluate the effect of *MDR1* genotype on the risk of rash or PK due to the small number of subjects.

1 Ge D, et al. Nature 2009;461: 399-401.

## 2 Submission Contents Related to Genomics/Biomarkers

The clinical development program for telaprevir consisted of 40 completed clinical trials including 8 Phase 2/3 trials in subjects with genotype 1 CHC: Five Phase 2 trials (104 [n=250], 104EU [n=323], 106 [n=453], 107 [n=117], C208 [n=161]) and three Phase 3 trials (108 [n=1088], 111 [n=540], C216 [n=662]). Trials included treatment-naïve subjects (108, 111, 104, 104EU, C208) and prior treatment-failure subjects (C216, 106, 107) with genotype 1 CHC. DNA was collected from trials C216, 104, 106, and 108 to evaluate drug disposition genes (metabolic enzymes and drug transporters), HLA haplotype for adverse events, or to explore genetic variants involved in treatment response.

*IL28B* genotype ascertainment rates in the Phase 2/3 clinical trials are shown in the table below. *IL28B* genotypes were obtained using TaqMan allelic discrimination. All of these trials were randomized, placebo-controlled, parallel-group, multiple-dose, double-blind trials, except 106, which was partially placebo-controlled and partially double-blind study. The trial endpoints were sustained virologic response at 24 weeks (SVR24) after the last administered dose ($SVR_{actual}$) or last planned dose ($SVR_{planned}$). Clinical data (e.g., demographics, disease characteristics) were only available for study C216; the datasets for trials 104, 106, and 108 contained only information on the efficacy endpoints, baseline HCV-RNA, and HCV genotype.

**Table 1. IL28B genotyping populations in Phase 2/3 trials**

| Study | Study Phase | Patients | DNA N/ Total N (%) | Drug Regimen | Primary Endpoint[†] |
|---|---|---|---|---|---|
| VX05-950-104 (104) | 2 | Treatment-naïve, genotype 1 (U.S. only) | 151/250 (60%) | T12/PR12[‡]<br>T12/PR24<br>T12/PR48<br>Pbo/PR48<br>(4:4:4:1 ratio) | SVR24 actual |
| VX07-950-108 (108) | 3 | Treatment-naïve, genotype 1 (U.S. only) | 459/1088 (42%) | T8/PR24-48 RGT<br>T12/PR24-48 RGT<br>Pbo/PR48<br>Randomized (1:1:1 ratio) | SVR24 planned |
| VX06-950-106 (106) | 2 | Treatment-failure, genotype 1 (U.S. only) | 237/453 (52%) | T24/PR48<br>T24/PR24<br>T12/PR24<br>Pbo/PR48<br>Randomized (1:1:1:1 ratio) | SVR24 actual |
| VX-950-TiDP24-C216 (C216) | 3 | Treatment-failure, genotype 1 | 527/662 (80%):<br>-relapsers 261/361 (72.3%)<br>-partial responders 99/131 (75.6%)<br>-null-responders 167/170 (98.2%) | T12/PR48<br>T12(DS*)/PR48<br>Pbo16/PR48<br>Randomized (2:2:1 ratio) | SVR24 planned |

* Telaprevir placebo for 4 weeks followed by telaprevir for 12 weeks in combination with PR for 48 weeks
† $SVR24_{actual}$, undetectable HCV RNA 24 weeks after the last administered dose of study drug; $SVR24_{planned}$, undetectable HCV RNA 24 weeks after the last planned dose of study drug
‡ None of the 17 subjects randomized to this arm were present in the PG substudy

For the HLA-rash association studies, DNA was analyzed in a total of 187 subjects (114 telaprevir-treated rash cases and 73 telaprevir-tolerant controls) from trials 104, 104EU, 108, and 111. HLA alleles were typed using a high resolution PCR based method designed to type subjects across 5,319 distinct HLA-A, HLA-B, HLA-CW, HLA-DRB and HLA-DQB loci. For *ABCB1* 3435C>T- and 1236C>T-rash and PK association studies, DNA was analyzed from 44 subjects from trial 104 (33 from telaprevir-treated rash cases and 11 telaprevir-tolerant controls).

**Table 2. Reports and datasets**

| **Reports** | **Location** |
|---|---|
| Clinical Study Report:*IL28B* Polymorphisms (VX-950-TiDP24-C216) | \Cdsesub1\evsprod\NDA201917\0005\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5323-stud-other-human-biomat\vx-950-tidp24-c216-il28b\c216-il28b.pdf |
| *IL28B* In vitro diagnostic assay development report: | \Cdsesub1\evsprod\IND071832\0511\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5323-stud-other-human-biomat\g170\vx-950-il28b.pdf |
| *MDR1* Polymorphisms in Selected Subjects from Study VX05-950-104† | \\cdsesub1\EVSPROD\NDA201917\\0005\m5\53-clin-stud-rep\535-rep-effic-safety-stud\chronic-hepatitis-c\5354-other-stud-rep\g200\g200.pdf |
| A Case-Control study of a potential HLA association with rash in subjects with genotype 1 hepatitis C treated with telaprevir in combination with peginterferon alfa-2a (Pegasys) and ribavirin (Copegus) | \Cdsesub1\evsprod\NDA201917\0005\m5\53-clin-stud-rep\535-rep-effic-safety-stud\chronic-hepatitis-c\5353-rep-analys-data-more-one-stud\g201\g201.pdf |
| **Datasets*** | **Location** |
| DMAD.xpt (C216) | \Cdsesub1\evsprod\NDA201917\0019\m5\datasets\vx-950-tidp24-c216-il28b\analysis \dmad.xpt |
| HCVAD.xpt (C216) | \Cdsesub1\evsprod\NDA201917\0019\m5\datasets\vx-950-tidp24-c216-il28b\analysis \hcvad.xpt |
| IL28.xpt | \Cdsesub1\evsprod\NDA201917\0018\m5\datasets\g170\analysis\il28.xpt |
| HLA.xpt | \Cdsesub1\evsprod\NDA201917\0015\m5\datasets\g201\analysis\hla.xpt |
| * Deidentified data cannot be linked with original trial records; analysis dataset includes key efficacy and safety variables<br>† Not reviewed | |

# 3 Key Questions and Summary of Findings

## 3.1 Does telaprevir efficacy differ by *IL28B* genotype?

*SVR rates differed significantly by IL28B genotype in subjects receiving Pbo/PR48; IL28B genotype effects remained but were less apparent in telaprevir-treated subjects. Among C/C subjects, telaprevir showed a small, but significant benefit over Pbo/PR48. However, treatment effects were substantially larger in C/T and T/T subjects. C/C subjects treated with telaprevir and, to a lesser extent Pbo/PR48, had rapid responses. IL28B genotype effects on treatment response were less apparent in previously-treated subjects, but consistent with those observed in treatment-naïve subjects. Subgroup comparisons of treatment effects should be interpreted cautiously in part because of potential differences and/or biases in the substudy population relative to the overall population. The results are still informative of potential benefits in subgroups defined by IL28B genotype, especially since the sampling was balanced across the treatment arms and the treatment effects in the PG substudy of the trials were generally similar to the overall populations*

### *3.1.1 Comparison of overall and PG-substudy populations to evaluate PG substudy bias*

Sampling rates ranged from 42% to 80% for the clinical trials. The proportion of patients providing DNA samples varied across the treatment arms the 104 and 106 PG substudy populations (58-72% and 44-63%, respectively), raising some concerns about attrition or selection bias. Sampling was balanced across the treatment arms in the Phase 3 trials.

**Table 3. DNA sampling across treatment arms (source: Applicant's report)**

| Trial | Treatment | Total N | DNA N | DNA % |
|---|---|---|---|---|
| 104 | T12/PR12 | 17 | 0 | 0 |
| | T12/PR24 | 79 | 47 | 59% |
| | T12/PR48 | 79 | 46 | 58% |
| | Pbo/PR48 | 75 | 54 | 72% |
| | **Total** | **233** | **147** | **63%** |
| 108 | T8/PR24-48 RGT | 364 | 153 | 42% |
| | T12/PR24-48 RGT | 363 | 140 | 39% |
| | Pbo/PR48 | 361 | 161 | 45% |
| | **Total** | **1088** | **454** | **42%** |
| 106 | T12/PR24 | 115 | 57 | 50% |
| | T24/PR48 | 113 | 50 | 44% |
| | T24/P24 | 111 | 58 | 52% |
| | Pbo/PR48 | 114 | 72 | 63% |
| | **Total** | **453** | **237** | **52%** |
| C216 | T12/PR48 | 266 | 212 | 80% |
| | T12(DS)/PR48 | 264 | 210 | 80% |
| | Pbo/PR48 | 132 | 105 | 80% |
| | **Total** | **662** | **527** | **80%** |

Differences in baseline characteristics between the PG substudy and overall trial population were observed for C216 (not shown; differences were not evaluable for trials 104, 106, and 108). However, response rates were generally similar between the Phase 3 (108 and C216) PG substudy and overall populations. Despite the potential for differences in the baseline characteristics between the PG substudy populations and the overall populations, treatment effects in the PG substudy of all four trials were generally similar to the overall populations as shown in the graph and table below. Modest evidence of heterogeneity was observed for some of the treatment arms (e.g., T12DS/PR48 in C216).

**Table 4. SVR rates and odds of response for PG substudies vs. overall trial populations (source: Reviewer)**

| Trial | Treatment Group | PG Substudy | | Overall | | $P_{het}$[†] |
|---|---|---|---|---|---|---|
| | | SVR rate % (n/N) | OR (95%CI)* | SVR rate % (n/N) | OR (95%CI)* | |
| 104 | Pbo/PR48 | 52 (28/54) | 1.00 (reference) | 41 (31/75) | 1.00 (reference) | |
| | T12/PR12* | 0 | … | 35 (6/17) | 0.77 (0.23-2.59) | … |
| | T12/PR24 | 70 (33/47) | 2.19 (0.96-4.98) | 61 (48/79) | 2.20 (1.15-4.19) | 0.99 |
| | T12/PR48 | 72 (33/46) | 2.36 (1.02-5.43) | 67 (53/79) | 2.89 (1.50-5.58) | 0.70 |
| 108 | Pbo/PR48 | 38 (61/161) | 1.00 (reference) | 44 (158/361) | 1.00 (reference) | |
| | T8/PR24-48 RGT | 67 (102/153) | 3.28 (2.06-5.21) | 69 (250/364) | 2.81 (2.08-3.82) | 0.59 |
| | T12/PR24-48 RGT | 78 (109/140) | 5.76 (3.46-9.60) | 75 (271/363) | 3.78 (2.76-5.18) | 0.17 |
| 106 | Pbo/PR48 | 8 (6/72) | 1.00 (reference) | 14 (16/114) | 1.00 (reference) | |
| | T12/PR24 | 54 (31/57) | 13.1 (4.90-35.1) | 51 (59/115) | 6.45 (3.93-12.3) | 0.23 |
| | T24/PR48 | 62 (31/50) | 17.9 (6.52-49.4) | 53 (60/113) | 6.93 (3.64-13.2) | 0.12 |
| | T24/P24 | 22 (13/58) | 3.18 (1.12-8.98) | 24 (27/111) | 1.97 (0.99-3.90) | 0.45 |

| Trial | Treatment Group | PG Substudy | | Overall | | $P_{het}$ [†] |
|---|---|---|---|---|---|---|
| | | SVR rate % (n/N) | OR (95%CI)* | SVR rate % (n/N) | OR (95%CI)* | |
| C216* | Pbo/PR48 | 17 (18/105) | 1.00 (reference) | 17 (22/132) | 1.00 (reference) | |
| | T12/PR48 | 62 (120/192) | 8.06 (4.49-14.5) | 64 (250/364) | 10.9 (6.59-18.2) | 0.44 |
| | T12 (DS)/PR48 | 51 (114/225) | 4.96 (2.08-8.79) | 66 (175/264) | 9.83 (5.82-16.6) | 0.08 |

* unadjusted
[†] p-value for heterogeneity of treatment odds ratios between substudy and overall population

### *3.1.2 Distribution of IL28B genotype by trial*

The proportion of subjects with the C/C, C/T and T/T genotypes were comparable between the treatment-naïve trials (104 and 108) and between the treatment-failure trials (106 and C216). As expected, the proportion of subjects with the C/C genotype was lower in the two trials with treatment-failure subjects (33-34% vs. 15-18%; see table below).

**Table 5. *IL28B* genotype frequencies by trial (source: Reviewer)**

| Population | Trial | N | *IL28B* Genotype, n (%) | | |
|---|---|---|---|---|---|
| | | | C/C | C/T | T/T |
| Pooled treatment-naïve | 104 | 147 | 50 (34) | 74 (50) | 23 (16) |
| | 108 | 454 | 150 (33) | 224 (49) | 80 (18) |
| Pooled treatment-failure | 106 | 237 | 36 (15) | 156 (66) | 45 (19) |
| | C216 | 527 | 93 (18) | 324(62) | 110 (21) |

The majority of the trial participants were Caucasian (77% in 104; 89% in 106 and 108, and 93% in C216). The distribution of *IL28B* genotype by race was available only for C216 (comprised of 94% Caucasians, 4% Blacks, 1% Asians and 1% other subjects). In Caucasians (n=495), 18% had the C/C genotype, 62% had the C/T genotype, and 20% the T/T genotype. In black subjects (n=20), 15% had the C/C genotype, 40% had the C/T genotype, and 45% the T/T genotype. Among Asian subjects (n=7), only the C/C (29%) and C/T (71%) genotypes were observed.

The frequency of the *IL28B* genotypes, rs12979860, were in Hardy-Weinberg equilibrium in trials 104 and 108 (P-values of 0.73 and 0.85, respectively), but not in trials 108 and C216 (P-values both <0.0001). This deviation from the Hardy-Weinberg equilibrium might be due to selection of treatment-experienced subjects in the selected trial population.

### *3.1.3 IL28B genotype and baseline characteristics*

The dataset for trials 104, 106, and 108 contained only information on baseline HCV-RNA and HCV genotype. The treatment arms were not significantly different with respect to these characteristics within the genotype groups, and these factors did not differ significantly across *IL28B* genotype groups when the treatment arms were pooled. Other clinical characteristics were not available for comparison across the treatment groups or genotypes. In C216, the baseline characteristics in the different treatment groups were similar in the *IL28B* genotype subgroups. The exceptions were more frequent cirrhosis for *IL28B* T/T subjects in the T12/PR48 group (35.1%) than in the T12 (DS)/PR48 group (16.3%); for female subjects which more frequently had the *IL28B* T/T genotype in the T12/PR48 group (43.2%) than in the

T12(DS)/PR48 group (27.9%). *IL28B* genotype was associated with high baseline HCV RNA (≥800,000 IU/mL) compared to subjects with the *IL28B* C/T or T/T genotypes.

**Table 6. Baseline characteristics by IL28B genotype (source: Applicant's report)**

| Parameter | Overall population | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | T12/PR48 N = 212 | | | T12(DS)/PR48 N = 210 | | | Pbo/PR48 N = 105 | | | All subjects N = 527 | | |
| | CC N = 41 | CT N = 134 | TT N = 37 | CC N = 35 | CT N = 132 | TT N = 43 | CC N = 17 | CT N = 58 | TT N = 30 | CC N = 93 | CT N = 324 | TT N = 110 |
| Baseline HCV RNA (IU/mL), n (%) | | | | | | | | | | | | |
| < 800000 | 1 (2.4) | 13 (9.7) | 8 (21.6) | 1 (2.9) | 16 (12.1) | 7 (16.3) | 1 (5.9) | 6 (10.3) | 8 (26.7) | 3 (3.2) | 35 (10.8) | 23 (20.9) |
| ≥ 800000 | 40 (97.6) | 121 (90.3) | 29 (78.4) | 34 (97.1) | 116 (87.9) | 36 (83.7) | 16 (94.1) | 52 (89.7) | 22 (73.3) | 90 (96.8) | 289 (89.2) | 87 (79.1) |
| Assessment of liver fibrosis, n (%) | | | | | | | | | | | | |
| Cirrhosis | 12 (29.3) | 32 (23.9) | 13 (35.1) | 9 (25.7) | 39 (29.5) | 7 (16.3) | 5 (29.4) | 12 (20.7) | 8 (26.7) | 26 (28.0) | 83 (25.6) | 28 (25.5) |
| No cirrhosis | 29 (70.7) | 102 (76.1) | 24 (64.9) | 26 (74.3) | 93 (70.5) | 36 (83.7) | 12 (70.6) | 46 (79.3) | 22 (73.3) | 67 (72.0) | 241 (74.4) | 82 (74.5) |
| HCV subtype (NS3), n (%) | | | | | | | | | | | | |
| 1a | 24 (58.5) | 66 (49.3) | 17 (45.9) | 22 (62.9) | 75 (56.8) | 26 (60.5) | 7 (41.2) | 29 (50.0) | 15 (50.0) | 53 (57.0) | 170 (52.5) | 58 (52.7) |
| 1b | 15 (36.6) | 66 (49.3) | 20 (54.1) | 13 (37.1) | 56 (42.4) | 17 (39.5) | 9 (52.9) | 28 (48.3) | 15 (50.0) | 37 (39.8) | 150 (46.3) | 52 (47.3) |
| other | 2 (4.9) | 2 (1.5) | 0 | 0 | 1 (0.8) | 0 | 1 (5.9) | 1 (1.7) | 0 | 3 (3.2) | 4 (1.2) | 0 |
| Race, n (%) | | | | | | | | | | | | |
| Black | 1 (2.4) | 1 (0.7) | 5 (13.5) | 0 | 5 (3.8) | 1 (2.3) | 2 (11.8) | 2 (3.4) | 3 (10.0) | 3 (3.2) | 8 (2.5) | 9 (8.2) |
| Caucasian/White | 39 (95.1) | 128 (95.5) | 31 (83.8) | 34 (97.1) | 126 (95.5) | 42 (97.7) | 14 (82.3) | 54 (93.1) | 27 (90.0) | 87 (93.5) | 308 (95.1) | 100 (90.9) |
| Oriental/Asian | 0 | 4 (3.0) | 0 | 1 (2.9) | 0 | 0 | 1 (5.9) | 1 (1.7) | 0 | 2 (2.2) | 5 (1.5) | 0 |
| Other | 1 (2.4) | 1 (0.7) | 1 (2.7) | 0 | 1 (0.8) | 0 | 0 | 1 (1.7) | 0 | 1 (1.1) | 3 (0.9) | 1 (0.9) |
| BMI (kg/m²) | | | | | | | | | | | | |
| < 25 | 10 (24.4) | 52 (38.8) | 12 (32.4) | 11 (31.4) | 43 (32.6) | 13 (30.2) | 3 (17.6) | 25 (43.1) | 10 (33.3) | 24 (25.8) | 120 (37.0) | 35 (31.8) |
| 25 ≤ BMI <30 | 15 (36.6) | 53 (39.6) | 15 (40.5) | 19 (54.3) | 50 (37.9) | 18 (41.9) | 6 (35.3) | 21 (36.2) | 13 (43.3) | 40 (43.0) | 124 (38.3) | 46 (41.8) |
| ≥30 | 16 (39.0) | 29 (21.6) | 10 (27.0) | 5 (14.3) | 38 (28.8) | 12 (27.9) | 8 (47.1) | 12 (20.7) | 7 (23.3) | 29 (31.2) | 79 (24.4) | 29 (26.4) |
| Sex | | | | | | | | | | | | |
| Female | 13 (31.7) | 42 (31.3) | 16 (43.2) | 9 (25.7) | 39 (29.5) | 12 (27.9) | 6 (35.3) | 17 (29.3) | 8 (26.7) | 28 (30.1) | 98 (30.2) | 36 (32.7) |
| Male | 28 (68.3) | 92 (68.7) | 21 (56.8) | 26 (74.3) | 93 (70.5) | 31 (72.1) | 11 (64.7) | 41 (70.7) | 22 (73.3) | 65 (69.9) | 226 (69.8) | 74 (67.3) |

N: number of subjects with data; n: number of subjects with that observation
Source: Display GMA.2

*C216 prior relapser, prior partial responder and prior null-responder populations*:

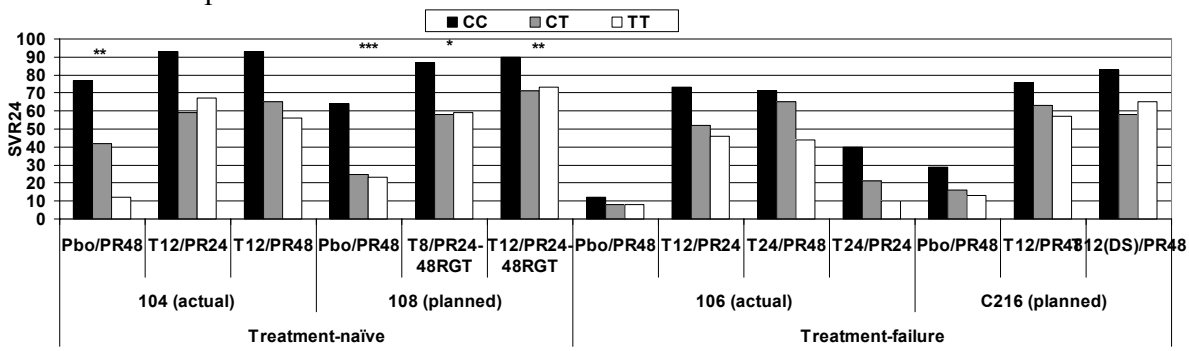
Baseline characteristics in the prior relapsers, prior partial responders and in prior null-responders were similar to the overall population. Cirrhosis was more common in subjects with the C/C genotype than in subjects with the C/T or T/T genotypes in prior relapsers and in prior partial responders.

### *3.1.4 SVR at 24 weeks by IL28B genotype*

The applicant presented retrospective analyses of the association between *IL28B* genotype and SVR, which generally modeled effects of the C/T and T/T genotypes relative to C/C genotype, rather than randomized treatment comparisons in the subgroups. In treatment-naïve subjects, Pbo/PR48 resulted in a high SVR rate in the C/C genotype group (77% in 104 and 64% in 108) compared to those with the C/T (42% in 104 and 25% in 108) or T/T (12% in 104 and 23% in 108) genotype, confirming earlier published results.2 In the telaprevir-containing arms, SVR rates were higher than in the PR arms in all genotype groups, but the SVR rates in the C/T and T/T genotype subjects remained lower than those in the C/C subjects in all of the arms. Telaprevir treatment effects did not appear to differ with regard to IL28B genotype (genotype × treatment P-interaction=0.92 and 0.96 for 104 and 108, respectively), although treatment effects tended to be larger in subjects with the C/T and T/T genotypes. Similar trends were apparent in

2 Thompson, A.J., et al. Gastroenterology 2010;139:120–129.

treatment-failure patients (genotype × treatment P-interaction=0.90 and 0.92 for 106 and C216, respectively). In trial 108, C/T and T/T subjects tended to respond more favorably to longer durations of telaprevir treatment.




*P<0.05, **P<0.01, ***P<0.001

**Figure 1. SVR rates by *IL28B* genotype, treatment arm, and trial in treatment-naïve and treatment-failure patients (source: Reviewer)**

Multivariate logistic regression was used to model relative treatment effects to test genotype × treatment interactions adjusting for baseline HCV-RNA and HCV genotype. The validity of the model fit was questionable for treatment comparisons by genotype in trials 104 and 106 because of the small number of subjects.

**Table 7. SVR rates by *IL28B* genotype, treatment arm, and trial (source: Reviewer)**

| Trial | Treatment Group | C/C | | C/T | | T/T | |
|---|---|---|---|---|---|---|---|
| | | SVR†, % (n/N) | OR (95%CI)‡ | SVR†, % (n/N) | OR (95%CI)‡ | SVR†, % (n/N) | OR (95%CI)‡ |
| 104 | Pbo/PR48 | 77 (17/22) | 1.00 (reference) | 42 (10/24) | 1.00 (reference) | 12 (1/8) | 1.00 (reference) |
| | T12/PR12* | 0 | … | 0 | … | 0 | … |
| | T12/PR24 | 87 (13/15) | 1.88 (0.31-11.4) | 57 (16/28) | NC | 67 (4/6) | NC |
| | T12/PR48 | 93 (13/14) | 1.98 (0.19-21.2) | 65 (15/23) | NC | 56 (5/9) | NC |
| 108 | Pbo/PR48 | 64 (36/56) | 1.00 (reference) | 24 (19/81) | 1.00 (reference) | 23 (6/26) | 1.00 (reference) |
| | T8/PR24-48 RGT | 84 (38/45) | 3.66 (1.34-9.99) | 57 (43/76) | 5.01 (2.39-10.5) | 59 (19/32) | 4.92 (1.54-15.8) |
| | T12/PR24-48 RGT | 90 (45/50) | 5.94 (1.95-18.1) | 71 (50/70) | 10.8 (4.94-23.8) | 71 (15/21) | 9.05 (2.36-34.7) |
| 106 | Pbo/PR48 | 12 (1/8) | 1.00 (reference) | 8 (4/50) | 1.00 (reference) | 8 (1/13) | 1.00 (reference) |
| | T12/PR24 | 73 (8/11) | 16.3 (1.32-202) | 52 (17/33) | 20.4 (5.00-83.5) | 46 (6/13) | NC |
| | T24/PR48 | 71 (5/7) | 15.4 (1.03-230) | 65 (22/34) | 35.0 (8.47-145) | 44 (4/9) | NC |
| | T24/PR24 | 40 (4/10) | 4.13 (0.34-50.8) | 21 (8/38) | 3.81 (0.91-15.9) | 10 (1/10) | NC |
| C216* | Pbo/PR48 | 29 (5/17) | 1.00 (reference) | 15 (9/58) | 1.00 (reference) | 13 (4/30) | 1.00 (reference) |
| | T12/PR48 | 76 (31/41) | 12.4 (2.86-53.8) | 63 (84/134) | 17.3 (7.01-42.9) | 29 (5/17) | 26.1 (4.95-138) |
| | T12 (DS)/PR48 | 83 (29/35) | 23.8 (4.58-123) | 58 (76/132) | 13.6 (5.59-33.3) | 15 (9/58) | 25.7 (5.27-126) |

* IL28B genotype data not available for this arm
† 104 and 106 SVRactual, 108 and C216 SVRplanned
‡ adjusted for HCV genotype and baseline viral load

The Applicant's analyses were reproduced.

### *3.1.4.1 SVR24 planned by IL28B genotype in C216 treatment-failure subpopulations*

In the treatment-failure subpopulations treated with Pbo/PR48, the highest $SVR_{planned}$ rates were observed in patients with C/C genotype. Telaprevir appears to increase the response rates irrespective of the *IL28B* genotype, even though the response rates are lower in non-responders than in relapsers. The response rates in the telaprevir-treated null-responder subjects were lower than those observed in the relapsers, non-responders or partial responders. Results from the partial responders and null-responders should be interpreted with caution due to the small number of subjects in most of the subgroups studied.

**Table 8. SVR rates in treatment-failure subgroups by *IL28B* genotype (source: Reviewer)**

| **C216** | | **$SVR_{planned}$** | | |
|---|---|---|---|---|
| **Population** | **Treatment group** | **C/C, % (n/N)** | **C/T, % (n/N)** | **T/T, % (n/N)** |
| Relapsers | T12/PR48 | 84.8 (28/33) | 84.7 (50/59) | 86.7 (13/15) |
| | T12(DS)/PR48 | 92.0 (23/25) | 86.2 (50/58) | 86.7 (16/19) |
| | Pbo/PR48 | 33.3 (4/12) | 20.0 (6/30) | 30.0 (3/10) |
| Non-responders | T12/PR48 | 37.5 (3/8) | 45.3 (34/75) | 36.4 (8/22) |
| | T12(DS)/PR48 | 60.0 (6/10) | 35.1 (26/74) | 50.0 (12/24) |
| | Pbo/PR48 | 20.0 (1/5) | 10.7 (3/28) | 5.0 (1/20) |
| Partial responders | T12/PR48 | 66.7 (2/3) | 66.7 (20/30) | 66.7 (4/6) |
| | T12(DS)/PR48 | 60.0 (3/5) | 48.1 (13/27) | 75.0 (6/8) |
| | Pbo/PR48 | 20.0 (1/5) | 20.9 (2/10) | 0 (0/5) |
| Null-responders | T12/PR48 | 0 (0/5) | 31.1 (14/45) | 25.0 (4/16) |
| | T12(DS)/PR48 | 0 (0/5) | 27.7 (13/47) | 37.5 (6/16) |
| | Pbo/PR48 | 0 (0/0) | 5.6 (1/18) | 6.7 (1/15) |

### *3.1.4.2 SVR by IL28B genotype in subgroups*

Analysis of SVR by race was not conducted due to insufficient sample size. Race and other clinical covariates were not provided for trials 104, 106, and 108, thus additional subgroup analyses were not conducted. Very few subjects had baseline viral loads <800,000 IU/ml, thus subgroup analysis was not performed.

Subgroup analyses of the C216 trial showed that the genetic effects were generally consistent across various subgroups. Telaprevir-treated subjects with cirrhosis had higher $SVR24_{planned}$ rates in the presence of the C/C genotype (76% vs. 34% vs. 45% for C/C, C/T, and T/T, respectively).

**Table 9. $SVR24_{planned}$ by *IL28B* genotype: Subgroup analyses (source: Applicant's report)**

| $SVR24_{planned}$ n (%) | Overall population | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pooled T12/PR48 N = 422 | | | | | | Pbo/PR48 N = 105 | | | | | |
| | CC N = 76 | | CT N = 266 | | TT N = 80 | | CC N = 17 | | CT N = 58 | | TT N = 30 | |
| | N | n (%) | N | n (%) | N | n (%) | N | n (%) | N | n (%) | N | n (%) |
| Baseline HCV RNA (IU/mL), n (%) | | | | | | | | | | | | |
| < 800000 | 2 | 1 (50.0) | 29 | 23 (79.3) | 15 | 14 (93.3) | 1 | 1 (100.0) | 6 | 2 (33.3) | 8 | 2 (25.0) |
| ≥ 800000 | 74 | 59 (79.7) | 237 | 137 (57.8) | 65 | 35 (53.8) | 16 | 4 (25.0) | 52 | 7 (13.5) | 22 | 2 (9.1) |
| Assessment of liver fibrosis, n (%) | | | | | | | | | | | | |
| Cirrhosis | 21 | 16 (76.2) | 71 | 24 (33.8) | 20 | 9 (45.0) | 5 | 1 (20.0) | 12 | 2 (16.7) | 8 | 1 (12.5) |
| No cirrhosis | 55 | 44 (80.0) | 195 | 136 (69.7) | 60 | 40 (66.7) | 12 | 4 (33.3) | 46 | 7 (15.2) | 22 | 3 (13.6) |
| HCV subtype (NS3), n (%) | | | | | | | | | | | | |
| 1a | 46 | 36 (78.3) | 141 | 75 (53.2) | 43 | 24 (55.8) | 7 | 3 (42.9) | 29 | 6 (20.7) | 15 | 2 (13.3) |
| 1b | 28 | 23 (82.1) | 122 | 82 (67.2) | 37 | 25 (67.6) | 9 | 2 (22.2) | 28 | 3 (10.7) | 15 | 2 (13.3) |
| other | 2 | 1 (50.0) | 3 | 3 (100.0) | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 |
| Race, n (%) | | | | | | | | | | | | |
| Oriental/Asian | 1 | 1 (100.0) | 4 | 3 (75.0) | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 |
| Black | 1 | 0 | 6 | 3 (50.0) | 6 | 3 (50.0) | 2 | 2 (100.0) | 2 | 0 | 3 | 1 (33.3) |
| Caucasian/White | 73 | 58 (79.5) | 254 | 153 (60.2) | 73 | 45 (61.6) | 14 | 3 (21.4) | 54 | 9 (16.7) | 27 | 3 (11.1) |
| Other | 0 | 0 | 1 | 1 (100.0) | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| BMI ($kg/m^2$) | | | | | | | | | | | | |
| < 25 | 21 | 18 (85.7) | 95 | 55 (57.9) | 25 | 14 (56.0) | 3 | 0 | 25 | 4 (16.0) | 10 | 2 (20.0) |
| 25 ≤ BMI <30 | 34 | 25 (73.5) | 103 | 71 (68.9) | 33 | 22 (66.7) | 6 | 0 | 21 | 4 (19.0) | 13 | 1 (7.7) |
| ≥30 | 21 | 17 (81.0) | 67 | 33 (49.3) | 22 | 13 (59.1) | 8 | 5 (62.5) | 12 | 1 (8.3) | 7 | 1 (14.3) |
| Sex | | | | | | | | | | | | |
| Female | 22 | 15 (68.2) | 81 | 44 (54.3) | 28 | 21 (75.0) | 6 | 2 (33.3) | 17 | 4 (23.5) | 8 | 2 (25.0) |
| Male | 54 | 45 (83.3) | 185 | 116 (62.7) | 52 | 28 (53.8) | 11 | 3 (27.3) | 41 | 5 (12.2) | 22 | 2 (9.1) |

N: number of subjects with data; n: number of subjects with SVR
Source: Display GMA.7

### *3.1.5 Selected secondary efficacy outcome and supportive analyses*

#### *3.1.5.1 eRVR rates and IL28B genotype*

The term eRVR is defined by undetectable HCV RNA at 4 and 12 weeks after treatment with all active drugs in the regimen were started (i.e., weeks 8 and 16 for the T12[DS]/PR48 group). Approximately 93% of the subjects who were undetectable at 4 weeks (RVR) were also classified as having eRVR (undetectable at 4 and 12 weeks), thus results for eRVR are presented. In treatment-naïve subjects, the eRVR rates were higher in the telaprevir groups than in the Pbo/PR48 group (with the exception of T8/PR48). The highest eRVR rates were observed in subjects with *IL28B* C/C genotype in the telaprevir groups. In treatment-failure subjects, the eRVR rates were higher in the telaprevir groups than in the Pbo/PR48 group for both trials (106 and C216). Higher eRVR rates were observed in telaprevir-treated subjects with the *IL28B* C/C genotype than the C/T or T/T genotypes. The number of subjects in some of the *IL28B* genotype subgroups studied was small and the results for those groups should be interpreted with caution.

**Table 10: eRVR rates in treatment-naïve and treatment-failure patients by *IL28B* genotype and trial (source: Reviewer)**

| Population | Trial | Treatment Group | eRVR, % (n/N) | | |
|---|---|---|---|---|---|
| Treatment-naïve | 104 | Pbo/PR48 | 23 (5/22) | 0 (0/24) | 13 (1/8) |

| | | | | | |
|---|---|---|---|---|---|
| | | T12/PR24 | 79 (11/14) | 67 (18/27) | 67 (4/6) |
| | | T12/PR48 | 86 (12/14) | 78 (18/23) | 56 (5/9) |
| | 108 | Pbo/PR48 | 16 (9/55) | 2.5 (2/80) | 0 (0/26) |
| | | T8/PR24-48 RGT | 64 (29/45) | 51 (39/76) | 50 (16/32) |
| | | T12/PR24-48 RGT | 78 (39/50) | 57 (39/68) | 46 (10/22) |
| Treatment-failure | 106 | Pbo/PR48 | 0 (0/8) | 0 (0/51) | 0 (0/13) |
| | | T12/PR24 | 73 (8/11) | 61 (20/33) | 54 (7/13) |
| | | T24/PR48 | 57 (4/7) | 35 (12/34) | 44.4 (4/9) |
| | | T24/P24 | 50 (5/10) | 45 (17/38) | 20 (2/10) |
| | C216 | Pbo/PR48 | 5.9 (1/17) | 0 (0/58) | 3.3 (1/30) |
| | | T12/PR48 | 66 (27/41) | 48 (64/134) | 46 (17/37) |
| | | T12 (DS)/PR48 | 83 (29/35) | 58 (76/132) | 65 (28/43) |

The eRVR rates were higher in the telaprevir-treated than in the Pbo/PR48-treated prior relapsers, prior non-responders, prior partial responders, and prior null-responders in C216 (shown in table below). The numbers of subjects in some of the subgroups were too small to draw any conclusions.

**Table 11: eRVR rates in treatment-failure patients by *IL28B* genotype and prior response subgroups in C216 (source: Applicant's report)**

| | eRVR | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Prior Response** | **T12/PR48** | | | | | | **T12(DS)/PR48** | | | | | | **Pbo/PR48** | | | | | |
| | CC | | CT | | TT | | CC | | CT | | TT | | CC | | CT | | TT | |
| | N | n (%) | N | n (%) | N | n (%) | N | n (%) | N | n (%) | N | n (%) | N | n (%) | N | n (%) | N | n (%) |
| Overall population | 41 | 27 (65.9) | 134 | 64 (47.8) | 37 | 17 (45.9) | 35 | 29 (82.9) | 132 | 76 (57.6) | 43 | 28 (65.1) | 17 | 1 (5.9) | 58 | 0 | 30 | 1 (3.3) |
| Relapser | 33 | 23 (69.7) | 59 | 38 (64.4) | 15 | 8 (53.3) | 25 | 22 (88.0) | 58 | 47 (81.0) | 19 | 17 (89.5) | 12 | 1 (8.3) | 30 | 0 | 10 | 0 |
| Non-responder | 8 | 4 (50.0) | 75 | 26 (34.7) | 22 | 9 (40.9) | 10 | 7 (70.0) | 74 | 29 (39.2) | 24 | 11 (45.8) | 5 | 0 | 28 | 0 | 20 | 1 (5.0) |
| Partial responder | 3 | 2 (66.7) | 30 | 18 (60.0) | 6 | 4 (66.7) | 5 | 4 (80.0) | 27 | 15 (55.6) | 8 | 5 (62.5) | 5 | 0 | 10 | 0 | 5 | 0 |
| Null-responder | 5 | 2 (40.0) | 45 | 8 (17.8) | 16 | 5 (31.3) | 5 | 3 (60.0) | 47 | 14 (29.8) | 16 | 6 (37.5) | 0 | 0 | 18 | 0 | 15 | 1 (6.7) |

N: number of subjects with data; n: number of subjects with observation
Source: Display GMA.6

### *3.1.5.2 Additional analyses of C216 – Response time course, viral breakthrough, and relapse*

*Response time course*

The rate of viral response (i.e., undetectable HCV RNA) was faster in the telaprevir groups compared to the Pbo/PR48 group. In the Pbo/PR48 group and in both telaprevir-containing arms, subjects with the *IL28B* C/C genotype achieved viral response (i.e., undetectable HCV RNA) more rapidly than subjects with the *IL28B* C/T or T/T genotype. Also, response rates were higher in subjects with the *IL28B* C/C genotype at all time points in all the groups. No clear differences between the telaprevir groups were observed in viral response rates by *IL28B* genotype.

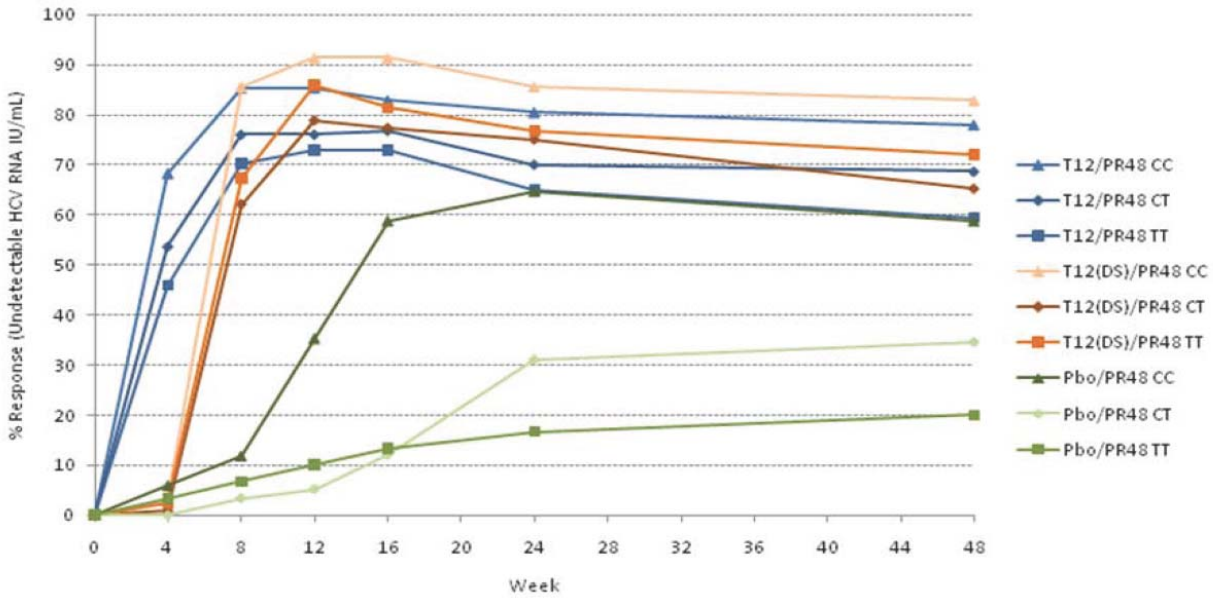



**Figure 2. Viral response (undetectable HCV RNA IU/mL) by *IL28B* genotype over time (source: Applicant's report)**

Similar tendencies for earlier responses were observed in each of the prior response subgroups (not shown). These include faster response rates for telaprevir compared to Pbo/PR48 in all the prior response subgroups, and faster viral response rate in subjects with C/C genotype compared to subjects with C/T or T/T genotype in the Pbo/PR48 arm (not shown). Again, small sample sizes prevent meaningful interpretation of these results.

*Viral breakthrough*

Viral breakthrough was defined as having a confirmed increase of >1-$\log_{10}$ in HCV RNA from the lowest level reached during treatment or a confirmed value of HCV RNA >100 IU/mL in subjects whose HCV RNA level had previously been <25 IU/mL during treatment. The lowest rates of viral breakthrough were observed in *IL28B* C/C subjects compared to *IL28B* C/T or *IL28B* T/T subjects. Viral breakthrough rates appeared to be lower in the relapser population compared to non-responder population. The numbers of subjects in the subgroups of the non-responders and genotypes are very small to draw firm conclusions of the impact of the genotypes on the subgroups.

**Table 12. Cumulative viral breakthrough rate by *IL28B* genotype and treatment in trial C216 (source: Applicant's report)**

| Prior Response | Viral Breakthrough | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | T12/PR48 | | | | | | T12(DS)/PR48 | | | | | | Pbo/PR48 | | | | | |
| | CC | | CT | | TT | | CC | | CT | | TT | | CC | | CT | | TT | |
| | N | n (%)[a] | N | n (%)[a] | N | n (%)[a] | N | n (%)[a] | N | n (%)[a] | N | n (%)[a] | N | n (%)[a] | N | n (%)[a] | N | n (%)[a] |
| Overall population | 41 | 3 (7.3) | 134 | 26 (19.4) | 37 | 11 (29.7) | 35 | 4 (11.4) | 132 | 29 (22.0) | 43 | 6 (14.0) | 17 | 1 (5.9) | 58 | 7 (12.1) | 30 | 1 (3.3) |
| Relapser | 33 | 0 | 59 | 1 (1.7) | 15 | 0 | 25 | 1 (4.0) | 58 | 1 (1.7) | 19 | 0 | 12 | 0 | 30 | 4 (13.3) | 10 | 0 |
| Non-responder | 8 | 3 (37.5) | 75 | 25 (33.3) | 22 | 11 (50.0) | 10 | 3 (30.0) | 74 | 28 (37.8) | 24 | 6 (25.0) | 5 | 1 (20.0) | 28 | 3 (10.7) | 20 | 1 (5.0) |
| Partial responder | 3 | 0 | 30 | 3 (10.0) | 6 | 1 (16.7) | 5 | 1 (20.0) | 27 | 6 (22.2) | 8 | 0 | 5 | 1 (20.0) | 10 | 1 (10.0) | 5 | 0 |
| Null-responder | 5 | 3 (60.0) | 45 | 22 (48.9) | 16 | 10 (62.5) | 5 | 2 (40.0) | 47 | 22 (46.8) | 16 | 6 (37.5) | 0 | 0 | 18 | 2 (11.1) | 15 | 1 (6.7) |

N: number of subjects with data; n: number of subjects with observation

[a] In each column, the total number of subjects with viral breakthroughs emerging during the telaprevir treatment phase (during which subjects received treatment with telaprevir and Peg-IFN/RBV) and with viral breakthroughs emerging after the telaprevir treatment phase and during treatment with Peg-IFN/RBV is presented.

Source: Display GMA.10

*Relapse*

Relapse was defined as having confirmed detectable HCV RNA levels during the entire follow-up period (relapse Week 72). Relapse was considered confirmed when the HCV RNA was detectable at two or more consecutive time points during follow-up or at the last observed time point. In the overall population, relapse rates were lower in subjects receiving telaprevir than in subjects in the control group. In the telaprevir treatment groups, relapse rates appeared to be lower in subjects with the *IL28B* C/C genotype than in subjects with *IL28B* C/T or T/T genotypes among telaprevir-treated subjects. Opposite trends, likely because of the small sample size, were apparent for Pbo/PR48.

**Table 13. Relapse rate by *IL28B* genotype – Overall population (source: Applicant's report)**

| Category n (%) | Overall population | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | T12/PR48 N = 212 | | | T12(DS)/PR48 N = 210 | | | Pooled T12/PR48 N = 422 | | | Pbo/PR48 N = 105 | | |
| | CC N = 41 | CT N = 134 | TT N = 37 | CC N = 35 | CT N = 132 | TT N = 43 | CC N = 76 | CT N = 266 | TT N = 80 | CC N = 17 | CT N = 58 | TT N = 30 |
| Undetectable at EOT | 36 | 101 | 24 | 32 | 95 | 36 | 68 | 196 | 60 | 11 | 23 | 7 |
| No relapse | 32 (88.9) | 85 (84.2) | 22 (91.7) | 30 (93.8) | 76 (80.0) | 28 (77.8) | 62 (91.2) | 161 (82.1) | 50 (83.3) | 5 (45.5) | 9 (39.1) | 4 (57.1) |
| Relapse | 3 (8.3) | 14 (13.9) | 2 (8.3) | 0 | 15 (15.8) | 7 (19.4) | 3 (4.4) | 29 (14.8) | 9 (15.0) | 6 (54.5) | 14 (60.9) | 3 (42.9) |
| No HCV RNA measurements during FU | 1 (2.8) | 2 (2.0) | 0 | 2 (6.3) | 4 (4.2) | 1 (2.8) | 3 (4.4) | 6 (3.1) | 1 (1.7) | 0 | 0 | 0 |

N: number of subjects with data; n: number of subjects with observation

Source: Display GMA.9

### *3.1.6 Predictive utility of IL28B and eRVR responses for SVR*

Early responses predict the likelihood of developing SVR. The predictive value of *IL28B* genotype relative to RVR in PR-treated subjects is summarized for treatment-naïve subjects in the table below (treatment-failure trials not analyzed given relatively low responses to PR48 retreatment). RVR was selected since this represents an early response assessment milestone, and given that approximately 93% of the subjects with RVR had eRVR. Positive predictive value (PPV) is a useful metric among PR48 treated subjects in that it identifies those who benefit from PR therapy without telaprevir. On the other hand, high negative predictive value (NPV) is useful to identify non-responders in whom telaprevir would be beneficial. Among PR48-treated subjects, *IL28B* genotype has better sensitivity and NPV for SVR than RVR, suggesting that *IL28B* genotype may better identify those likely to be non-responsive. However, RVR has 100% PPV (i.e., early responders will have SVR) for PR48, although the number of subjects

experiencing RVR on PR48 was relatively small. For telaprevir, PPVs were similar for RVR and *IL28B* genotype and the NPV was somewhat higher for the RVR. When the PPV and NPV were determined for the *IL28B* C/C genotype in the context of RVR, the PPV was higher than RVR. These analyses suggest that the likelihood of response can be predicted just as well from *IL28B* genotype as from early responses.

**Table 14. Clinical performance characteristics of IL28B genotype and early response profiles for SVR in trial 108 (source: Reviewer)**

| 108 | PR48 | | | | Pooled Telaprevir | | | |
|---|---|---|---|---|---|---|---|---|
| | **Sens** (TP/ TP+FN) | **Spec** (TN/ TN+FP) | **PPV** (TP/ TP+FP) | **NPV** (TN/ TN+FN) | **Sens** (TP/ TP+FN) | **Spec** (TN/ TN+FP) | **PPV** (TP/ TP+FP) | **NPV** (TN/ TN+FN) |
| rs12979860 Pos=CC Neg=CT | **65** (36/55) | **76** (62/82) | **64** (36/56) | **77** (62/81) | **47** (83/176) | **82** (53/65) | **87** (83/95) | **27** (53/196) |
| rs12979860 Pos=CC Neg=TT | **86** (36/42) | **50** (20/40) | **64** (36/56) | **77** (20/26) | **71** (83/117) | **61** (19/31) | **87** (83/95) | **36** (19/53) |
| rs12979860 Pos=CC Neg=CT,TT | **59** (36/61) | **80** (82/102) | **64** (36/56) | **77** (82/107) | **40** (83/210) | **86** (72/84) | **87** (83/95) | **36** (72/199) |
| RVR Pos=RVR Neg=no RVR | **19** (12/62) | **100** (103/103) | **100** (12/12) | **67** (103/153) | **78** (164/210) | **67** (56/84) | **85** (164/192) | **55** (56/102) |
| rs1297960 C/C only Pos=eRVR Neg=no eRVR | **27** (14/52) | **100** (25/25) | **100** (14/14) | **40** (25/63) | **81** (89/110) | **85** (11/13) | **98** ( 89/91) | **34** (11/33) |

TP=true positive, C/C or RVR+ with SVR; FP=false positive, C/C or RVR+ without SVR; FN=false negative, C/T, T/T or RVR- with SVR, TN=true negative, C/T, T/T or RVR- without SVR
Sensitivity is the proportion of subjects with SVR predicted to be responders; Specificity is the proportion of subjects without SVR predicted to be nonresponders; PPV is the proportion of subjects predicted to be responders with SVR; NPV is the proportion of subjects predicted to be nonresponders without SVR

RVR was apparent in approximately 44% of the patients. The majority of early responders ultimately achieve SVR. As shown in the table below, all subjects exhibiting RVR in the PR48 arm (12/165 subjects), most of whom had the C/C genotype, ultimately had a SVR. Very few subjects exhibited RVR to PR48, yet many had SVR, particularly among C/Cs; the differences between RVR and SVR rates in the C/C subgroup suggest that the response trajectory may be slower for PR48. Telaprevir resulted in RVR in many of the C/T and T/T subjects, translating to consistently high SVR rates in these early responders. Among the subjects who did not have a RVR, approximately one-third had a SVR, with a higher likelihood of response in C/C subjects for all treatments. Subjects without RVR, particularly those with the C/T and T/T genotypes, appeared to benefit from longer telaprevir treatment duration.

**Table 15. SVR rates by RVR, *IL28B* genotype, treatment arm in trial 108 (source: Reviewer)**

| Treatment-naïve, trial 108 | Treatment | SVR, n/N (%) | | | |
|---|---|---|---|---|---|
| | | **All** | **C/C** | **C/T** | **T/T** |
| RVR + | Pbo/PR48 | 100% (12/12) | 100% (10/10) | 100% (2/2) | 0% (0/0) |
| | T8/PR24-48 | 82% (78/95) | 94% (30/32) | 72 % (34/47) | 88% (14/16) |
| | T12/PR24-48 | 89% (86/97) | 93% (39/42) | 88% (38/43) | 75% (9/12) |
| RVR – | Pbo/PR48 | 33% (50/153) | 57% (26/46) | 22% (17/79) | 23% (6/26) |
| | T8/PR24-48 | 38% (22/58) | 62% (8/13) | 31% (9/29) | 31% (5/16) |
| | T12/PR24-48 | 55% (24/44) | 75% (6/8) | 44% (12/27) | 67% (6/9) |

## 3.2 Are HLA variants associated with rash in subjects treated with telaprevir, PEG-IFN/RBV?

*Severe cases of rash, including SJS and DRESS, have been observed with telaprevir. The Applicant tested associations of 143 HLA alleles (HLA-A, HLA-B, HLA-CW, HLA-DRB1, and HLADQB1) in a rash case-control study. For rash of any severity, HLA-DQB1*0202 was the top-ranking allele, with an odds ratio of 3.42 (95% confidence interval 1.53-7.61, unadjusted P=0.0026); the negative predictive value was high. Overall, the HLA associations with rash are only nominally significant in light of multiplicity and replication would be necessary. Alternative genotyping strategies (e.g., genome-wide) should be undertaken.*

### *3.2.1 Design and methods*

PR therapy is associated with adverse events that include rash. Addition of telaprevir to PR increases the incidence and severity of rash. Cases of Stevens-Johnson syndrome and DRESS were observed in the clinical development program. Recently, it has been shown that severe cutaneous adverse reactions induced by various drugs are associated with HLA.3 Thus, the Applicant investigated possible association of HLA alleles to telaprevir/PR-induced rash.

A total of 187 subjects from trials 104, 104EU, 108, and 111 were included in this case-control study: 114 had developed a rash during telaprevir treatment and 73 were tolerant to telaprevir treatment for 12 weeks. All 73 controls were from trial 111. It does not appear that cases and controls were matched on any clinical variables (e.g., age, sex, race, treatment duration).

The primary analysis compared subjects with a rash event of any severity to subjects who did not have a rash. A sample size of 73 controls and 114 cases provides 64% power to detect an odds ratio (OR) of 3.0 (i.e., allele is a risk factor) and 80% power to detect an OR of 0.33 (i.e., allele is protective), assuming a population allele carrier rate of 35% and at a significance level of 0.01. The sample size is adequate for detecting a strong association between a common HLA alleles and rash. Each HLA allele was considered as an independent predictor of rash events and was tested for association with rash events using a 2-sided Wald test from logistic regression at a significance level of 0.01. The Sidak method was used to adjust for multiplicity.

### *3.2.2 HLA associations with rash of any severity*

As shown in the following table, five HLA alleles were significant at the 0.01 level based on uncorrected P-values: 2 that were risk factors for rash events (DQB1*0202, OR=3.42; DRB1*0701, OR=2.75) and 3 that were protective (DRB1*1501, DQB1*0602, CW*0702). No alleles were significant after correction for multiple comparisons.

3 Phillips EJ and Mallal SA. Pharmacogenomics 2010;11: 973-987.

**Table 16. HLA allele distribution in rash cases and controls for 20 most significant alleles (source: Applicant's report)**

| Allele | Total (N=187) n | % | Rash (N=114) n | % (Se) | Control (N=73) n | % (1-Sp) | OR unadj | p-val Wald unadj | p-val age adj | p-val region adj | p-val exact |
|---|---|---|---|---|---|---|---|---|---|---|---|
| DQB10202 | 46 | 24.6 | 37 | 32.5 | 9 | 12.3 | 3.42 | 0.0026 | 0.0014 | 0.0011 | 0.0017 |
| DRB11501 | 47 | 25.1 | 20 | 17.5 | 27 | 37.0 | 0.36 | 0.0033 | 0.0034 | 0.0227 | 0.0034 |
| DQB10602 | 48 | 25.7 | 21 | 18.4 | 27 | 37.0 | 0.38 | 0.0053 | 0.0061 | 0.0253 | 0.0060 |
| CW0702 | 44 | 23.5 | 19 | 16.7 | 25 | 34.2 | 0.38 | 0.0066 | 0.0076 | 0.0194 | 0.0078 |
| DRB10701 | 52 | 27.8 | 40 | 35.1 | 12 | 16.4 | 2.75 | 0.0066 | 0.0041 | 0.0052 | 0.0071 |
| DRB10401 | 32 | 17.1 | 25 | 21.9 | 7 | 9.6 | 2.65 | 0.0332 | 0.0348 | 0.0239 | 0.0301 |
| DQB10302 | 40 | 21.4 | 30 | 26.3 | 10 | 13.7 | 2.25 | 0.0433 | 0.0343 | 0.0557 | 0.0453 |
| A2601 | 6 | 3.2 | 1 | 0.9 | 5 | 6.8 | 0.12 | 0.0556 | 0.0372 | 0.0143 | 0.0344 |
| B0702 | 43 | 23.0 | 21 | 18.4 | 22 | 30.1 | 0.52 | 0.0654 | 0.0683 | 0.1491 | 0.0756 |
| DRB10404 | 13 | 7.0 | 11 | 9.6 | 2 | 2.7 | 3.79 | 0.0892 | 0.0877 | 0.0416 | 0.0826 |
| DQB10603 | 28 | 15.0 | 13 | 11.4 | 15 | 20.5 | 0.50 | 0.0913 | 0.0792 | 0.0825 | 0.0966 |
| B3901 | 5 | 2.7 | 1 | 0.9 | 4 | 5.5 | 0.15 | 0.0958 | 0.0877 | 0.0340 | 0.0770 |
| B3801 | 7 | 3.7 | 2 | 1.8 | 5 | 6.8 | 0.24 | 0.0962 | 0.0602 | 0.0864 | 0.1122 |
| CW1203 | 26 | 13.9 | 12 | 10.5 | 14 | 19.2 | 0.50 | 0.0996 | 0.0928 | 0.0326 | 0.1286 |
| B4001 | 19 | 10.2 | 15 | 13.2 | 4 | 5.5 | 2.61 | 0.1000 | 0.1368 | 0.0484 | 0.1352 |
| CW0501 | 36 | 19.3 | 26 | 22.8 | 10 | 13.7 | 1.86 | 0.1269 | 0.1052 | 0.2284 | 0.1334 |
| B4402 | 33 | 17.6 | 24 | 21.1 | 9 | 12.3 | 1.90 | 0.1310 | 0.1417 | 0.2147 | 0.1686 |
| DRB11301 | 29 | 15.5 | 14 | 12.3 | 15 | 20.5 | 0.54 | 0.1312 | 0.1278 | 0.1338 | 0.1492 |
| CW0304 | 27 | 14.4 | 20 | 17.5 | 7 | 9.6 | 2.01 | 0.1365 | 0.1586 | 0.0849 | 0.1425 |
| A2501 | 14 | 7.5 | 6 | 5.3 | 8 | 11.0 | 0.45 | 0.1573 | 0.1700 | 0.2442 | 0.1644 |

Alleles are ordered by the Wald unadjusted *P*-value (i.e., Wald test of the allele indicator variable in a univariate logistic model). The age-adjusted *P*-value was based on a Wald test of the allele indicator variable in a multivariate logistic model that adjusts for age (>45 years vs <=45 years). The region-adjusted *P*-value was based on an exact Cochran-Mantel-Haenszel (CMH) test, stratified by region (North America and non-North America). The exact *P*-value was based on the Fisher exact test. *P*-values were uncorrected for the 143 comparisons. Assuming a simple classifier based on presence/absence of an allele, column 5 provides sensitivity (Se), and column 7 provides the complement of specificity (1-Sp). Reported OR is unadjusted for covariates.

Odds ratios were relatively unaffected by adjustment for age or geographic region, as shown in the table below.

**Table 17. Odds ratios for association between HLA alleles and rash (source: Applicant's report)**

| Model [1] | Unadjusted OR (95% CI) | Unadjusted *P*-value | Adj for age OR [2] (95% CI) | Adj for age *P*-value [2] | Adj for region OR [3] (95% CI) | Adj for region *P*-value [3] |
|---|---|---|---|---|---|---|
| 1 **DQB1*0202** | 3.42 (1.53; 7.61) | 0.0026 | 3.82 (1.68; 8.69) | 0.0014 | 3.76 (1.60; 9.69) | 0.0011 |
| 2 **DRB1*0701** | 2.75 (1.33; 5.69) | 0.0066 | 2.98 (1.41; 6.28) | 0.0041 | 2.95 (1.34; 6.86) | 0.0052 |

Age coded as >45 years vs. <= 45 years. Geographic region is coded as North America vs. non-North America]
[1] Models have a single *HLA* predictor.
[2] Adjustment for age using logistic regression.
[3] Adjustment for region using exact CMH test.

### *3.2.3 HLA associations with severe rash*

HLA associations with severe rash (n=59) compared to no, mild, and moderate rash subjects (n=128), based on corrected P-values, identified no alleles that were significant at the 0.01 level. However, 5 alleles were found to be significant at the 0.05 level based on uncorrected P-values. Two were risk factors for severe rash events (B*4402, OR=2.43; DQB1*0202, OR=2.01) and 3 that were protective (DQB1*0602, CW*0702, DRB1*1501). Upon adjustment for region, only one risk factor, DQB1*0602 remained significant. No alleles were significant after adjustment for multiple comparisons. Geographic region (North America vs. non-North America) was strongly associated with severe rash events at the 0.05 level. The OR for the association between

HLA allele and severe rash was relatively unaffected by adjustment for age and region covariates. The PPV of DQB1*0202 was 0.07 and the NPV was 1.00, based on a 24.6% DQB1*0202 prevalence and a 5.2% severe rash rate among T/PR-treated subjects. Sensitivity and specificity were 33.9% and 79.7%, respectively.

**Table 20. Secondary analysis of association of HLA allele predictor and severe rash (source: Applicant's report)**

| | Unadjusted | | Adj for age | | Adj for region | |
|---|---|---|---|---|---|---|
| Model [1] | OR (95% CI) | *P*-value | OR [2] (95% CI) | *P*-value [2] | OR [3] (95% CI) | *P*-value |
| 1 DQB1*0202 | 2.01 (1.00; 4.01) | 0.0470 | 2.05 (1.02; 4.12) | 0.0421 | 2.14 (1.00; 4.63) | 0.0396 |
| 2 B*4402 | 2.43 (1.13; 5.24) | 0.0235 | 2.42 (1.12; 5.22) | 0.0243 | 2.30 (0.97; 5.46) | 0.0556 |

[Age coded as >45 years vs. <= 45 years. Geographic region is coded as North America vs. non-North America.]
[1] Models have a single *HLA* predictor.
[2] Adjustment for age using logistic regression.
[3] Adjustment for region using exact CMH test.

### *3.2.4 Exploratory analyses for severe rash using alternative control definitions*

The first exploratory analysis compared severe rash (n=59) to subjects with no rash (n=73) and 133 HLA alleles were represented in the dataset: 23 HLA-A, 39 HLA-B, 24 HLA-CW, 31 HLA-DRB1, and 16 HLA-DQB1. This analysis also identified 5 alleles to be nominally significant. Thus, excluding mild/moderate rash subjects did not affect the significance of the findings. Four HLA alleles were significant at the 0.01 level based on uncorrected P-values: 1 allele was a risk factor for severe rash (DQB1*0202, OR=3.65), and 3 alleles were protective (DRB1*1501, DQB1*0602, CW*0702). The 5 additional HLA alleles significant at the 0.05 level based on uncorrected P values included allele DRB1*0701 (OR=2.81), noted in the primary analysis. Again, no alleles were significant after correction for multiple comparisons. For DQB1*0202, the PPV was 0.08 and the NPV was 0.44, based on a 22.0% DQB1*0202 prevalence, a 5.2% severe rash event rate among T/PR-treated subjects, and a 39.1% no rash event rate among T/PR-treated subjects. Sensitivity and specificity were 33.9% and 87.7%, respectively. For DRB1*0701, positive and negative predictive values were 0.07 and 0.44, based on a 25.0% DRB1*0701 prevalence. Sensitivity and specificity were 35.6% and 83.6%, respectively.

The second exploratory analysis compared severe rash (n=59) to subjects with mild/moderate rash (n=55). 125 HLA alleles were represented in the dataset: 22 HLA-A, 36 HLA-B, 22 HLA-CW, 31 HLA-DRB1, and 14 HLA-DQB1. Of the 5 alleles identified in the secondary analysis as the most significant, only HLA-B*4402 was among the 5 most significant in this exploratory analysis. No HLA alleles were significant after correction for multiple comparisons. For B*4402, the PPV was 0.07 and the NPV was 0.60, based on a 21.1% HLA-B*4402 prevalence, a 5.2% severe rash rate among telaprevir/PR-treated subjects, and a 55.8% mild/moderate rash rate among telaprevir/PR-treated subjects. Sensitivity and specificity were 27.1% and 85.5%, respectively.

## 4. Summary and Conclusions

*Substudy bias and prognostic imbalances:* Information on baseline characteristics, including consent dates for the voluntary PG substudies was not available in the PG population for trials 104, 106 and 108. In trial C216, subjects consenting to DNA analysis differed from the overall population in terms of baseline characteristics and treatment effects. However, treatment effects in the PG substudy of the trials were only modestly different between the PG substudy and overall populations, and *IL28B* genotype effects are consistent with the published literature. Subgroup comparisons of treatment effects should be interpreted cautiously in part because of these potential differences, although the results are still informative of potential benefits in subgroups defined by *IL28B* genotype.

*IL28B genotype effects on Pbo/PR48 and telaprevir/PR48 response in treatment-naïve subjects*: The findings of this PG substudy confirm earlier reports of *IL28B* genotype effects in the Pbo/PR48 arm. SVR rates differed significantly by *IL28B* genotype in subjects receiving Pbo/PR48. Among C/C subjects, telaprevir showed a small, but significant benefit over Pbo/PR48. However, treatment effects were larger in C/T and T/T subjects. C/C subjects treated with telaprevir and Pbo/PR48 had rapid responses, whereas C/C subjects treated with Pbo/PR48 responded slowly.

*IL28B genotype effects on Pbo/PR48 and telaprevir/PR48 response in treatment-experienced subjects*: *IL28B* genotype effects on treatment response were less apparent in previously-treated subjects with 29% SVR in C/C 15% SVR in C/T and 13% SVR in TT subjects in the Pbo/PR48 arm in study C216. The SVR was highest in the C/C subjects, consistent with that observed in treatment-naïve subjects. C/C subjects treated with telaprevir and Pbo/PR48 had rapid rates of viral responses, whereas C/C subjects treated with Pbo/PR48 showed slower rates of viral response.

*Predictive utility of IL28B genotype in treatment-naïve subjects*: *IL28B* genotype was highly predictive of SVR in subjects treated with PR48. Rapid virologic response (RVR: PCR-negativity at 4 weeks) as well as extended virologic response (eRVR: PCR-negativity at 4 and 12 weeks) were also highly predictive of response. Among the subjects who did not have a RVR, approximately one-third had a SVR, with a higher likelihood of response in C/C subjects for all treatments. *IL28B* genotype has predictive performance characteristics that are similar to RVR and has the advantage that subjects need not be exposed to PR to ascertain responsiveness. Subjects without RVR, particularly those with the C/T and T/T genotypes, appeared to benefit from longer telaprevir treatment duration.

*Rash:* Severe cases of rash, including SJS and DRESS, have been observed with telaprevir. The Applicant tested associations of 143 HLA alleles (HLA-A, HLA-B, HLA-CW, HLA-DRB1, and HLADQB1) with rash in 114 cases (59 severe cases) and 73 controls. For rash of any severity, seven alleles were nominally significant at $P<0.05$, although none were significant after correcting for multiple comparisons. HLA-DQB1*0202 was the top-ranking allele, with an odds ratio of 3.42 (95% confidence interval 1.53-7.61, unadjusted $P=0.0026$). The PPV of DQB1*0202 was 0.07 and the NPV was 1.00. Sensitivity and specificity were 33.9% and 79.7%, respectively. This allele was also nominally significantly associated with severe rash. Overall, the HLA associations with rash are only nominally significant and replication of these results

with more appropriately selected cases and controls would be necessary. Alternative genotyping strategies such as a genome-wide association study would be desirable to help characterize the pathogenesis of rash in telaprevir-treated subjects and to identify markers that are potentially useful in minimizing the risk of this adverse event.

In an exploratory analysis (report not reviewed), the association of MDR1 polymorphisms to rash was evaluated with a small number of subjects treated with telaprevir/PR, and the Applicant concluded that no trend was discerned for the presence of a C3435T or C1236T genotype and the severity of rash. Additionally, telaprevir exposures did not appear to differ based on either genotype.

## 5. Recommendations

The Genomics Group has reviewed the pharmacogenomic substudies submitted with NDA 201,917. The results support a large and robust effect of *IL28B* genotype on PR response, with or without concomitant telaprevir. Based on the extent of replication for the *IL28B* marker and the potential clinical utility, descriptive results of the pharmacogenomic substudy should be included in labeling bearing appropriate precautions about the retrospective nature of the analyses while appropriately controlled trials are being conducted. Additional exploratory pharmacogenomic studies should be conducted to further characterize the mechanistic basis of rash in telaprevir-treated subjects and to identify patients at risk for severe rash.

## 5.1 Label recommendations

**12 Clinical Pharmacology**

...

(b) (4)


## 5.2 Post-marketing studies

Conduct a genome-wide association study (GWAS) to identify factor(s) associated with severe skin reactions to telaprevir/peginterferon/ribavirin using cases from existing DNA substudies and appropriately selected controls.

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/s/

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SHIRLEY K SEO
04/25/2011

JIANG LIU
04/25/2011

MICHAEL A PACANOWSKI
04/25/2011

PRAVIN R JADHAV
04/25/2011
Concur

SARAH M ROBERTSON
04/25/2011

| BIOPHARMACEUTICS REVIEW<br>Office of New Drugs Quality Assessment | | | |
|---|---|---|---|
| **Application No.:** | NDA 201-917 (000) | **Reviewer:** Sandra Suarez Sharp, Ph.D | |
| **Division:** | DAP | | |
| **Sponsor:** | Vertex Pharmaceuticals Inc. | **Team Leader:** Angelica Dorantes, Ph.D<br>. | |
| **Trade Name:** | -- | **Supervisor:** Patrick J. Marroum, Ph.D | |
| **Generic Name:** | Telaprevir film-coated IR tablets | **Date Assigned:** | Jul 21, 2010 |
| **Indication:** | for the treatment of genotype 1 chronic hepatitis C | **Date of Review:** | April 15, 2011 |
| **Formulation** | Immediate Release Tablet | | |
| **Route of Administration** | Oral | | |

| **SUBMISSIONS REVIEWED IN THIS DOCUMENT** | | | |
|---|---|---|---|
| **Submission date** | **CDER Stamp Date** | **Date of informal/Formal Consult** | **PDUFA DATE** |
| Jul 14, 2010; Oct 8, 2011 Mar 28, 2011; Apr 4, 2011 | Jul 17, 2010 | Jul 16, 2010 | May 2011 |
| **Type of Submission:** | Rolling NDA | | |
| **Type of Consult:** | Dissolution method and specifications and role of dissolution on QbD | | |

**REVIEW SUMMARY:**

Telaprevir is a reversible, covalent, tight-and slow-binding inhibitor of the HCV NS3·4A protease developed by Vertex for the treatment of Hepatitis C. Telaprevir drug product is an immediate-release film-coated tablet for oral administration. Each tablet contains 375 mg of telaprevir drug substance. (b) (4) The product and process development of telaprevir was conducted under a Quality by Design (QbD) paradigm to ensure desired product performance in terms of quality, safety, and efficacy.

This review focuses on: a) the acceptability of the dissolution method and specifications; b) the role of dissolution as a methodology that ensures control of the physical form (b) (4) of telaprevir tablets; and c) the role of dissolution on the construction of the design space for telaprevir film-coated tablets.

**a) Dissolution Method and Specification**

The proposed dissolution method and specifications for Telaprevir IR tablets is as follows:

| USP Apparatus | Spindle Rotation | Media Volume | Temperature | Medium | Acceptance criteria |
|---|---|---|---|---|---|
| II | 50 rpm | 900mL | 37°C | 1% SLS aqueous medium | Q= (b) (4) |

The proposed dissolution method is able to discriminate against material attributes and tablet properties that could affect product performance, such a as (b) (4) particle size (PS) and bulk density (BD), tablet

hardness, and presence of [redacted] telaprevir, and therefore, is deemed acceptable. However, the proposed dissolution specification was considered too permissive. The following dissolution acceptance criteria for release testing was proposed and agreed upon in a telecom with the sponsor that took place on March 29, 2011:

| Acceptance criteria |
| --- |
| Q= [redacted] at 20 min |

The dissolution specification of Q= [redacted] in 20 min was established based on mean dissolution values from clinical drug product release and drug product stability testing and on dissolution profiles of batches used in a pivotal BE study (Study 017). The submission dated April 4, 2011 contains an updated specification sheet which reflects the recommended dissolution specification.

**b) Dissolution as a Methodology to Control the Physical Form [redacted] of Telaprevir IR Tablets**

The control of the [redacted] telaprevir is crucial in assuring adequate dissolution and therefore, appropriate bioavailability. The sponsor's proposal of using mean dissolution of [redacted]

**c) The role of dissolution on the construction of the design space for telaprevir film-coated tablets**

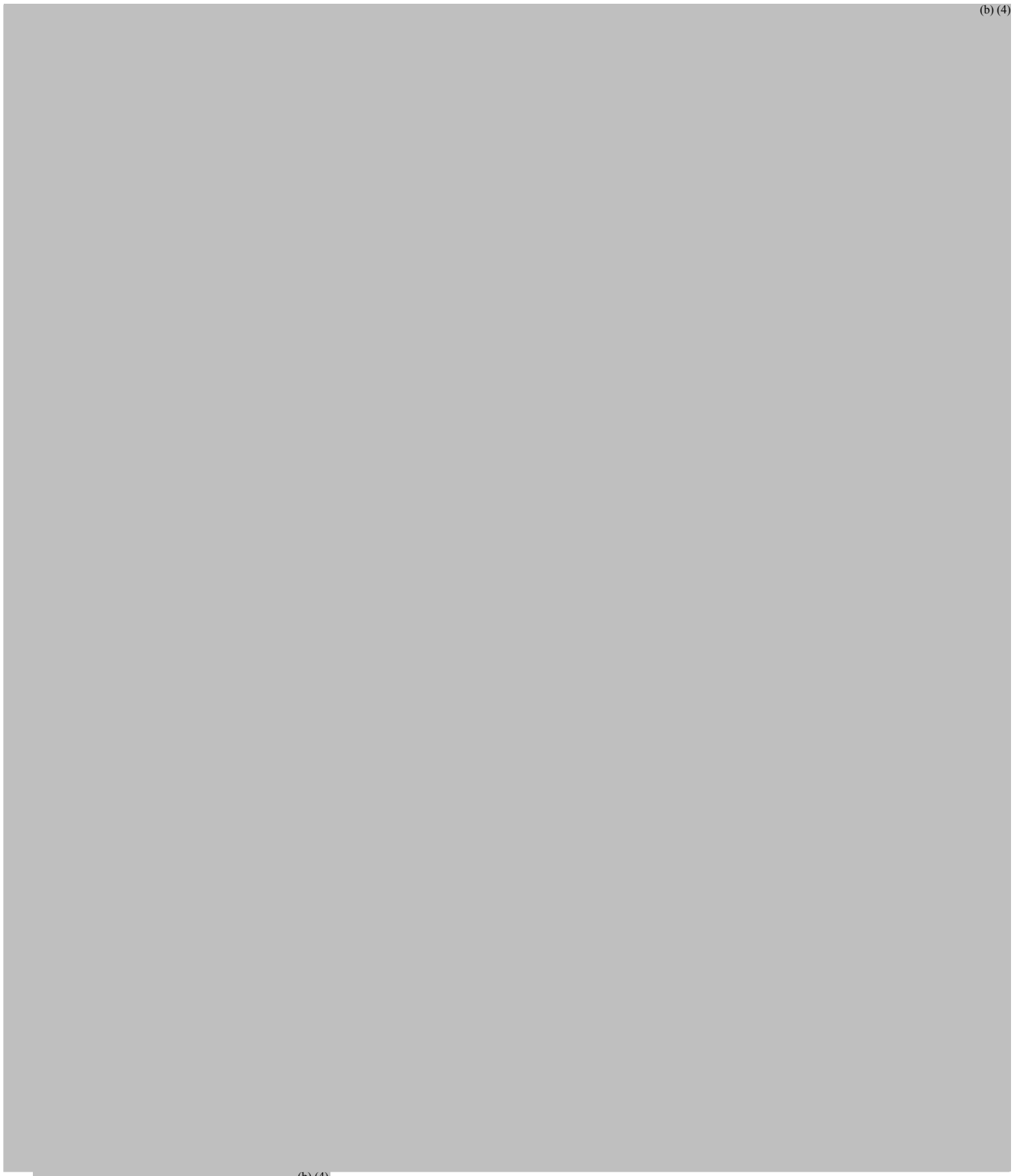
In this submission the sponsor proposes to use dissolution as a CQA in the construction of the design space. During development of the telaprevir drug product, it was determined that the primary factors affecting dissolution of telaprevir tablets were the particle size (PS) and bulk density (BD) of the [redacted] used to manufacture the tablets, as well as the final tablet average hardness ( $\overline{H}$ ). [redacted]

Specifically, the CQAs identified for the drug product are: appearance, identification, assay, [redacted], physical form, tablet weight, tablet hardness, tablet thickness, dosage form uniformity and dissolution. The reason for dissolution being considered as CQA is because [redacted] dissolution of the active substance is rate-limiting to absorption (its window for absorption is relatively short) i.e. the 3-5 hr transit time through the small intestine.

The overall product control strategy to assure rapid dissolution *in vivo* and consequently good bioavailability includes the following:

- Controlling the [redacted] required particle size and bulk density is produced;
- Controlling [redacted] parameters to achieve the desired range of tablet hardness; and,
- Testing tablet dissolution at release;

[redacted]




(b) (4) In conclusion, the proposed design space for H, PS and BD is supported by the dissolution model since the model is able to accurately predict dissolution at (b) (4) within the DS and even outside the DS.

During the review cycle, the ONDQA review team advised the sponsor to consider the proposed dissolution model as a surrogate for in lab dissolution testing with a dissolution specification of Q= (b) (4) at

(b) (4)

(b) (4)

These comments are being captured as post-meeting notes in the meeting minutes for a teleconference with the sponsor that took place on March 29, 2011. The sponsor's proposal for model maintenance plan is based on the assumption that the dissolution model would be used as a surrogate for in lab dissolution testing. Therefore, it needs to be updated to reflect the current agreement.

**RECOMMENDATION:**

The ONDQA/Biopharmaceutics team has reviewed NDA 201-917 for telaprevir IR tablets submitted on July 14, 2010, Oct 8, 2010, March 28, 2011, and April 4, 2011. We found this NDA acceptable from the Biopharmaceutics perspective. The recommended dissolution specification was agreed upon in a teleconference data March 29, 2011. The submission dated April 4, 2011 contains an updated specification sheet which reflects the recommended (see table below) dissolution specification. There are no additional comments to the sponsor.

Recommended Dissolution Method and Specification for Telaprevir film-coated IR Tablets

| USP Apparatus | Spindle Rotation | Media Volume | Temperature | Medium | Acceptance criteria |
|---|---|---|---|---|---|
| II | 50 rpm | 900mL | 37°C | 1% SLS aqueous medium | Q= (b) (4) at 20 min |

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: DHenry, ADorantes, ChChartterjee, CMoore, SMiller, GLunn, Qlin, BKurtyka, DMatecka, Chough, MShen, Shah.

## INTRODUCTION

Telaprevir is a reversible, covalent, tight-and slow-binding inhibitor of the HCV NS3·4A protease developed by Vertex for the treatment of Hepatitis C. Telaprevir drug product is an immediate-release film-coated tablet for oral administration. Each tablet contains 375 mg of telaprevir drug substance.

### Drug Substance

Telaprevir drug substance is a (b) (4) material of high purity. The chemical structure of telaprevir is shown in Figure 1.

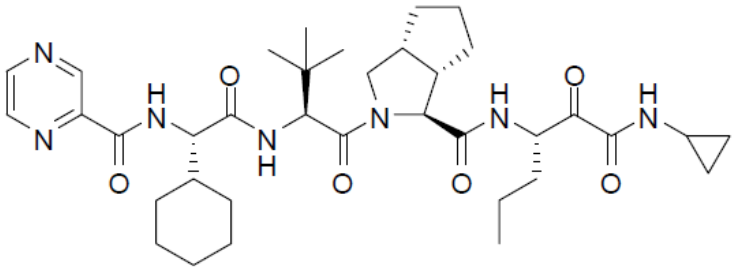


**Figure 1.** Chemical Structure of Telaprevir

(b) (4)

(b) (4)

Based on the current understanding of solubility and permeability of telaprevir, (b) (4) , dissolution of the active substance is rate-limiting to absorption given that telaprevir has negligible colonic absorption, so the window for absorption is relatively short, i.e. the 3-5 hr transit time through the small intestine. For these reasons, it is believed that dissolution is directly related to BA and therefore dissolution of the tablets is considered a critical quality attribute.

**Drug Product**

The components and composition of Telaprevir tablets are summarized in Table 1.

**Table 1**. Batch Formula for Telaprevir Tablet, 375 mg

| **Component** | **Quality Reference** | **Amount per Batch (kg)[a]** |
|---|---|---|
| (b) (4) | (b) (4) | (b) (4) |
| Dibasic calcium phosphate, anhydrous | USP | |
| Microcrystalline cellulose | USP/NF | |
| Croscarmellose sodium | USP/NF | |
| Colloidal silicon dioxide | USP/NF | |
| Sodium stearyl fumarate | USP/NF | |
| (b) (4) | | |
| | DMF No. (b) (4) | |
| | USP | |
| Total | -- | (b) (4) |

**Formulation Development of Film-Coated Tablet, 375 mg**

As part of formulation development, a purple (b) (4) film coat was chosen. (b) (4)

**DISSOLUTION METHOD**

The dissolution method that is currently being proposed as a quality control tool for Telaprevir film-coated IR tablets, 375 mg is summarized below:

| USP Apparatus | Spindle Rotation | Media Volume | Temperature | Analysis | Medium |
|---|---|---|---|---|---|
| II | 50 rpm | 900mL | 37°C | Reverse-phase HPLC | 1% SLS aqueous medium |

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***Reviewer's Comments***

*The information presented above namely, effect of (b) (4) particle size, bulk density, tablet hardness, and presence of (b) (4) telaprevir on telaprevir IR tablets dissolution demonstrate the existence of a dissolution method with discriminating ability.*

**DISSOLUTION SPECIFICATION**

The following dissolution specification is being proposed by the sponsor as a QC for the release of Telaprevir IR, tablets:

| Dissolution Specification |
| --- |
| Q= (b) (4) |

According to the sponsor, this specification is being proposed since the (b) (4) time point is the most sensitive to changes in (b) (4) content (see discussion below about this issue).

**Reviewer's Recommended Dissolution Specification**

The following dissolution specification is recommended as a QC for the release of Telaprevir IR, tablets:

| Dissolution Specification |
| --- |
| Q (b) (4) at 20 min |

The dissolution specification of Q=8(b) (4) in 20 min was established based on the following information:

- Mean dissolution values from the clinical drug product release and the drug product stability testing
- Dissolution profile of batches used in the pivotal BE study

**Dissolution Profiles from the Clinical and Stability Batches**

Figure 11 shows the mean dissolution profiles (b) (4) for about 33 batches, including clinical, commercial, and stability batches. The plot indicates that a specification of Q= (b) (4) is appropriate for this product since all the mean values at (b) (4).


**Dissolution profile of batches used in pivotal the BE study**

The sponsor conducted a bioequivalence study (Study 017) to link the formulation used in the phase 3 clinical trials (core tablet) to the commercial formulation (film-coated tablet, FCT). The clinical pharmacology reviewer (refer to Dr. Sherley Seo's review) concluded that these two formulations are considered BE based on exposure-response data despite the fact that Cmax did not meeting the 80-125 goal post for BE. The dissolution profiles obtained from these two formulations used in the pivotal BE study are shown in Figure 12. This figure shows that the core tablet presents a slower dissolution profile compared to the FCT. The slower profile supports a later time point specification (Q= (b) (4) in 20 min) and therefore, was used to set the speciation given that it is BE to the profile for the FCT.

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SANDRA SUAREZ
04/20/2011

PATRICK J MARROUM
04/20/2011

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS**
**FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

## Office of Clinical Pharmacology

New Drug Application Filing and Review Form

| | Information | | Information |
|---|---|---|---|
| **NDA/BLA Number** | **201-917** | **Brand Name** | (b) (4) |
| **OCP Division (I, II, III, IV, V)** | **DCP IV** | **Generic Name** | **Telaprevir** |
| **Medical Division** | **DAVP** | **Drug Class** | **HCV protease inhibitor** |
| **OCP Reviewer** | **Shirley K. Seo, Ph.D.** | **Indication(s)** | **Treatment of chronic HCV genotype 1 infection** |
| **OCP Team Leader** | **Sarah Robertson, Pharm.D.** | **Dosage Form** | **375-mg Tablet** |
| **Pharmacometrics Reviewer** | **Jiang Liu, Ph.D.** | **Dosing Regimen** | **750 mg q8h** |
| **Date of Submission** | **11/23/10** | **Route of Administration** | **Oral** |
| **Estimated Due Date of OCP Review** | **4/25/11** | **Sponsor** | **Vertex** |
| **Medical Division Due Date** | | **Priority Classification** | **Priority** |
| **PDUFA Due Date** | **5/23/11** | | |

## Clin. Pharm. and Biopharm. Information

| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
|---|---|---|---|---|
| **STUDY TYPE** | | | | |
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | **X** | | | |
| **Tabular Listing of All Human Studies** | **X** | | | |
| **HPK Summary** | **X** | | | |
| **Labeling** | **X** | | | |
| **Reference Bioanalytical and Analytical Methods** | | | | |
| **I. Clinical Pharmacology** | **X** | | | |
| **Mass balance:** | **X** | | | |
| **Isozyme characterization:** | **X** | | | |
| **Blood/plasma ratio:** | **X** | | | |
| **Plasma protein binding:** | **X** | | | |
| **Pharmacokinetics (e.g., Phase I) -** | **X** | | | |
| **Healthy Volunteers-** | | | | |
| single dose: | **X** | | | |
| multiple dose: | **X** | | | |
| **Patients-** | | | | |
| single dose: | **X** | | | |
| multiple dose: | **X** | | | |
| **Dose proportionality -** | | | | |
| fasting / non-fasting single dose: | **X** | | | |
| fasting / non-fasting multiple dose: | **X** | | | |
| **Drug-drug interaction studies -** | | | | |
| In-vivo effects on primary drug: | **X** | | | |
| In-vivo effects of primary drug: | **X** | | | |
| In-vitro: | **X** | | | |
| **Subpopulation studies -** | | | | |
| ethnicity: | **X** | | | |
| gender: | **X** | | | |
| pediatrics: | **--** | | | **Requests for waiver and deferral of pediatric studies were submitted** |
| geriatrics: | **--** | | | |

| | | | | |
|---|---|---|---|---|
| renal impairment: | **X** | | | |
| hepatic impairment: | **X** | | | |
| **PD -** | | | | |
| Phase 2: | **X** | | | |
| Phase 3: | **X** | | | |
| **PK/PD -** | | | | |
| Phase 1 and/or 2, proof of concept: | **X** | | | |
| Phase 3 clinical trial: | **X** | | | |
| **Population Analyses -** | | | | |
| Data rich: | **X** | | | |
| Data sparse: | **X** | | | |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability** | **--** | | | |
| **Relative bioavailability -** | **X** | | | |
| solution as reference: | **X** | | | |
| alternate formulation as reference: | **X** | | | |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | **X** | | | |
| replicate design; single / multi dose: | **--** | | | |
| **Food-drug interaction studies** | **X** | | | |
| **Bio-waiver request based on BCS** | **--** | | | |
| **BCS class** | **X** | | | |
| **Dissolution study to evaluate alcohol induced dose-dumping** | **--** | | | |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies** | **X** | | | |
| **Chronopharmacokinetics** | **--** | | | |
| **Pediatric development plan** | **X** | | | |
| **Literature References** | **X** | | | |
| **Total Number of Studies** | | | | |
| | | | | |

On **initial** review of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | N/A | Comment |
|---|---|---|---|---|---|
| **Criteria for Refusal to File (RTF)** | | | | | |
| 1 | Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials? | | X | | The tablet used in the phase 3 studies is the same as the to-be-marketed tablet |
| 2 | Has the applicant provided metabolism and drug-drug interaction information? | X | | | |
| 3 | Has the sponsor submitted bioavailability data satisfying the CFR requirements? | X | | | |
| 4 | Did the sponsor submit data to allow the evaluation of the validity of the analytical assay? | X | | | |
| 5 | Has a rationale for dose selection been submitted? | X | | | |
| 6 | Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin? | X | | | |
| 7 | Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin? | X | | | |
| 8 | Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work? | X | | | |
| **Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)** | | | | | |
| | **Data** | | | | |

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS**
**FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

| | | | | | |
|---|---|---|---|---|---|
| 9 | Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)? | X | | | |
| 10 | If applicable, are the pharmacogenomic data sets submitted in the appropriate format? | | X | | |
| **Studies and Analyses** | | | | | |
| 11 | Is the appropriate pharmacokinetic information submitted? | X | | | |
| 12 | Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)? | X | | | |
| 13 | Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance? | X | | | |
| 14 | Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics? | X | | | |
| 15 | Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective? | | | X | |
| 16 | Did the applicant submit all the pediatric exclusivity data, as described in the WR? | | | X | |
| 17 | Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label? | | X | | |
| **General** | | | | | |
| 18 | Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? | X | | | |
| 19 | Was the translation (of study reports or other study information) from another language needed and provided in this submission? | | | X | |

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**

**YES**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. We received your submission of bioanalytical reports for studies VX-950-TiDP24-C121, VX-950-TiDP24-C123, VX-950-TiDP24-C124, VX-950-TiDP24-C130, VX-950-TiDP24-C132, VX-950-TiDP24-C133, VX-950-TiDP24-C134, VX-950-TiDP24-C135, VX-950-TiDP24-C208 as previously communicated to you. However, for studies VX-950-TiDP24-C123 and VX-950-TiDP24-C135, we did not receive the bioanalytical report for the determination of VX-950 and VRT-127394 in human plasma samples. (You submitted the reports for the interacting drugs only.) Please submit the reports for VX-950 and VRT-127394 for these two studies.

2. We received your submission of PK concentration and parameter datasets for studies VX-950-TiDP24-C122, VX-950-TiDP24-C124, VX-950-TiDP24-C130, VX06-950-106, VX-950-TiDP24-C208. However, we did not receive the datasets for study VX09-950-021. Please submit

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS**
**FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

PK concentration and parameter datasets for VX-950, cyclosporine, and tacrolimus in study VX09-950-021.

Shirley K. Seo, Ph.D.

Reviewing Clinical Pharmacologist Date

Sarah M. Robertson, Pharm.D.

Team Leader/Supervisor Date

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/s/

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SHIRLEY K SEO
01/06/2011

SARAH M ROBERTSON
01/06/2011